Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende ozanimod til behandling af attakvis multipel sklerose

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Sundhedsøkonomisk afrapportering

Ozanimod

Attaksvis multipel sklerose

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

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for ozanimod til attakvis multipel sklerose, samt en gennemgang af ansøgers modelantagelser til den sundhedsøkonomiske model. Sekretariatet vil kommentere på ansøgers modelantagelser under afsnittene "Sekretariatets vurdering". Her vil sekretariatets vurdering fremgå sammen med eventuelle ændrede modelantagelser og begrundelser herfor.
Afsnit 2.4 indeholder en tabel, der opsummerer både ansøgers og sekretariatets modelantagelser med det formål tydeligt at vise, hvordan sekretariatets sundhedsøkonomiske analyse afviger fra ansøgers sundhedsøkonomiske analyse. Resultatafsnittet baserer sig på sekretariatets modelantagelser og sundhedsøkonomiske analyse.

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Indholdsfortegnelse

1. Liste over forkortelser

AIP	Apotekernes indkøbspris
DRG	Diagnose Relaterede Grupper
EMA	*European Medicines Agency*
EPAR	*European public assessment report*
JCV	John Cunningham virus
PPMS	Primær progressiv multipel sklerose
RRMS	Recidiverende remitterende multipel sklerose
SAIP	Sygehusapotekernes indkøbspriser
SPMS	Sekundær progressiv multipel sklerose
SPC	*Summary of Product Characteristics*

2. Opsummering

Baggrund
Ozanimod er som monoterapi indiceret til behandling af voksne patienter med attakvis (relapserende-remitterende) multipel sklerose med aktiv sygdom defineret ved kliniske eller radiologiske fund. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af Bristol Myers Squibb på vegne af Celgene.
Det vurderes af ansøger, at 375 nye patienter årligt kandiderer til førstelinjebehandling af den ansøgte indikation i Danmark. Baseret på fagudvalgets vurdering kandiderer omkring 422 nye patienter årligt til andenlinjebehandling.

Analyse
Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med ozanimod over en tidshorisont på 3 år. Ozanimod sammenlignes med hhv. dimethylfumarat til patienter med gennemsnitlig sygdomsaktivitet (førstelinjebehandling) og fingolimod til patienter med høj sygdomsaktivitet (andenlinjebehandling).

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger for ozanimod ca. [redacted] DKK sammenlignet med dimethylfumarat over en tidshorisont på 3 år. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 21.000 DKK pr. patient.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af ozanimod som standardbehandling i første linje vil være ca. [redacted]. DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenserne ca. 7,2 mio. DKK i år 5. Estimaterne er baseret på ansøgers antagelser om patientantallet, der kandiderer til behandling, samt det forventede markedsoptag af ozanimod ved en anbefaling.

I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger for ozanimod ca. [redacted] DKK sammenlignet med fingolimod over en tidshorisont på 3 år. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 10.000 DKK pr. patient.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af ozanimod som standardbehandling i anden linje vil være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 4,9 mio. DKK i år 5. Estimaterne er baseret på fagudvalgets antagelser om patientantallet, der kandiderer til behandling, samt det forventede markedsoptag af ozanimod ved en anbefaling.

Konklusion
Ozanimod er forbundet med inkrementelle omkostninger sammenlignet med hhv. dimethylfumarat som førstelinjebehandling og fingolimod som andenlinjebehandling.

Idet der er usikkerheder forbundet med ansøgers antagelser i den økonomiske analyse, bør analysens resultater for den gennemsnitlige inkrementelle omkostning pr. patient fortolkes med disse in mente. Usikkerhederne vedrører antagelser om den gennemsnitlige behandlingslængde samt bivirkningsrelaterede omkostninger.

Resultaterne af budgetkonsekvensanalysen for klinisk spørgsmål 1 er baseret på ansøgers antagelser om patientantal og markedsoptag, idet fagudvalget ikke kan komme med konkrete estimater på, hvad patientantallet og markedsoptaget reelt vil være, hvis ozanimod anbefales.

3. Baggrund for den sundhedsøkonomiske analyse

Bristol Myers Squibb, som er markedsføringstilladelsesindehaver af ozanimod (herefter omtalt som ansøger), har på vegne af Celgene indsendt en ansøgning til Medicinrådet den 20. november 2020 om anbefaling af ozanimod som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Medicinrådets sekretariat, på vegne af Medicinrådet, den sundhedsøkonomiske analyse, ansøger har indsendt. Denne rapport er sekretariatets vurdering af den fremsendte sundhedsøkonomiske analyse (herefter omtalt som analysen).

3.1 Patientpopulation

Multipel sklerose (MS) er en kronisk neurologisk lidelse, som hyppigst debuterer i alderen 25-45 år og forekommer ca. dobbelt så ofte hos kvinder som hos mænd. Årsagen er ukendt, men der findes flere disponerende arvelige og miljømæssige faktorer. Der findes overordnet tre typer af MS: Recidiverende remitterende multipel sklerose (RRMS) eller attakvis MS, sekundær progressiv multipel sklerose (SPMS) og primær progressiv multipel sklerose (PPMS). Den hyppigste type er RRMS, som er defineret ved attakvise tilbagefald med forværring af symptomer, eventuelt efterfulgt af en periode med forbedring af symptomer [1,2]. I Danmark har knap 16.500 personer MS, hvilket svarer til 250 pr. 100.000. Antallet af nye tilfælde har ligget nogenlunde konstant på ca. 600 personer om året siden år 2000 [3].

3.1.1 Subpopulationer

Lægemidlerne til behandling af attakvis multipel sklerose er delt op i to grupper i Medicinrådets behandlingsvejledning og lægemiddelrekommandation [4,5]. De kaldes første og anden linje, men det skal ikke opfattes således, at samtlige patienter nødvendigvis vil blive behandlet med et førstelinjelægemiddel først og dernæst med et andenlinjelægemiddel.
Patienterne, som kan behandles med lægemidler fra gruppen af førstelinjepræparater, omfatter patienter med gennemsnitlig sygdomsaktivitet (defineret radiologisk og klinisk).

Skift mellem lægemidler inden for gruppen af førstelinjepræparater kan ske på grund af fx betydende bivirkninger eller ønske om graviditet.
Patienterne, som kan behandles med lægemidler fra gruppen af andenlinjepræparater, er patienter med fortsat sygdomsaktivitet (defineret radiologisk og klinisk) på et førstelinjepræparat, og patienter med høj sygdomsaktivitet (defineret radiologisk og klinisk), som ikke tidligere har været behandlet. Patienter, som behandles med lægemidler fra gruppen af andenlinjepræparater, opdeles yderligere efter, om de har antistoffer for John Cunningham virus (JCV) eller ej.

3.1.2 Komparator

Medicinrådet har defineret dimethylfumarat og fingolimod som komparatorer til ozanimod for populationerne specificeret i afsnit 3.1.1, se Tabel 1.

Tabel 1. Definerede populationer og komparatorer

Population	Komparator
Patienter med gennemsnitlig sygdomsaktivitet (defineret radiologisk og klinisk). Populationen omfatter kun mænd samt kvinder, som benytter effektiv antikonception.	Dimethylfumarat
Patienter med høj sygdomsaktivitet (defineret radiologisk og klinisk) uanset JCV-status. Populationen omfatter kun mænd samt kvinder, som benytter effektiv antikonception.	Fingolimod

3.2 Problemstilling

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af ozanimod som standardbehandling på danske hospitaler af den nævnte indikation.
Medicinrådet har vurderet den kliniske merværdi af ozanimod og specificeret følgende kliniske spørgsmål:

Klinisk spørgsmål 1:
Hvilken værdi har ozanimod sammenlignet med dimethylfumarat for patienter med attakvis multipel sklerose og gennemsnitlig sygdomsaktivitet (førstelinjebehandling)?

Klinisk spørgsmål 2:
Hvilken værdi har ozanimod sammenlignet med fingolimod for patienter med attakvis multipel sklerose og høj sygdomsaktivitet (andenlinjebehandling)?

4. Vurdering af den sundhedsøkonomiske analyse

Ansøger har indsendt en sundhedsøkonomisk analyse, der estimerer de inkrementelle omkostninger pr. patient for ozanimod sammenlignet med henholdsvis dimethylfumarat og fingolimod. I det nedenstående vil den sundhedsøkonomiske model, som ligger til grund for estimeringen af de inkrementelle omkostninger pr. patient, blive præsenteret.

4.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger ved første- og andenlinjebehandling af attakvis multipel sklerose.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en simpel omkostningsmodel for behandling af patienter i de nævnte populationer. Baseret på resultaterne af en netværksmetaanalyse, udført af ansøger, antages det af ansøger, at der ikke er statistisk signifikant og klinisk meningsfuld forskel i effekt mellem ozanimod og hhv. dimethylfumarat og fingolimod. Ansøger har derfor ikke inkluderet hverken klinisk effekt- eller sikkerhedsdata i modellen. Netværksmetaanalysen, der beskriver den indbyrdes effekt mellem ozanimod og hhv. dimethylfumarat og fingolimod, baserer sig på data fra følgende 8 kliniske studier: RADIANCE (del b) [6], SUNBEAM [7], CONFIRM [8], DEFINE [9], FREEDOMS [10], FREEDOMS II [11], TRANSFORMS [12] og BRAVO [13]. For yderligere information om ansøgers netværksmetaanalyse henvises til sekretariatets vurderingsrapport af ozanimod til behandling af attakvis multipel sklerose.

Ansøger antager, at den gennemsnitlige behandlingslængde med ozanimod, dimethylfumarat og fingolimod er 5 år. Dette estimat er baseret på et studie af Ryerson et al. [14], hvori de inkluderede RRMS-patienter, som blev behandlet med dimethylfumarat, blev evalueret efter et *retrospective chart review*. Studiet fandt, at 20-29 % af patienterne var ophørt i behandling med dimethylfumarat efter en follow-up-periode på 14 måneder. Ansøger pointerer, at lignende rater er blevet rapporteret i et dansk retrospektivt studie [15], hvor follow-up-perioden dog ikke kendes.
Ansøger har anvendt en eksponentiel funktion til at estimere den gennemsnitlige behandlingslængde på baggrund af raten for behandlingsophør fra Ryerson et al.-studiet på 20-29 %. Ansøger antager i denne sammenhæng en årlig *discontinuation*-rate på 20 % pr. 14. måned. Resultatet af ansøgers udregning er en gennemsnitlig behandlingslængde på 5,2 år, som ansøger har valgt at runde ned til 5 år.

Sekretariatets vurdering
For klinisk spørgsmål 1 udtrykker fagudvalget bekymringer i forhold til risikoen for *rebound*-effekt samt alvorlige bivirkninger og langtidsbivirkninger ved behandling med ozanimod. På baggrund af dette noterer sekretariatet sig, at der potentielt kan være inkrementelle omkostninger afledt af bivirkninger grundet behandling med ozanimod,

som ikke indfanges i ansøgers analyse for klinisk spørgsmål 1, da disse bivirkninger vil ses efter længere tid. I sammenligningen mellem ozanimod og fingolimod antager fagudvalget, at bivirkningsprofilen inden for den tidsramme, som de kliniske studier har været fulgt i, ikke er markant forskellig mellem de to præparater. Sekretariatet antager derfor, at der ikke vil være inkrementelle bivirkningsomkostninger for klinisk spørgsmål 2.

Vedr. behandlingslængden pointerer fagudvalget, at behandlingen med præparaterne i denne analyse ikke er tidsbegrænset. Det vil sige, at stabile patienter uden nævneværdige bivirkninger kan behandles med dimethylfumarat og fingolimod i flere år, herunder også over 5 år, som ansøger antager i sin hovedanalyse. På trods af denne kliniske observation påpeger fagudvalget, at ansøgers antagelse om en gennemsnitlig behandlingslængde på 5 år synes høj sammenlignet med dansk klinisk praksis, uagtet om patienterne behandles med ozanimod, dimethylfumarat eller fingolimod. I stedet estimerer fagudvalget, at den gennemsnitlige behandlingstid nærmere er 3 år for de tre præparater. Det understreges dog af fagudvalget, at der er usikkerheder forbundet med dette estimat.
På baggrund af dette ændrer sekretariatet behandlingslængden i hovedanalysen til 3 år for både klinisk spørgsmål 1 og 2. Sekretariatet er opmærksom på, at lægemidlerne i den nuværende behandlingsvejledning for attakvis multipel sklerose er sammenlignet på baggrund af en tidshorisont på hhv. 1 år for førstelinjebehandling og 4 år for andenlinjebehandling.
Sekretariatet foretager følsomhedsanalyser med en behandlingslængde på 1 og 5 år for at belyse usikkerheden forbundet med behandlingslængden af ozanimod, dimethylfumarat og fingolimod.

Sekretariatet noterer sig, at ansøgers ekskludering af bivirkningsrelaterede omkostninger kan have en betydning for de inkrementelle omkostninger i sammenligningen mellem ozanimod og dimethylfumarat. Sekretariatet diskuterer dette yderligere under afsnit 7.1. Sekretariatet vælger i hovedanalysen at ændre den gennemsnitlige behandlingslængde til 3 år for præparaterne i begge kliniske spørgsmål samt udarbejde følsomhedsanalyser for behandlingslængden (1 og 5 år), men accepterer ellers ansøgers tilgang vedr. modelantagelser.

4.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv og en tidshorisont på 5 år. Denne tidshorisont er valgt, da ansøger argumenterer for, at den gennemsnitlige behandlingslængde med ozanimod, dimethylfumarat og fingolimod er 5 år, se afsnit 4.1.1. Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %.

Sekretariatets vurdering
Idet ansøgers tidshorisont for omkostningsanalysen er betinget af behandlingslængden, ændres tidshorisonten, jf. sekretariatets vurdering under afsnit 4.1.1, til 3 år for begge kliniske spørgsmål.

Sekretariatet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af ozanimod sammenlignet med dimethylfumarat og fingolimod. De inkluderede omkostninger i ansøgers analyse er lægemiddelomkostninger inkl. spild, hospitalsomkostninger, herunder monitoreringsomkostninger og patientomkostninger.
Ansøger har ikke inkluderet bivirkningsrelaterede omkostninger i analysen, grundet at der ifølge ansøger ikke er evidens for, at ozanimod er forbundet med statistisk signifikante eller klinisk relevante forskelle i sikkerhed sammenlignet med hverken dimethylfumarat eller fingolimod. Derudover har ansøger ikke inkluderet omkostninger forbundet med administration, da de tre behandlinger administreres oralt. Endelig har ansøger ikke inkluderet omkostninger til efterfølgende behandling i analysen.

Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet udskifter med SAIP.

4.2.1 Lægemiddelomkostninger

De anvendte doser er hentet i de respektive produkters produktresuméer (SPC'er).

- Ozanimod: 0,23 mg (dag 1-4), 0,46 mg (dag 5-7), 0,92 mg (dag 8 og derefter) oralt én gang dagligt
- Dimethylfumarat: 120 mg (dag 1-7), 240 mg (dag 8 og derefter) oralt to gange dagligt
- Fingolimod: 0,5 mg oralt én gang dagligt.

Ozanimod administreres oralt én gang dagligt, og behandlingen initieres med et dosiseskaleringsprogram efterfulgt af en vedligeholdelsesdosis. På dag 1-4 i dosiseskaleringsprogrammet doseres ozanimod med 0,23 mg, hvorefter doseringen øges til 0,46 mg på dag 5-7. Den efterfølgende anbefalede vedligeholdelsesdosis er 0,92 mg. Dimethylfumarat administreres oralt to gange dagligt, og behandlingen indledes (dag 1-7) med en dosis på 120 mg, hvorefter dosis øges til den anbefalede vedligeholdelsesdosis på 240 mg. Fingolimod 0,5 mg administreres oralt én gang dagligt.

Tabel 2. Anvendte lægemiddelpriser, SAIP (november 2020)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Ozanimod	0,23 + 0,46 mg	4 + 3 stk.	[redacted]	Amgros
	0,92 mg	28 stk.	[redacted]	
Dimethylfumarat	120 mg	14 stk.	[redacted]	Amgros
	240 mg	56 stk.	[redacted]	
Fingolimod	0,5 mg	28 stk.	[redacted]	Amgros

I ansøgers hovedanalyse for både klinisk spørgsmål 1 og 2 inkluderes en engangsomkostning for lægemiddelspild af ozanimod, dimethylfumarat og fingolimod. Engangsomkostningen udgør 50 % af omkostningen for én vedligeholdelsespakke, svarende til 14 dages behandling.

Sekretariatets vurdering
Vedrørende spild finder fagudvalget det som udgangspunkt rimeligt at antage, at der i gennemsnit spildes en halv vedligeholdelsespakke af hhv. ozanimod, dimethylfumarat eller fingolimod pr. patientforløb. Fagudvalget påpeger dog, at der er usikkerhed forbundet med dette estimat. Usikkerheden skyldes bl.a., at der ikke foreligger nogen retningslinjer, hvori det er beskrevet, hvor mange pakninger sygehusafdelingen eller sygehusapoteket skal udlevere ad gangen. Det betyder, at hvis patienten får udleveret pakninger til flere måneder for derefter at ophøre med behandling tidligere end forventet, kan spildet være større end ansøgers antagelse om en halv pakning, svarende til 14 dages behandling.

Sekretariatet accepterer ansøgers antagelser vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Ansøger har inkluderet hospitalsomkostninger i form af monitoreringsbesøg i analysen, herunder initierende ambulant besøg, initierende dagsbesøg, follow-up-besøg og blodprøvetagning. Ansøger har estimeret ressourceforbruget forbundet med monitorering på baggrund af Medicinrådets dokument "Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til attakvis multipel sklerose" [4].

For ambulant besøg, dagsbesøg, follow-up-besøg og blodprøver anvender ansøger 2020 DRG-takster, se Tabel 3.

Tabel 3. Monitoreringsomkostninger

	Enhedsomkostning [DKK]	Kode	Kilde
Ambulant besøg	3.375,00	01MA98	DRG 2020 MDC01 1-dagsgruppe, pat. mindst 7 år
Dagsbesøg	3.375,00	01MA98	DRG 2020 MDC01 1-dagsgruppe, pat. mindst 7 år
Follow-up-besøg	3.375,00	01MA98	DRG2020 MDC01 1-dagsgruppe, pat. mindst 7 år

	Enhedsomkostning [DKK]	Kode	Kilde
Blodprøve	129,00	65TE01	DRG 2020 Telefon- og e-mail-konsultation samt skriftlig kommunikation ved prøvesvar

Frekvensen af monitoreringsbesøgene ses i Tabel 4.

Ansøger antager, at patienterne ved behandlingsopstart initierende enten har et kortere ambulant besøg eller et dagsbesøg. Hvilket af de initierende monitoreringsbesøg patienten får, er afhængigt af valg af behandling.

For follow-up-besøgene antager ansøger, at besøgsfrekvensen er henholdsvis tre i år 1 samt to i år 2 og årene derefter. Ansøger antager, at frekvensen for besøgene er ens for ozanimod, dimethylfumarat og fingolimod.

For blodprøvetagning antager ansøger, at patienter, der behandles med dimethylfumarat, får taget 1 blodprøve hver anden uge de første 26 uger efterfulgt af en blodprøvetagning hver ottende uge. For fingolimod og ozanimod antager ansøger, at disse patienter får foretaget 4 blodprøver det første år (måned 1, 3, 9 og 12) efterfulgt af en blodprøve hvert halve år. Ansøger antager derudover, at alle patienter får taget 1 blodprøve forud for behandlingsstart, uagtet hvilket af de tre præparater patienten behandles med. Ansøger antager, at omkostningen forbundet med denne blodprøve er inkluderet i DRG-taksten for det initierende besøg.

Tabel 4. Monitoreringsfrekvenser

	Ozanimod		Dimethylfumarat		Fingolimod	
	År 1	**År 2+**	**År 1**	**År 2+**	**År 1**	**År 2+**
Initierende ambulant besøg/dagsbesøg	1		1		1	
Follow-up-besøg	3	2	3	2	3	2
Blodprøve	4	2	16,25	6,5	4	2

Ansøger antager, at alle patienter vil få foretaget én MR-scanning ved diagnosetidspunktet, og derfor vælger ansøger at simplificere analysen ved at ekskludere omkostninger forbundet med MR-scanninger i den økonomiske analyse.

Sekretariatets vurdering
Fagudvalget vurderer, at frekvensen af follow-up-besøgene er underestimeret i ansøgers analyse, hvis disse besøg både inkluderer kontrol hos læge og sygeplejersker. Ved sygdomsmodificerende behandling af MS er monitorering nødvendigt, idet det kliniske personale ved kontrollerne har mulighed for at opfange eventuelle opstartsvanskeligheder, komplikationer, complianceproblemer og/eller bivirkninger hos patienterne. Fagudvalget pointerer, at der kan være variation mellem klinikkerne vedr. frekvensen af sygeplejerskekontroller. Fagudvalget mener dog, at det er rimeligt at antage, at antallet og omfanget af kontroller vil være ens for ozanimod, dimethylfumarat og fingolimod.
Sekretariatet vælger derfor at ekskludere omkostningerne forbundet med follow-up-besøgene hos både læge og sygeplejersker i hovedanalysen.

Vedrørende blodprøvetagning pointerer fagudvalget, at frekvensen af blodprøver ifm. behandling med dimethylfumarat er overestimeret. Fagudvalget vurderer, at antallet af blodprøver som udgangspunkt er 4 pr. år, svarende til en blodprøvetagning hver tredje måned. For fingolimod og ozanimod vurderer fagudvalget ligeledes, at ansøgers estimater for frekvensen af blodprøver er for højt. Fagudvalget vurderer, at antallet af blodprøver som udgangspunkt er 5 det første år (måned 1, 3, 6, 9 og 12) og 4 blodprøver de efterfølgende år, svarende til en blodprøvetagning hver tredje måned.

Sekretariatet ekskluderer omkostninger forbundet med follow-up-besøgene og ændrer i frekvensen for blodprøvetagning, så denne stemmer overens med dansk klinisk praksis. Foruden dette accepterer sekretariatet ansøgers tilgang vedr. hospitalsomkostninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af monitoreringsbesøg på hospitalet og inkluderer patientens effektive tid brugt på monitorering, ventetid og transport. Ansøgers estimerede patienttid kan ses i Tabel 5.

Tabel 5. Ansøgers estimat af effektiv patienttid

	Patienttid [minutter]
Ambulant besøg	90
Dagsbesøg	420
Follow-up-besøg	90
Blodprøve	45

Ansøger anvender Medicinrådets katalog for "Værdisætning af enhedsomkostninger" til at estimere enhedsomkostningerne for den effektive tid, som patienterne bruger på behandling. Herunder antager ansøger en gennemsnitlig transportdistance til og fra sygehusbehandling på 28 km, skattefri kørselsgodtgørelse på 3,52 DKK/km og en gennemsnitlig timeløn på 179 DKK/time.

Ansøger antager, at blodprøverne foretages på en lokal klinik frem for på hospitalet. For ressourceforbruget associeret med blodprøvetagning har ansøger estimeret, at den effektive tid for patienten er 50 % af den effektive tid, som patienten bruger på et ambulant besøg.

Ansøger antager, at 5 % af de patienter, der behandles med ozanimod, bliver monitoreret efter første dosis. De 5 % afspejler andelen af patienter med lav hvilepuls, andengrads-AV-blok eller historie med AV-blok eller hjertesvigt. Ansøger baserer denne antagelse på EMAs *EPAR* for ozanimod [16]. Ansøger estimerer, at denne andel (5 %) af patienterne bruger 7 timer (420 min.) på monitorering efter første dosis. For de resterende patienter (95 %) antager ansøger, at disse bruger 1,5 time (90 min.) på et ambulant besøg.
Ansøger antager desuden, at 100 % af patienterne, der behandles med dimethylfumarat, modtager et initierende ambulant besøg, mens 100 % af patienterne, der behandles med fingolimod, modtager et initierende dagsbesøg.

Ansøgers estimerede patientomkostninger pr. måned fremgår af Tabel 6.

Tabel 6. Ansøgers estimerede patientomkostninger pr. år, ikke-diskonterede afrundede tal

	Ozanimod		Dimethylfumarat		Fingolimod	
	År 1	**År 2+**	**År 1**	**År 2+**	**År 1**	**År 2+**
Patienttid, omkostning [DKK]	1.661	806	3.256	1.410	2.596	806
Transportomkostning [DKK]	591	295	1.195	517	591	295
Patientomkostning år [DKK]	**2.252**	**1.101**	**4.451**	**1.927**	**3.187**	**1.101**

Sekretariatets vurdering
Fagudvalget pointerer, at tidsforbruget for blodprøvetagning på 45 minutter umiddelbart virker højt. Fagudvalget vælger dog at acceptere ansøgers antagelse, da der vil være regional variation i, om patienterne får taget blodprøven hos egen læge eller møder op på en lokal sygehusafdeling.

Som følge af ændringer foretaget i afsnit 4.2.2 vedr. follow-up-besøgene for ozanimod, dimethylfumarat og fingolimod ekskluderes patientens effektive tid forbundet med disse kontroller ligeledes.

Sekretariatet ekskluderer patientomkostningerne forbundet med follow-up-besøg og accepterer ellers ansøgers tilgang vedr. patientomkostninger i sin hovedanalyse.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen. Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. De undersøgte parametre er ens, uagtet om ozanimod sammenlignes med dimethylfumarat eller fingolimod.
Følgende følsomhedsanalyser er udført:

- Behandlingslængde 1 år, 3 år og 10 år.
- 0 % monitoreres ved første dosis ozanimod.
- 10 % monitoreres ved første dosis ozanimod.
- 50 % reduktion i besøgsomkostninger.
- Ingen lægemiddelspild.
- Lægemiddelspild: Én hel vedligeholdelsespakke.

Sekretariatets vurdering
Sekretariatet vurderer, at ansøgers følsomhedsanalyser er relevante og vælger derfor at præsentere resultaterne af disse. For den gennemsnitlige behandlingslængde udfører sekretariatet dog kun følsomhedsanalyser for 1 år og 5 år.

Sekretariatet vælger at præsentere ansøgers følsomhedsanalyser, men vælger at justere scenarierne for den gennemsnitlige behandlingslængde.

4.4 Opsummering af basisantagelser

I Tabel 7 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 7. Basisantagelser for ansøgers og sekretariatets hovedanalyse

Basisantagelser	Ansøger	Sekretariatet
Tidshorisont	5 år	3 år
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddel Monitorering Patienttid og transport	Lægemiddel Monitorering Patienttid og transport
Behandlingslinje	1.- og 2.-linjebehandling	1.- og 2.-linjebehandling
Behandlingslængde		
Ozanimod:	5 år	3 år
Dimethylfumarat:	5 år	3 år
Fingolimod:	5 år	3 år

Basisantagelser	Ansøger	Sekretariatet
Inkludering af spild	Ja	Ja
Monitorerings- og patientomkostninger forbundet med follow-up-besøg	Inkluderes	Ekskluderes
Frekvens for blodprøver		
Dimethylfumarat	År 1: 16,25 År 2+: 6,5	År 1: 4 År 2+: 4
Fingolimod og ozanimod	År 1: 4 År 2+: 2	År 1: 5 År 2+: 4
Andre væsentlige antagelser	Effekt og bivirkningsprofil er identisk mellem ozanimod og dimethylfumarat samt mellem ozanimod og fingolimod	Effekt og bivirkningsprofil er identisk mellem ozanimod og dimethylfumarat samt mellem ozanimod og fingolimod

5. Resultater

5.1 Resultatet af sekretariatets hovedanalyse

Sekretariatets hovedanalyser for de to kliniske spørgsmål bygger på samme antagelser som ansøgers hovedanalyser, men med følgende justeringer:

- Behandlingslængden ændres til 3 år for ozanimod, dimethylfumarat og fingolimod.
- Monitoreringsomkostninger forbundet med follow-up-besøg ekskluderes.
- Patientomkostninger forbundet med follow-up-besøg ekskluderes.
- Frekvens for blodprøvetagning ændres for ozanimod, dimethylfumarat og fingolimod.

For klinisk spørgsmål 1 bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 3 år i sekretariatets hovedanalyse. Udføres analysen med AIP, bliver den inkrementelle omkostning pr. patient ca. 21.000 DKK.

Resultaterne fra sekretariatets hovedanalyse for klinisk spørgsmål 1 præsenteres i Tabel 8.

Tabel 8. Resultatet af sekretariatets hovedanalyse ved sammenligning med dimethylfumarat, DKK, diskonterede tal

	Ozanimod	Dimethylfumarat	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	4.993	4.864	129
Patientomkostninger	2.719	2.486	233
Totale omkostninger	[redacted]	[redacted]	[redacted]

For klinisk spørgsmål 2 bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 3 år i sekretariatets hovedanalyse. Udføres analysen med AIP, bliver den inkrementelle omkostning pr. patient ca. 10.000 DKK.

Resultaterne fra sekretariatets hovedanalyse for klinisk spørgsmål 2 præsenteres i Tabel 9.

Tabel 9. Resultatet af sekretariatets hovedanalyse ved sammenligning med fingolimod, DKK, diskonterede tal

	Ozanimod	Fingolimod	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	4.993	4.993	0
Patientomkostninger	2.719	3.654	-935
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af sekretariatets følsomhedsanalyser

Ved samme antagelser som i sekretariatets hovedanalyse for meromkostninger udfører sekretariatet følsomhedsanalyserne præsenteret i Tabel 10.

Tabel 10. Resultatet af sekretariatets følsomhedsanalyser sammenlignet med hovedanalysenerne, DKK

Scenarie	Inkrementelle omkostninger Klinisk spørgsmål 1	Inkrementelle omkostninger Klinisk spørgsmål 2
Hovedanalysens resultat	[redacted]	[redacted]
Behandlingslængde 1 år	[redacted]	[redacted]
Behandlingslængde 5 år	[redacted]	[redacted]

Scenarie	Inkrementelle omkostninger Klinisk spørgsmål 1	Inkrementelle omkostninger Klinisk spørgsmål 2
0 % monitoreres ved første dosis ozanimod	[redacted]	[redacted]
10 % monitoreres ved første dosis ozanimod	[redacted]	[redacted]
50 % reduktion i besøgsomkostninger	[redacted]	[redacted]
Ingen lægemiddelspild	[redacted]	[redacted]
Lægemiddelspild: Én hel vedligeholdelsespakke	[redacted]	[redacted]

6. Budgetkonsekvenser

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

- Ozanimod bliver anbefalet som standardbehandling af Medicinrådet til de indikationer, som denne analyse omhandler.
- Ozanimod bliver ikke anbefalet som standardbehandling.

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

Ansøger antager, at 375 nye patienter pr. år kandiderer til behandling med ozanimod i førstelinjebehandling. Heraf vil 125 af patienterne være mænd, 100 vil være kvinder, som anvender prævention, men med et fremtidigt (inden for det næste år) ønske om graviditet, og 150 vil være kvinder, der anvender prævention, og som ikke ønsker at opnå graviditet. Ansøger baserer disse estimater på RADS' baggrundsnotat for sygdomsmodificerende behandling af multipel sklerose fra 2016 [1]. Tabel 11 viser estimatet af antal patienter årligt i budgetkonsekvenserne for klinisk spørgsmål 1.

Ansøger antager, at markedsoptaget for ozanimod vil være 60 % i år 1. I de efterfølgende år antager ansøger en stigning i markedsoptaget på 10 % pr. år, således at markedsoptaget i år 5 er 100 %. Dog antager ansøger, at en andel (3,3 %) af patienterne ekskluderes fra behandling med ozanimod grundet kontraindikationer (myokardieinfarkt, stroke/TIA, angina eller hjertesvigt). Ansøger baserer dette estimat på et studie om

komorbiditet hos patienter med multipel sklerose af Persson et al. [17]. Studiet er baseret på data fra US Department of Defense's database.
Da ansøger vælger at ekskludere 3,3 % af patienterne i det endelige markedsoptag, betyder det, at det reelle markedsoptag ca. er 58 % i år 1 og ca. 97 % i år 5.

Tabel 11. Ansøgers estimat af antal nye patienter pr. år for klinisk spørgsmål 1

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Ozanimod	218	254	290	326	363
Dimethylfumarat	157	121	85	49	12
Anbefales ikke					
Ozanimod	0	0	0	0	0
Dimethylfumarat	375	375	375	375	375

For andenlinjebehandling antager ansøger, at 250 nye patienter årligt kandiderer til behandling med ozanimod. Ansøger baserer dette estimat på en afrapportering fra Amgros vedrørende ocrelizumab, hvor ansøger antager, at imellem 233 og 291 patienter kandiderede til andenlinjebehandling med fingolimod i år 2018. Ansøger anvender det laveste estimat (233 patienter) og en vækstrate på 3 % til at estimere patientantallet, der kandiderer til andenlinjebehandling med fingolimod i år 2020, som ifølge ansøgers udregning vil være 248 patienter. Ansøger runder dette estimat op til 250 patienter og antager, at disse patienter vil kandidere til andenlinjebehandling med ozanimod pr. år.

Tabel 12 viser estimatet af antal patienter årligt i budgetkonsekvenserne for klinisk spørgsmål 2.

Tabel 12. Ansøgers estimat af antal nye patienter pr. år for klinisk spørgsmål 2

Anbefales					
Ozanimod	150	175	200	225	250
Fingolimod	100	75	50	25	0
Anbefales ikke					
Ozanimod	0	0	0	0	0
Fingolimod	250	250	250	250	250

Sekretariatets vurdering
Fagudvalget kan ikke komme med konkrete alternative estimater vedr. patientantal og markedsandel for førstelinjebehandling, men kan alene udtale, at estimaterne forventes at være markant lavere end ansøgers.

Fagudvalget påpeger, at ansøgers estimat for antal patienter, der kandiderer til andenlinjebehandling med ozanimod, er lavere, end hvad der kan forventes i dansk klinisk praksis ved en anbefaling. Fagudvalget har kendskab til data fra 2017-2019, der bekræfter, at ansøgers estimat er underestimeret. På baggrund af disse data vurderer fagudvalget, at 422 patienter vil kandidere til andenlinjebehandling med ozanimod om året. De 422 patienter afspejler både nydiagnosticerede patienter og patienter, der skifter fra førstelinjebehandling til andenlinjebehandling. Fagudvalget påpeger dog, at der er faktorer, som har indflydelse på, hvor mange patienter der kandiderer til behandling, herunder lokal praksis og tolkning af krav mht. sygdomsaktivitet. Derfor er fagudvalgets estimat forbundet med en vis usikkerhed.
Fagudvalget vurderer, at ansøgers antagelse om et markedsoptag på 60 % i år 1 er et realistisk estimat for ozanimod som andenlinjebehandling, men vurderer, at markedsoptaget vil stige hurtigere i de efterfølgende år, end hvad ansøger forventer. Mere præcist forudser fagudvalget, at ozanimod potentielt kan opnå et markedsoptag på 80 % i år 2 og 100 % i år 3. Dette begrundes med, at sygehusafdelingerne hurtigt kan implementere en ny behandling som ozanimod. I sekretariatets hovedanalyse antages det, at markedsoptaget ligeledes er 100 % i år 4 og 5. Fagudvalget pointerer, at markedsoptaget for ozanimod i fremtiden kan blive påvirket af, at fingolimod (Gilenya) går af patent i år 2022, og at der kan opstå en markedssituation, hvor et eller flere generiske lægemidler kommer på markedet.

Sekretariatet udarbejder en budgetkonsekvensanalyse med ansøgers estimater for klinisk spørgsmål 1 og vælger derfor hverken at ændre eller acceptere ansøgers antagelser om patientantal og markedsoptag. I sekretariatets budgetkonsekvensanalyse for klinisk spørgsmål 2 ændres patientantallet til 422 patienter pr. år og markedsoptaget for ozanimod til 60 % i år 1, 80 % i år 2 og 100 % i de efterfølgende tre år.

6.2 Sekretariatets budgetkonsekvensanalyse

Ved brug af ansøgers estimater vedr. patientantal og markedsoptag estimerer sekretariatet, at anvendelse af ozanimod i førstelinjebehandling kan resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 13.

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

Tabel 13. Sekretariatets analyse af totale budgetkonsekvenser ved et markedsoptag på ca. 58 % i år 1 efterfulgt af en lineær stigning på 10 % pr. år, mio. DKK, ikke-diskonterede tal

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

For klinisk spørgsmål 2 har sekretariatet korrigeret følgende estimater i budgetkonsekvensanalysen i forhold til ansøgers budgetkonsekvensanalyse:

- Antallet af nye patienter, der årligt kandiderer til andenlinjebehandling med ozanimod, ændres til 422 patienter.
- Markedsoptaget for ozanimod som andenlinjebehandling ændres til 60 % i år 1, 80 % i år 2 og 100 % i år 3, 4 og 5.

Sekretariatet estimerer, at anvendelse af ozanimod i andenlinjebehandling vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 14.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 4,9 mio. DKK i år 5.

Tabel 14. Sekretariatets analyse af totale budgetkonsekvenser ved et markedsoptag på 60 % i år 1, 80 % i år 2 og 100 % i år 3-5, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Ozanimod er forbundet med inkrementelle omkostninger sammenlignet med hhv. behandling med dimethylfumarat i førstelinjebehandling og fingolimod i andenlinjebehandling.

7.1 Usikkerheder

Bivirkningsprofiler og associerede omkostninger
Ansøger antager i analysen, at ozanimod er klinisk ækvivalent, også i forhold til bivirkninger, sammenlignet med både dimethylfumarat og fingolimod. På baggrund af denne antagelse har ansøger ekskluderet omkostninger forbundet med bivirkninger i analysen.

Fagudvalget pointerer dog, at der potentiel vil observeres en forskel i bivirkningsfrekvens, heriblandt langvarige og alvorlige bivirkninger, når ozanimod sammenlignes med dimethylfumarat. Fagudvalget vurderer i denne sammenhæng, at bivirkningerne afledt af behandling med ozanimod kan medføre et øget regionalt ressourcebrug, herunder klinisk udredning, undersøgelse og/eller behandlingsskift. Grundet dette kan det antages, at den gennemsnitlige inkrementelle omkostning pr. patient er underestimeret i analysens kliniske spørgsmål 1. Det bør dog understreges, at denne antagelse bygger på, at ozanimod har en bivirkningsprofil tilsvarende fingolimods hvad angår langsigtede bivirkninger.
I sammenligningen mellem ozanimod og fingolimod forventer fagudvalget, at bivirkningsprofilerne for de to præparater vil være sammenlignelige – også hvad angår langsigtede bivirkninger. På baggrund af dette vurderer sekretariatet, at den gennemsnitlige inkrementelle omkostning pr. patient hverken er under- eller overestimeret for klinisk spørgsmål 2 mht. bivirkningsrelaterede omkostninger.

Behandlingslængde
Fagudvalget vurderer, at der er usikkerheder forbundet med at estimere den gennemsnitlige behandlingslængde for ozanimod, dimethylfumarat og fingolimod, idet behandlingerne ikke er tidsbegrænsede. I sekretariatets hovedanalyse antages en gennemsnitlig behandlingslængde på 3 år. Fagudvalget pointerer, at patienterne kan behandles i både kortere og længere tid. Derfor kan de inkrementelle omkostninger pr. patient for både klinisk spørgsmål 1 og 2 være under- eller overestimerede. Sekretariatets følsomhedsanalyser for forskellige behandlingslængde-scenarier understøtter denne vurdering.

Patientantal og markedsoptag for ozanimod (førstelinjebehandling)
På baggrund af forbeholdene vedrørende patientantal og markedsoptag ved anbefaling af ozanimod som standardbehandling vurderer sekretariatet, at der er store usikkerheder forbundet med resultaterne af budgetkonsekvensanalysen for klinisk spørgsmål 1.

Det pointeres desuden af fagudvalget, at ethvert estimat om patientantallet, der kandiderer til behandling med ozanimod, er forbundet med betydelige kliniske udfordringer og usikkerheder. Disse involverer bl.a. overvejelser om, hvilke fertile kvindelige patienter, der bør opstartes med behandling, seponering ved graviditetsønske, *rebound*-effekt, *bridging* samt behandlingsskifte.

Markedsoptag for ozanimod (andenlinjebehandling)
Fagudvalget pointerer, at der er sandsynlighed for, at et eller flere generiske lægemidler for fingolimod kommer på markedet, når patentet på Gilenya udløber i 2022. Hvis dette skulle blive en realitet inden for budgetkonsekvensanalysens tidshorisont, er der risiko for, at markedsoptaget i analysens budgetkonsekvenser er overestimeret for ozanimod som andenlinjebehandling. Hvis dette er tilfældet, og hvis den generiske pris for fingolimod er lavere end ozanimod, vil budgetkonsekvenserne i denne analyse være underestimeret.

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9. Bilag

9.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse for klinisk spørgsmål 1 bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 15.

Tabel 15. Resultatet af ansøgers hovedanalyse for klinisk spørgsmål 1, DKK, diskonterede tal

	Ozanimod	Dimethylfumarat	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	39.454	43.142	-3.687
Patientomkostninger	6.249	11.446	-5.197
Totale omkostninger	[redacted]	[redacted]	[redacted]

I ansøgers hovedanalyse for klinisk spørgsmål 2 bliver den inkrementelle omkostning pr. patient ca. -339.000 DKK over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 16.

Tabel 16. Resultatet af ansøgers hovedanalyse for klinisk spørgsmål 2, DKK, diskonterede tal

	Ozanimod	Fingolimod	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	39.454	39.454	0
Patientomkostninger	6.249	7.184	-935
Totale omkostninger	[redacted]	[redacted]	[redacted]

9.2 Ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen.

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger for klinisk spørgsmål 1, at anvendelse af ozanimod vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne for ozanimod sammenlignet med dimethylfumarat fremgår af Tabel 17.

Tabel 17. Ansøgers hovedanalyse for totale budgetkonsekvenser for klinisk spørgsmål 1, mio. DKK, ikke-diskonterede tal

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

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger for klinisk spørgsmål 2, at anvendelse af ozanimod vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne for ozanimod sammenlignet med fingolimod fremgår af Tabel 18.

Tabel 18. Ansøgers hovedanalyse for totale budgetkonsekvenser for klinisk spørgsmål 2, mio. DKK, ikke-diskonterede tal

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

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Forhandlingsnotat

Dato for behandling i Medicinrådet	24.02.2021
Leverandør	BMS
Lægemiddel	Zeposia (Ozanimod)
EMA-indikation	Ozanimod er som monoterapi indiceret til behandling af voksne patienter med attakvis (relapserende-remitterende) multipel sklerose med aktiv sygdom defineret ved kliniske eller radiologiske fund.

Forhandlingsresultat

Amgros har forhandlet en pris med rabat på Ozanimod. Prisen kan ses i tabellen nedenfor.

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet Indkøbspris SAIP (DKK)	Rabatprocent ift. AIP
Zeposia (Ozanimod)	0,23 MG + 0,46 MG	Startpakning 4 stk + 3 stk	2907,84	[redacted]	[redacted]
Zeposia (Ozanimod)	0,92 mg	28 stk	11631,36	[redacted]	[redacted]

Amgros har indgået en kontrakt med leverandøren om ozanimod. Kontrakten er gældende fra d. 22.02.2021 til d. 30.09.2021. Det er planen, at alle lægemidlerne indenfor multipel sklerose udbydes med en kontraktstart pr. 01.10.2021, baseret på den gældende behandlingsvejledning. Udbuddet bliver publiceret så snart det nye udvidede sammenligningsgrundlag er blevet godkendt på et af de kommende Medicinrådsmøder.

Ekstra rabat ved betinget pris på klinisk spørgsmål 1:

Prisen ovenfor er gældende uanset Medicinrådets anbefaling. Leverandøren har tilbudt en yderligere rabat, som er betinget af at ozanimod bliver anbefalet til standardbehandling til populationen i klinisk spørgsmål 1. Prisen nedenfor er altså kun gældende såfremt Medicinrådet anbefaler ozanimod til populationen i både spørgsmål 1 og 2. Anbefales ozanimod ikke til populationen i klinisk spørgsmål 1 er prisen på side 1 gældende.

Amgros har forhandlet nedenstående betingede pris på ozanimod ved godkendelse af populationen i klinisk spørgsmål 1. [redacted]

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet Indkøbspris SAIP (DKK)	Rabatprocent ift. AIP
Zeposia (ozanimod)	0,23 MG + 0,46 MG	Startpakning 4 stk + 3 stk	2907,84	[redacted]	[redacted]
Zeposia (ozanimod)	0,92 mg	28 stk	11631,36	[redacted]	[redacted]

Prisen vil være gældende fra d. 25.2.2021, såfremt indikationen på kliniske spørgsmål 1, bliver godkendt.

Vurdering af forhandlingsresultatet

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

[redacted]

Konklusion

Betinget pris på klinik spørgsmål 1:

Amgros vurderer, at prisen er acceptabel til kliniske spørgsmål 1, sammenlignet med dimethylfumerat til behandling af attakvis multipel sklerose med gennemsnitlig sygdomsaktivitet.

Den betingede pris kan derudover danne udgangspunkt for et nyt og lavere prisniveau, for de lægemidler, der bliver brugt i 2. linje.

Forhandlet pris på klinisk spørgsmål 2 (basispris – ikke betinget af en anbefaling):
Amgros vurderer, at prisen er acceptabel til populationen vurderet i klinisk spørgsmål 2 sammenlignet med fingolimod med attakvis multiple sklerose og høj sygdomsaktivitet.

I relation til markedet:

Nedenstående tabel indeholder priserne for et års behandling i rene lægemiddelpriser i 1 linje. Tabellen indeholder priserne for dimethylfumerat og ozanimod.

Lægemiddel	Styrke/dosis	Antal pakninger 52 uger	AIP (DKK)	Forhandlet Indkøbspris SAIP (DKK)	Et års behandling (DKK)
Dimethylfumerat (inkl. Startpakning)	240 mg	13	11.087	[redacted]	[redacted]
Ozanimod (betinget pris inkl. startpakning)	0,92 mg	13	11.631,36	[redacted]	[redacted]

Nedenstående tabel indeholder priserne for et års behandling med de lægemidler, der bruges i 2 linje.

Lægemiddel	Styrke/dosis	Antal pakninger 52 uger	AIP (DKK)	Forhandlet Indkøbspris SAIP (DKK)	Et års behandling (DKK)
Natalizumab	300 mg	13	9.852,29	[redacted]	[redacted]
Ocrelizumab	600 mg	4	38.755,52	[redacted]	[redacted]
Fingolimod	0,5 mg	13	11.337,6	[redacted]	[redacted]
Ozanimod (inkl. Startpakning)	0,92 mg	13	11.631,36	[redacted]	[redacted]

[redacted]

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To the Medicines Council,

Consultation reply from Bristol Myers Squibb, Denmark, regarding the draft clinical and economic assessment of ozanimod (Zeposia ®) in relapsing and remitting multiple sclerosis.

Bristol Myers Squibb aspires to provide fast and broad access for patients to ozanimod. We generally agree to the efficacy assessment of ozanimod, but are concerned that safety considerations may have been exaggerated in the draft clinical assessment. While ozanimod is a S1P modulator like fingolimod, its mode of action (MOA) is more selective and the EMA label for ozanimod allows for 1L use of ozanimod as it was considered an effective and safe treatment option compared to current 1L options. Specifically, we believe that the data supports the use of ozanimod as an equal alternative to dimethyl fumarate (Tecfidera ®). As a general comment related to safety of ozanimod, specifically potential risk for women of childbearing potential, risk of progressive multifocal leukoencephalopathy (PML), rebound and long term side effects, we do not believe the draft clinical assessment reflect a balanced and fair view of the risk-benefit associated with treatment of ozanimod. For this reason, Bristol Myers Squibb has decided to provide its input in advance of the Council meeting on the 27th of January 2021.

Safety of ozanimod compared to dimethyl fumarate and fingolimod

When comparing like-for-like data on serious adverse events (SAE), i.e. using the available phase III data, the network meta-analysis supports a non-inferiority conclusion of ozanimod versus dimethyl fumarate with a relative risk (RR) of 0.92 (95% credibility interval (CrI): 0.37-2.23), and ozanimod versus fingolimod RR 0.81 (95% CrI: 0.37-1.73).

MOA of ozanimod and long term side effects

Though ozanimod is an S1P modulator, its receptor pharmacology differs from that of other S1P modulators as it specifically activates subtypes 1 and 5 of the S1P receptor family, compared to fingolimod which activates receptor subtypes 1 and 3-5 (Tran JQ et al. 2017 cited in application).The scientific committee correctly points out, that Bristol Myers Squibb cannot provide 1:1 evidence on receptor subtype activity and link this activity to certain adverse events or side effects to treatment with ozanimod. However, as it is proven that ozanimod is more selective than fingolimod, the off-target activation is inevitably less.

In support of the argument made above, ozanimod clinically demonstrates a more favorable and benign cardiac side effect profile, a lower risk of infections, malignancies, and macular edema indirectly compared to fingolimod (Swallow et al. 2020 cited in application). The cardiac safety profile of ozanimod allows for less cumbersome evaluation of most patients prior to treatment start which is highly relevant for routine clinical practice. In addition, when comparing to other S1P modulators, the side effect profile demonstrated in the clinical development program for ozanimod does show fewer and less severe side effects, which ultimately has led to the broader EMA approved indication for use. Moreover, the side effect profile of ozanimod was not significantly different from the comparator in the trials, interferon, which is a 1L treatment option.

Teratogenic risks of ozanimod

It is correct that non-clinical investigations in rabbits and rats have shown embryo lethality and teratogenic effects. This is reflected in the SmPC including, but not limited to, a contraindication for pregnancy, and a contraindication for women of childbearing potential *not* using effective contraception. We have provided information from our clinical development program related to pregnancy and childbirth that does not show any abnormalities related to pregnancy, fetal development or childbirth in women who became pregnant during the clinical trials, and who had been exposed to ozanimod. The females, their fetuses and babies did not differentiate from the general healthy population. At Bristol Myers Squibb, we take the potential risk for fetal development seriously; however, we do not agree on the wording around the risks for women of childbearing potential that the scientific committee suggests in the draft clinical assessment. *De facto*, this wording will contraindicate all women of childbearing potential to ozanimod treatment. This would be a significant limitation of the indication for use that is not in line with EMA approved indication, and does not reflect standard of care for women of childbearing potential in treatment with fingolimod. Moreover, we would like to acknowledge that dimethyl fumarate is not recommend for use in pregnant women and fingolimod is contraindicated for pregnant women, but not women of childbearing potential in general.

Risk of rebound

The scientific committee highlights that the "*risk of rebound is a potential limiting factor*" for the use of ozanimod. It is correct that EMA has included a warning regarding potential risk for rebound, which is considered a class effect of common S1P modulators. As discussed in the EMA EPAR and in the final application, there is to date no evidence of rebound effect associated with the cessation of ozanimod. Thus, there seem to be no evidence of additional risk of rebound related to treatment with ozanimod, compared to other compounds, nor that the potential risk of rebound should exclude all women of childbearing potential from treatment with ozanimod.

Risk of PML

Specifically related to the risk of PML, there has been no cases of PML in ozanimod-treated subjects to date. PML is a general concern with all immunosuppressive agents for treatment of MS, and this is clearly underscored by the fact that even current first line treatment, dimethyl fumarate, has reported several cases of PML, the most recent case seen in the Fall 2020. Thus, and in contrast to ozanimod, current first line treatment had PML listed as a known side effect at the time of EMA approval. The attention towards the risk of PML is therefore a general consideration for all compounds in question of this assessment in all lines of treatment. Hence, ozanimod comes with general warnings related to mitigating this potential risk, as described in the SmPC.

Cognition and quality of life

Contrary to the concise conclusions made on cognition and quality of life; Bristol Myers Squibb did submit data on the two important outcome measures for cognitive function measured with SDMT (Table 20) from the Phase III trial SUNBEAM and Quality of Life measured with MSQOL-54 (Table 21) from both Phase III trials SUNBEAM and RADIANCE.

In fact, all five phase III trials investigating the comparators efficacy did not include SDMT measurements of cognitive function and MSQOL-54 measurements of quality of life; therefore, the evidence network could not be connected and without data for comparators, BMS cannot perform quantitative analyses. Moreover, the Medicines Council treatment guideline reviewing the class of 2L MS compounds reached the same conclusion, i.e. that none of the phase III trials in scope provided SDMT data and MSQOL-54 data

On a general note, this means that there is a risk of not evaluating potentially additive benefits of new drugs as the method does not allow for inclusion of new, relevant clinical endpoints as comparisons are made backwards. This is a limitation of the method that may potentially obscure the review of added clinical value, not in favor for patients.

Health economic calculations

Bristol Myers Squibb agrees with the health economic assessment on the point that the combined administration and patient costs associated with ozanimod are lower than for fingolimod and this is directly linked to the reduced need for first dose monitoring associated with ozanimod.

By extension, the argument made above would also mean that ozanimod is less costly than dimethyl fumarate because the current expanded cost-comparison conducted by Amgros [DK: det udvidede sammenligningsgrundlag] concludes that even fingolimod is less costly than dimethyl fumarate.

The current expanded cost-comparison conducted by Amgros concludes that 48 months of fingolimod treatment is associated with a cost of 37,332.00 DKK and that 12 months of dimethyl fumarate treatment is associated with a cost of 10,602.00 DKK. In other words, 48 months treatment with dimethyl fumarate is more costly than 48 months treatment with fingolimod as 4*10,602.00 > 37,332.00.

Bristol Myers Squibb argues that current expanded cost-comparison is supportive of the base-case analysis we submitted. This model estimated that ozanimod is associated with a cost-saving (2144 DKK per year) on the combined administration and patient costs versus dimethyl fumarate.

Sincerely,

Anders Thelborg

Anders Thelborg
General Manager
Bristol Myers Squibb, Denmark

Medicinrådet

Medicinrådets vurdering vedrørende ozanimod til behandling af attakvis multipel sklerose

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 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	27. januar 2021
Dokumentnummer	103542
Versionsnummer	1.0

Indholdsfortegnelse

1. Medicinrådets konklusion

- Medicinrådet finder, at den samlede værdi af ozanimod sammenlignet med dimethylfumarat til patienter med gennemsnitlig sygdomsaktivitet ikke kan kategoriseres. Vurderingen er baseret på en netværksmetaanalyse, hvor der er stor usikkerhed på estimaterne. Medicinrådet er enig i fagudvalgets bekymringer for alvorlige og langsigtede bivirkninger og vurderer derfor, at sikkerhedsprofilen for ozanimod kan være dårligere end sikkerhedsprofilen for dimethylfumarat.
- Medicinrådet finder, at den samlede værdi af ozanimod sammenlignet med fingolimod til patienter med høj sygdomsaktivitet ikke kan kategoriseres. Vurderingen er baseret på en netværksmetaanalyse, hvor der er stor usikkerhed på estimaterne. Da der ikke findes data med lang opfølgningstid for ozanimod kan Medicinrådet ikke vurdere, om der er forskel på de to lægemidlers effekt og bivirkninger på langt sigt.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 27. januar 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 (fx 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

AR	*Adverse Reaction*
CDP	*Confirmed Disabilty Progression*
CI:	Konfidensinterval
CrI	*Credible Interval*
DMT	*Disease Modifying Therapy*
EDSS	*Expanded Disability Status Scale*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
ITT:	*Intention-to-treat*
JCV	John Cunningham virus
MR	Magnetisk Resonans
MS	Multipel sklerose
MSQOL-54	*Multiple Sclerosis Quality of Life-54*
OR:	*Odds ratio*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PML	Progressiv multifokal leukoencefalopati
PP:	*Per Protocol*
PPMS	Primær progressiv multipel sklerose
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RMS	Relapserende multipel sklerose
RR:	Relativ risiko
RRMS	Recidiverende relapserende multipel sklerose
SDMT	*Symbol Digit Modality Test*
SMD	*Standardized Mean Difference*
SPMS	Sekundær progressiv multipel sklerose

3. Introduktion

Formålet med Medicinrådets vurdering af ozanimod til attakvis multipel sklerose er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Bristol Meyers Squib på vegne af Celgene. Medicinrådet modtog ansøgningen d. 20. november 2020.

De kliniske spørgsmål er:

1. Hvilken værdi har ozanimod sammenlignet med dimethylfumarat for patienter med attakvis multipel sklerose og gennemsnitlig sygdomsaktivitet (førstelinjebehandling)?

2. Hvilken værdi har ozanimod sammenlignet med fingolimod for patienter med attakvis multipel sklerose og høj sygdomsaktivitet (andenlinjebehandling)?

3.1 Attakvis multipel sklerose

Multipel sklerose (MS) er en kronisk neurologisk lidelse, som hyppigst debuterer i alderen 25-45 år og forekommer ca. dobbelt så ofte hos kvinder som hos mænd. Årsagen er ukendt, men der findes flere disponerende arvelige og miljømæssige faktorer. Disse kan medvirke til en autoimmun reaktion mod molekyler på overfladen af en bestemt type celler (oligodendrocytter), som normalt beskytter og isolerer nervecellernes udløbere (aksoner) ved at omgive dem med myelinskeder. Sygdommen er karakteriseret ved spredte områder i centralnervesystemet med inflammation, demyelinisering og tab af aksoner [1]. Patienter med MS vil i varierende grad være præget af både fysiske og kognitive symptomer såsom synsnedsættelse, dobbeltsyn, spastiske lammelser af arme og/eller ben, føleforstyrrelser, dårlig balance, vandladningsforstyrrelser, forstoppelse, problemer med seksualfunktionen, smerter, træthed samt hukommelses- og koncentrationsproblemer. Patienternes livskvalitet kan være meget påvirket af både fysiske og kognitive symptomer samt træthed.
Der findes overordnet tre typer af MS: Recidiverende remitterende multipel sklerose (RRMS) eller attakvis MS, sekundær progressiv multipel sklerose (SPMS) og primær progressiv multipel sklerose (PPMS). Den hyppigste type, som ses hos mere end 80 % af patienterne, er RRMS, som er defineret ved attakvise tilbagefald med forværring af symptomer eventuelt efterfulgt af en periode med forbedring af symptomer. Denne type kaldes også attakvis multipel sklerose. RRMS kan ændre karakter, så der kommer tiltagende symptomer uden bedring og dermed gå over i et progressivt forløb kaldet SPMS [2]. Endelig bruges betegnelsen recidiverende multipel sklerose (RMS) om patienter med RRMS samt patienter med SPMS, som oplever attakker.
I Danmark har knap 16.500 personer MS, hvilket svarer til 250 pr. 100.000 danskere. Antallet af nye tilfælde har ligget nogenlunde konstant på ca. 600 personer om året siden år 2000 [3].

3.2 Ozanimod

Ozanimod er en sphingosine 1-phosphate receptor modulator, som binder med høj affinitet til sphingosine 1-phosphate receptor-subtyperne 1 og 5. Ozanimod virker ved at forhindre immunforsvarets T- og B-celler i at forlade lymfeknuderne, og de forhindres dermed i at infiltrere centralnervesystemet. Ozanimod begrænser derved inflammation og ledsagende vævsskade i centralnervesystemet.
Der findes to andre sphingosine 1-phosphate receptor modulatorer, som benyttes til behandling af MS. Fingolimod, som er anbefalet af Medicinrådet til andenlinjebehandling af attakvis MS (se afsnittet ”2.3 Nuværende behandling”), og siponimod, som er under vurdering til SPMS.

Ozanimod har af EMA fået følgende indikation:
”Behandling af voksne patienter med RRMS”

Angående EMA-indikationen bemærker vi, at EMA-indikationen er bredere end for fingolimod, som har en tilsvarende virkningsmekanisme. Fingolimod er indiceret til patienter, som fortsat har sygdomsaktivitet på førstelinjebehandling, eller patienter med høj sygdomsaktivitet, som ikke tidligere har været behandlet. Den bredere indikation for ozanimod er diskuteret i EMAs EPAR, som lægger vægt på en tendens mod at sætte tidligere ind med højeffektiv behandling og flere klinikeres ønske om et mere liberalt scenarie for valg af behandling, hvor højeffektiv behandling er en mulighed i første linje. EMAs formål med den bredere indikation er altså at give større valgfrihed i behandlingen af MS i forskellige lande. Forholdet mellem effekt og sikkerhed er diskuteret af en ekspertgruppe, der også kommer ind på muligheden for rebound-aktivitet som en mulig begrænsende faktor. Fagudvalget vedrørende multipel sklerose har læst ekspertgruppens diskussion og forholder sig til den i sin konklusion vedrørende ozanimod.

Den anbefalede vedligeholdelsesdosis af ozanimod er 0,92 mg oralt én gang dagligt. Behandlingen skal i den første uge indledes med et dosiseskaleringsprogram, som er vist i tabel 1.

Tabel 1. Dosis, eskalation

Dosis, eskalation	
Dag 1-4	0,23 mg én gang dagligt
Dag 5-7	0,46 mg én gang dagligt
Dag 8 og vedligehold	0,92 mg én gang dagligt

3.3 Nuværende behandling

Der findes ingen behandling, som kan helbrede MS. Den nuværende behandling er delt op i symptomlindrende behandling og sygdomsmodificerende behandling (Disease Modifying Therapies (DMT's)). De nuværende DMT's er overvejende virksomme ved attakvis sygdom. Målet med behandlingen er at forsinke udvikling af fysiske og mentale funktionstab, undgå attakker og derved give patienten den bedst mulige livskvalitet. Udover kliniske undersøgelser bliver patienter med MS fulgt ved radiologiske undersøgelser. Fagudvalget har i Medicinrådets behandlingsvejledning for attakvis MS anbefalet magnetisk resonansscanning (MR) én gang om året [4]. På scanningen kan klinikerne se tegn på aktiv inflammatorisk aktivitet, nye og gamle læsioner og atrofi (tab af hjernevolumen).

Inddeling af patienter

Lægemidlerne til behandling af attakvis multipel sklerose er delt op i to grupper i Medicinrådets behandlingsvejledning og lægemiddelrekommandation [4][5]. De kaldes første og anden linje, men det skal ikke opfattes således, at samtlige patienter nødvendigvis vil blive behandlet med et førstelinjelægemiddel først og dernæst med et andenlinjelægemiddel. Det skal derimod forstås således, at de mest effektive og potentielt mest bivirkningstunge lægemidler kaldes andenlinjelægemidler og forbeholdes patienter med størst sygdomsaktivitet eller patienter, hvor førstelinjebehandling viser sig ikke at være effektiv nok.

Patienterne, som kan behandles med lægemidler fra gruppen af førstelinjepræparater, omfatter patienter med gennemsnitlig sygdomsaktivitet (defineret radiologisk og klinisk). Skift mellem lægemidler inden for gruppen af førstelinjepræparater kan ske på grund af fx betydende bivirkninger eller ændringer i forbindelse med graviditetsønske.

Patienterne, som behandles med lægemidler fra gruppen af førstelinjepræparater, opdeles i den nuværende behandlingsvejledning efter graviditetsønske og anvendelse af antikonception. Baggrunden for dette er, at der anbefales forskellige udvaskningsperioder for lægemidlerne inden graviditet. I den nuværende rekommandation er dimethylfumarat førstevalg til mænd og til de kvinder, som benytter antikonception [5]. I rekommandationen er denne population delt i to, men dimethylfumarat er førstevalg for begge: "Mænd og kvinder, som anvender antikonception og ikke har graviditetsønske" og "kvinder, som anvender antikonception og har graviditetsønske inden for ca. et år".

Patienterne, som kan behandles med lægemidler fra gruppen af andenlinjepræparater, er:

- patienter med fortsat sygdomsaktivitet (defineret radiologisk og klinisk) på et førstelinjepræparat
- patienter med høj sygdomsaktivitet (defineret radiologisk og klinisk), som ikke tidligere har været behandlet.

Patienter, som behandles med lægemidler fra gruppen af andenlinjepræparater, opdeles yderligere efter, om de har antistoffer for John Cunningham-virus (JCV) eller ej. Baggrunden for dette er, at behandling med nogle DMT's (hovedsageligt natalizumab) i observationelle studier har vist at kunne medføre risiko for den dødelige sygdom progressiv multifokal leukoencefalopati (PML), som forårsages af JCV [1].

Det paradigme, som er beskrevet her, kaldes også ”eskalationsbehandling”. Tanken er, at flertallet af patienter først behandles med et førstelinjepræparat. For de patienter, hvor det ikke er tilstrækkeligt til at opnå sygdomskontrol, går man videre til en behandling med højere effektivitet, men måske også større risiko for alvorlige bivirkninger. Der har gennem de seneste år i klinisk praksis været et ønske om at behandle flere patienter efter et andet paradigme med ”tidlig højeffektiv behandling”. Ønsket om et skift i behandlingsparadigme er delvist begrundet i godkendelse af flere lægemidler med høj effektivitet og fordelagtig sikkerhedsprofil. Det er særdeles vanskeligt at finde evidens fra randomiserede studier for den langsigtede effekt på sygdomskontrol af de to paradigmer over for hinanden, men der fremkommer i disse år mange observationelle data, deriblandt fra Det Danske Skleroseregister [6][7].

4. Metode

Medicinrådets protokol for vurdering vedrørende ozanimod til attaktis multipel sklerose 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

5.1.1 Litteratur

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

Ansøger har udvalgt 8 fuldtekstartikler til at svare på de to kliniske spørgsmål. Data fra de 8 fuldtekstartikler ligger til grund for en netværksmetaanalyse, der beskriver den indbyrdes effekt af ozanimod vs. dimethylfumarat vs. fingolimod for effektmålene *vedvarende sygdomsforværring, alvorlige bivirkninger* og *årlig attakrate*. Der er altså samme datagrundlag for spørgsmål 1 og 2 for de tre effektmål. Syv af fuldtekstartiklerne er identificeret med udgangspunkt i søgestrengen fra protokollen. Derudover har ansøger inkluderet en artikel [8], som ikke blev identificeret ved den systematiske litteraturgennemgang. Denne artikel er fundet gennem Medicinrådets behandlingsvejledning for attakvis multipel sklerose, hvor den også indgik i en netværksmetaanalyse. Ansøger har inkluderet artiklen for at muliggøre en indirekte sammenligning mellem ozanimod og dimethylfumarat. Ansøger har ikke fundet artikler, der kunne ligge til grund for en indirekte sammenligning mellem ozanimod og dimethylfumarat for effektmålene *kognitiv funktion* og *livskvalitet*.
En oversigt over baselinekarakteristika i de inkluderede studier kan findes i bilag 2.

Cohen JA et al.: RADIANCE, del B

RADIANCE-studiet var delt op i to dele: del A og del B. Ansøger har i sin ansøgning indsendt data for del B, da det er denne del af studiet, der kan bruges til at besvare de kliniske spørgsmål.

RADIANCE, del B, er et randomiseret, dobbeltblindet fase III-studie, hvor effekten af ozanimod sammenlignes med effekten af interferon beta-1a hos patienter med recidiverende multipel sklerose.

Studie- og patientkarakteristika

Patienter i RADIANCE-studiet var randomiseret 1:1:1 til ozanimod 0,5 mg (N=443), ozanimod 1 mg (N=434) eller interferon beta-1a 30 µg (N=443). Patienter blev stratificeret efter land og baseline Expanded Disability Status Scale (EDSS)-score (≤ 3,5 vs. > 3,5). Patienterne skulle være mellem 18 og 55 år og have en EDSS-score mellem 0 og 5 for at kunne deltage i studiet. Patienterne skulle også have haft mindst ét attak inden for det seneste år eller ét attak inden for de seneste 24 måneder og mindst én gadoliniumopladende læsion på en MR-scanning inden for det seneste år (tegn på pågående fokal inflammatorisk aktivitet).

Patienterne i studiet havde i gennemsnit haft MS-symptomer i 6,5 år og en MS-diagnose i 3,7 år op til studiestart. 98,2 % af patienterne havde diagnosen RRMS. Patienterne i studiet havde i gennemsnit en EDSS-score på 2,5, og 98,1 % havde haft ét eller flere attakker inden for det seneste år op til studiestart. 22,9 % blev defineret som havende høj sygdomsaktivitet, og 28,9 % havde tidligere modtaget sygdomsmodificerende behandling. Studiet havde en opfølgningstid på 24 måneder.

Comi G et al.: SUNBEAM

SUNBEAM er et randomiseret, dobbeltblindet fase III-studie, hvor effekten af ozanimod sammenlignes med effekten af interferon beta-1a hos patienter med recidiverende multipel sklerose.

Studie- og patientkarakteristika

Patienter i SUNBEAM-studiet var randomiseret 1:1:1 til ozanimod 0,5 mg (N=451), ozanimod 1 mg (N=447) eller interferon beta-1a 30 µg (N=448). Patienterne blev stratificeret efter land og baseline EDSS-score (≤ 3,5 vs. > 3,5). Patienterne skulle være mellem 18 og 55 år og have en EDSS-score mellem 0 og 5 for at kunne deltage i studiet. Patienterne skulle også have haft mindst ét attak inden for det seneste år eller ét attak inden for de seneste 24 måneder og mindst én gadoliniumopladende læsion inden for det seneste år.

Patienterne i studiet havde i gennemsnit haft MS-symptomer i 7,0 år og en MS-diagnose i 3,7 år op til studiestart. 98,2 % af patienterne havde diagnosen RRMS. Patienterne i studiet havde i gennemsnit en EDSS-score på 2,6, og 98,2 % havde haft ét eller flere attakker inden for det seneste år op til studiestart. 22,7 % havde høj sygdomsaktivitet, og 30,5 % havde tidligere modtaget sygdomsmodificerende behandling. Studiet havde en opfølgningstid på 24 måneder.

Fox RJ et al.: CONFIRM

CONFIRM er et randomiseret, placebokontrolleret, dobbeltblindet fase III-studie, hvor effekten af dimethylfumarat sammenlignes med effekten af placebo eller

glatirameracetat hos patienter med remitterende recidiverende multipel sklerose (RRMS).

Studie- og patientkarakteristika

Patienter i CONFIRM-studiet var randomiseret 1:1:1:1 til dimethylfumarat 240 mg to gange dagligt (N=359), dimethylfumarat 240 mg tre gange dagligt (N=345), glatirameracetat 20 mg (N=448) eller placebo (N=363). Patienterne skulle være mellem 18 og 55 år, have en EDSS-score mellem 0 og 5 samt have diagnosen RRMS for at kunne deltage i studiet. Patienterne skulle også have haft mindst ét attak inden for det seneste år eller mindst én gadoliniumopladende læsion på MR-scanning inden for de seneste 6 uger op til randomiseringen.
Patienterne i studiet havde i gennemsnit haft MS-symptomer i 7,1 år og en MS-diagnose i 4,7 år op til studiestart. Patienterne i studiet havde i gennemsnit en EDSS-score på 2,6, og 1,4 attakker i året op til studiestart. Omkring 10 % havde høj sygdomsaktivitet, og 29 % havde tidligere modtaget sygdomsmodificerende behandling.
Behandlingstiden i studiet var mellem 85,1 og 88,5 måneder.

Gold R et al.: DEFINE

DEFINE er et randomiseret, placebokontrolleret, dobbeltblindet fase III-studie, hvor effekten af dimethylfumarat sammenlignes med effekten af placebo hos patienter med remitterende recidiverende multipel sklerose (RRMS).

Studie- og patientkarakteristika

Patienter i DEFINE-studiet var randomiseret 1:1:1 til dimethylfumarat 240 mg to gange dagligt (N=410), dimethylfumarat 240 mg tre gange dagligt (N=416) eller placebo (N=408). Patienterne blev stratificeret efter studielokalitet. Patienterne skulle være mellem 18 og 55 år, have en EDSS-score mellem 0 og 5 samt have diagnosen RRMS for at kunne deltage i studiet. Patienterne skulle også have haft mindst ét attak inden for det seneste år eller mindst én gadoliniumopladende læsion inden for de seneste 6 uger op til randomiseringen.
Patienterne i studiet havde i gennemsnit haft MS-symptomer i 8,3 år og en MS-diagnose i 5,5 år op til studiestart. Patienterne i studiet havde i gennemsnit en EDSS-score på 2,4 og 1,3 attakker i året op til studiestart. Omkring 14 % havde høj sygdomsaktivitet, og 41 % havde tidligere modtaget sygdomsmodificerende behandling.
Studiet havde en opfølgningstid på to år.

Kappos L et al.: FREEDOMS

FREEDOMS er et randomiseret, placebokontrolleret, dobbeltblindet fase III-studie, hvor effekten af fingolimod sammenlignes med effekten af placebo hos patienter med remitterende recidiverende multipel sklerose (RRMS).

Studie- og patientkarakteristika

Patienter i FREEDOMS-studiet var randomiseret 1:1:1 til fingolimod 0,5 mg (N=425), fingolimod 1,25 mg (N=429) eller placebo (N=418). Patienterne blev stratificeret efter studielokalitet. Patienterne skulle være mellem 18 og 55 år, have en EDSS-score mellem 0 og 5,5 samt have diagnosen RRMS for at kunne deltage i studiet. Patienterne skulle

også have haft mindst ét attak inden for det seneste år eller to eller flere inden for de seneste to år op til studiestart.
Patienterne i studiet havde i gennemsnit haft MS-symptomer i 8,2 år og havde i gennemsnit en EDSS-score på 2,4 og 1,5 attakker i året op til studiestart. 41 % havde tidligere modtaget sygdomsmodificerende behandling.
Studiet havde en opfølgningstid på to år.

Calabresi PA et al.: FREEDOMS II
FREEDOMS II er et randomiseret, placebokontrolleret, dobbeltblindet fase III-studie, hvor effekten af fingolimod sammenlignes med effekten af placebo hos patienter med remitterende recidiverende multipel sklerose (RRMS).

Studie- og patientkarakteristika
Patienter i FREEDOMS II-studiet var randomiseret 1:1:1 til fingolimod 0,5 mg (N=358), fingolimod 1,25 mg (N=370) eller placebo (N=355). Patienterne blev stratificeret efter studielokalitet. Patienterne skulle være mellem 18 og 55 år, have en EDSS-score mellem 0 og 5,5 samt have diagnosen RRMS for at kunne deltage i studiet. Patienterne skulle også have haft mindst ét attak inden for det seneste år eller to eller flere inden for de seneste to år op til studiestart.
Patienterne i studiet havde i gennemsnit haft MS-symptomer i 10,4-10,8 år og havde i gennemsnit en EDSS-score på 2,4-2,5 og 1,4-1,5 attakker i året op til studiestart. 75 % havde tidligere modtaget sygdomsmodificerende behandling.
Studiet havde en opfølgningstid på to år.

Cohen JA et al.: TRANSFORMS
TRANSFORMS er et randomiseret, dobbeltblindet fase III-studie, hvor effekten af fingolimod sammenlignes med effekten af interferon beta-1a hos patienter med remitterende recidiverende multipel sklerose (RRMS).

Studie- og patientkarakteristika
Patienter i TRANSFORMS-studiet var randomiseret 1:1:1 til fingolimod 0,5 mg (N=431), fingolimod 1,25 mg (N=426) eller interferon beta-1a 30 µg (N=435). Patienterne blev stratificeret efter studielokalitet. Patienterne skulle være mellem 18 og 55 år, have en EDSS-score mellem 0 og 5,5 samt have diagnosen RRMS for at kunne deltage i studiet. Patienterne skulle også have haft mindst ét attak inden for det seneste år eller to eller flere inden for de seneste to år op til studiestart.
Patienterne i studiet havde i gennemsnit haft MS-symptomer i 7,4 år og havde i gennemsnit en EDSS-score på 2,2 og 1,5 attakker i året op til studiestart. 57 % havde tidligere modtaget sygdomsmodificerende behandling.
Studiet havde en opfølgningstid på et år.

Vollmer TL et al.: BRAVO
BRAVO er et randomiseret, placebokontrolleret, dobbeltblindet fase III-studie, hvor effekten af interferon-1a og laquinimod sammenlignes med effekten af placebo hos patienter med remitterende recidiverende multipel sklerose (RRMS). BRAVO-studiet er inkluderet for at gøre netværket fuldstændigt, ligesom det blev gjort i Medicinrådets behandlingsvejledning for attakvis multipel sklerose.

Studie- og patientkarakteristika

Patienter i BRAVO-studiet var randomiseret 1:1:1 til laquinimod 0,6 mg (N=434), interferon beta-1a 30 µg (N=443) eller placebo (N=449). Patienterne blev stratificeret efter studielokalitet. Patienterne skulle være mellem 18 og 55 år, have en EDSS-score mellem 0 og 5,5 samt have diagnosen RRMS for at kunne deltage i studiet. Patienterne skulle også have haft mindst ét attak inden for det seneste år, to attakker inden for de seneste to år, eller ét attak 12-24 måneder før studiestart samt en gadoliniumopladende læsion på en MR-scanning i året op til studiestart.
Patienterne i studiet havde i gennemsnit haft MS-symptomer i 6,6-7,0 år og havde i gennemsnit en EDSS-score på 2,6-2,7 og 1,3 attakker i året op til studiestart. Omkring 14 % havde høj sygdomsaktivitet, og 6-9,4 % havde tidligere modtaget sygdomsmodificerende behandling.
Studiet havde en opfølgningstid på to år.

Vurdering af sammenlignelighed af patientpopulationerne

Samlet vurderer fagudvalget, at der er forskelle mellem studiepopulationerne på flere områder:

Antallet af patienter, som tidligere har modtaget sygdomsmodificerende behandling, varierer mellem studierne og er særlig højt i FREEDOMS II (ca. 75 % i forhold til omkring 30 % i andre studier). I nogle af studierne kan patienterne tidligere have modtaget behandlinger, som i dansk klinisk praksis karakteriseres som førstelinjebehandling (interferon-1a, glatirameracetat) og andenlinjebehandling (natalizumab). Effekten af lægemidlerne er sandsynligvis forskellig hos behandlingsnaive patienter og patienter, som har modtaget flere tidligere sygdomsmodificerende behandlinger, så denne forskel vil medføre usikkerhed. Fagudvalget kan ikke vurdere, i hvilken retning usikkerheden vil være.

Studierne af dimethylfumarat og fingolimod er afsluttet omkring 2010-2011, mens studierne af ozanimod er udført senere og afsluttet omkring 2016-2017. Klinisk praksis kan have ændret sig undervejs. Den tidsmæssige forskel kan derfor medføre usikkerhed, men fagudvalget vurderer ikke, at usikkerheden har stor betydning. Fagudvalget vægter højt, at inklusion af patienter i alle studier er afsluttet før 2017, hvor der kom nye diagnostiske kriterier for MS.

Andelen af patienter med høj sygdomsaktivitet varierer mellem studierne. Effekten af lægemidlerne er sandsynligvis forskellig hos patienter med høj og lav sygdomsaktivitet, så denne forskel vil medføre usikkerhed. Fagudvalget kan ikke vurdere, i hvilken retning usikkerheden vil være.

Fagudvalget bemærker, at inklusionskriterierne i studierne er sammenlignelige. Samlet vurderer fagudvalget, at studierne med ovennævnte forbehold godt kan anvendes til en NMA. En oversigt over de artikler som indgår ses i tabel 2.

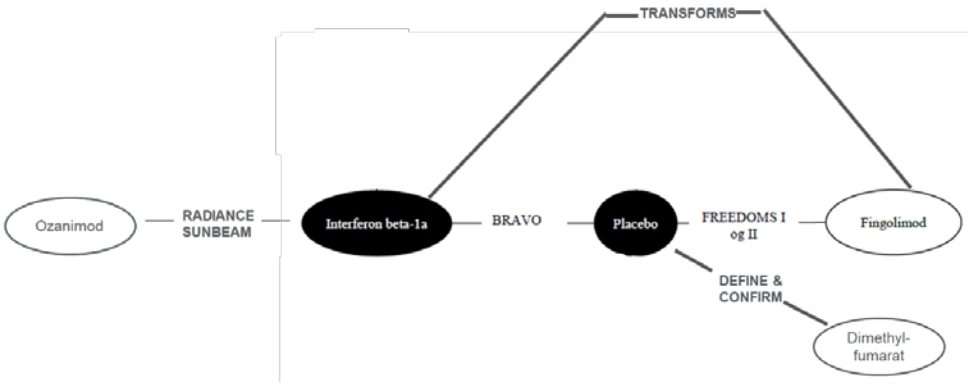
Tabel 2. Oversigt over artikler som indgår i netværksmetaanalysen

Lægemiddel	Publikation	Klinisk forsøg og NCT-nummer	Dato for studiestart og forventet slutdato
Ozanimod vs. interferon beta-1a	Cohen JA, Comi G, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. Lancet Neurol. 2019;18(11). [9]	**RADIANCE.** NCT02047734	3. december 2013 - 27. marts 2017
Ozanimod vs. interferon beta-1a	Comi G, Kappos L, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol. 2019;18(11). [10]	**SUNBEAM.** NCT02294058	3. december 2014 - 22. december 2016
Dimethylfumarat vs. placebo	Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis. N Engl J Med. 2012;367(12). [11]	**CONFIRM.** NCT00451451	Juni 2007 - august 2011
Dimethylfumarat vs. placebo	Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis. N Engl J Med. 2012;367(12). [12]	**DEFINE.** NCT00420212	Januar 2007 - august 2011
Fingolimod vs. placebo	Kappos L, Radue E-W, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401. [13]	**FREEDOMS.** NCT00289978	Januar 2006 - juli 2009
Fingolimod vs. placebo	Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6). [14]	**FREEDOMS II.** NCT00355134	Juni 2006 - august 2011
Fingolimod vs. Interferon beta-1a	Cohen JA, Barkhof F, Comi G, Hartung H-P, Khatri BO, Montalban X, et al. Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis. N Engl J Med. 2010;362(5). [15]	**TRANSFORMS.** NCT00340834	Maj 2006 – juli 2011
Interferon beta-1a vs. placebo	Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol. 2014;261(4). [8]	**BRAVO.** NCT00605215	April 2008 - december 2011

5.1.2 Databehandling og analyse

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

Ansøger har udført en netværksmetaanalyse (NMA), som danner grundlag for både klinisk spørgsmål 1 og 2, effektmålene vedvarende sygdomsforværring, bivirkninger og årlig attakrate. Denne tilgang var forinden diskuteret med og godkendt af Medicinrådets biostatistikere. I figur 1 ses netværket.



Figur 1. Netværket for ansøgers netværksmetaanalyse fra den endelige ansøgning. De sorte udfyldninger er interventioner, der ikke indgår i Medicinrådets kliniske spørgsmål, men er medtaget for at gøre netværket fuldstændigt. De hvide cirkler rummer lægemidler, der indgår i de kliniske spørgsmål.

NMA'en er udført med en standardmetode baseret på Bayesiansk statistik, og ansøger har på grund af et begrænset evidensgrundlag valgt en "fixed effects-model" frem for en "random effects-model". Ansøger har vurderet inkonsistens i NMA'en gennem de forbindelser, hvor der både er direkte og indirekte evidens. Ansøger har brugt Buchers metode og fandt ikke signifikant inkonsistens.

Resultaterne er angivet som en Hazard Ratio (HR) for sygdomsprogression, en "rate ratio" (dvs. forholdet mellem de årlige rater) for årlig attakrate og en Relativ Risiko (RR) for uønskede hændelser. De absolutte forskelle er udregnet ud fra formlen i Medicinrådets Metodehåndbog, appendix 5. Usikkerheden omkring estimaterne er angivet som 95 % Credible Interval (CrI). Dette er angivet i stedet for et 95 % konfidensinterval (CI), som bruges i frekventistisk statistik. I Bayesiansk statistik bruges CrI analogt med CI for frekventistisk statistik, selvom de filosofisk set er forskellige. I denne vurdering er CrI angivet og fortolkes som et CI i relation til kategoriseringen.

Medicinrådet accepterer ansøgers analyse og udførelsen af den, men bemærker, at antagelsen om "joint randomization" er væsentlig for at kunne sammenligne forskellige studier i en NMA. Det betyder, at man som udgangspunkt skal forvente, at alle patienterne i studierne kunne være randomiseret til de forskellige behandlinger i ét samlet studie. Da den samme analyse indgår i besvarelsen af Medicinrådets to kliniske

spørgsmål til forskellige patientpopulationer (patienter, som er kandidater til førstelinjebehandling og andenlinjebehandling), er det vanskeligt at forestille sig, at denne antagelse kan gælde fuldstændigt. Derfor er det nødvendigt at tolke resultatet af analysen med forbehold, og fagudvalget gør opmærksom på denne usikkerhed i sin samlede konklusion. I afsnit 5.1.1 har fagudvalget vurderet sammenligneligheden af de studier, som indgår i NMA'en, og finder, at der er forskelle, som medfører usikkerhed, men at analysen virker forsvarlig at udføre. På trods af ovennævnte usikkerheder accepterer Medicinrådet ansøgers analyse og lægger den til grund for vurderingen.

Derudover er der mellem ozanimod og dimethylfumarat to trin, hvilket giver større grad af indirekthed og risiko for bias, end hvis lægemidlerne var undersøgt mod en fælles komparator.

For effektmålet bivirkninger har ansøger indleveret data for uønskede hændelser, da studierne for flere lægemidler, som indgår i analysen, ikke rapporterede data for bivirkninger. Medicinrådet bemærker, at bivirkninger blev valgt som effektmål, da uønskede hændelser inden for kliniske studier af MS ofte indeholder sygdomsprogression. Derved kan et mindre effektivt lægemiddel eller placebo fremstå med en dårligere sikkerhedsprofil end et mere effektivt lægemiddel. Grundet denne usikkerhed baseres vurderingen af effektmålet bivirkninger især på den narrative gennemgang af bivirkningsprofiler, mens de kvantitative data tillægges mindre vægt. Denne usikkerhed indgår også i vurderingen af evidensens kvalitet.

For effektmålene kognitiv funktion og livskvalitet er der ikke indleveret komparative data, hvorfor effekten på disse ikke kan kategoriseres. Begge effektmål indgik i de kliniske studier af ozanimod, men der er ikke data, som tillader en sammenligning med den valgte komparator i noget klinisk spørgsmål.

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 for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 1).

For klinisk spørgsmål 1 er der nedgraderet for inkonsistens og unøjagtighed for effektmålene *vedvarende sygdomsforværring, alvorlige bivirkning* og *årlig attakrate*. For deleffektmålet *alvorlige bivirkninger* er der også nedgraderet for indirekthed, fordi der kun foreligger data på alvorlige uønskede hændelser. Inkonsistensen er nedgraderet for alle effektmålene, fordi der var forskelle i studiepopulationerne. Derudover er der kun ét studie for sammenligningen mellem interferon beta-1a og placebo. Der er nedgraderet for unøjagtighed, fordi CrI for effektmålene er meget brede og både omfatter positive og negative resultater. For de øvrige effektmål *livskvalitet* og *kognitiv funktion* er det ikke muligt at vurdere evidensen kvalitet med GRADE, fordi der ikke ligger en formel analyse til grund for sammenligningen.

Evidensens kvalitet er dermed meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen. Da datagrundlaget er det samme for begge kliniske spørgsmål, gør samme overvejelser sig gældende for begge kliniske spørgsmål.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at risikoen for bias er lav.

Vurdering af risikoen for bias ved de enkelte studier fremgår af bilag 1.

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

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CrI)	Foreløbig værdi	Forskel (95 % CrI)	Foreløbig værdi	
Vedvarende sygdomsforværring bekræftet ved 3 måneder (CPD3)	Andel patienter, der oplever en ændring i CPD, der fastholdes over tre måneder (MKRF: 10 %)	Kritisk	5 % (-8; 28)	Kan ikke kategoriseres	HR: 1,32 (0,48-3,25)	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel patienter, der oplever én eller flere alvorlige bivirkninger (MKRF: 3 %)	Kritisk	-1,48 (-11; 22)	Kan ikke kategoriseres	RR: 0,92 (0,37; 2,23)	Kan ikke kategoriseres	Kan ikke kategoriseres
Årlig attakrate	Antal attakker pr. patient om året (MKRF: 0,1 attakker pr. patient om året)	Vigtig	-0,03 (-0,10; 0,11)	Kan ikke kategoriseres	Rate ratio: 0,85 (0,5; 1,58)	Kan ikke kategoriseres	Kan ikke kategoriseres
Kognitiv funktion	Andel patienter, der undgår en 10 %'s forværring på SDMT (MKRF: 10 %)	Vigtig	Ikke opgjort	Kan ikke kategoriseres	Ikke opgjort	Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	Gennemsnit ændring på MSQOL54 (MKRF: 0,5 SMD)	Vigtig	Ikke opgjort	Kan ikke kategoriseres	Ikke opgjort	Kan ikke kategoriseres	Kan ikke kategoriseres

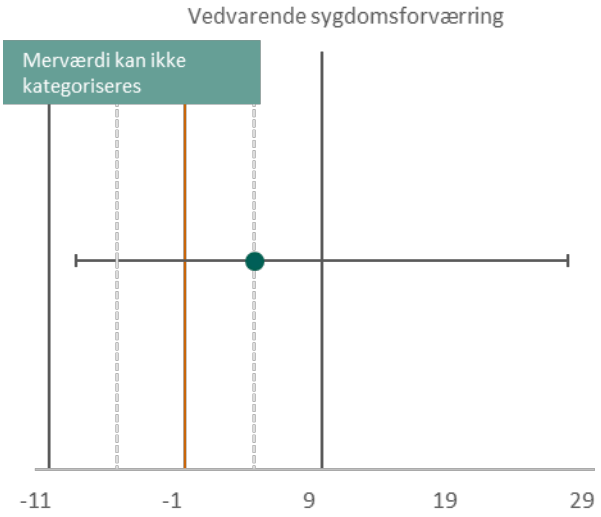
Konklusion	
Samlet kategori for lægemidlets værdi	Fagudvalget vurderer, at den samlede værdi af ozanimod sammenlignet med dimethylfumarat til patienter med attakvis multipel sklerose og gennemsnitlig sygdomsaktivitet ikke kan kategoriseres. På baggrund af det forelagte data og klinisk erfaring finder fagudvalget det sandsynligt, at sikkerhedsprofilen af ozanimod kan være dårligere end den for dimethylfumarat, grundet bekymring for langsigtede og alvorlige bivirkninger.
Kvalitet af den samlede evidens	Meget lav

CI = Konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = Relativ risiko, SDMT = Symbol Digit Modality Test, CDP = Confirmed Disease Progression, MSQOL54 = Multiple Sclerosis Quality of Life-54, SMD = Standard Mean Difference.

Vedvarende sygdomsforværring (kritisk)
Som beskrevet i protokollen er effektmålet *vedvarende sygdomsforværring* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi et centralt mål med behandlingen er at forsinke progression af sygdommen. Effektmålet dækker over andelen af patienter, der oplever vedvarende sygdomsforværring, hvorved en positiv ændring er et negativt resultat for patienterne.

Grundlaget for kategorisering på dette effektmål er som tidligere beskrevet en NMA. Medicinrådet vurderer, at analysen er et acceptabelt valg og korrekt udført, men at der er væsentlige usikkerheder forbundet med den kvantitative sammenligning.

Ansøger estimerer på baggrund af sin NMA, at der en forskel på 5 %-point (95 % CrI -8; 28) for patienter behandlet med ozanimod og dimethylfumarat.



Figur 2. Punktestimat og 95 % CrI for den absolutte forskel for vedvarende sygdomsforværring. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Den absolutte forskel er vist i figur 2 ovenfor.
Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. CrI omfatter både positive og negative værdier. Derfor kan den foreløbige værdi af ozanimod vedr. vedvarende sygdomsforværring ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som er en HR på 1,32 (95 % CrI 0,48-3,25), har ozanimod foreløbigt en **værdi, der ikke kan kategoriseres** vedr. vedvarende sygdomsforværring. Det brede CrI omfatter både væsentlige positive og negative effekter af ozanimod i forhold til dimethylfumarat.

Samlet har ozanimod en **værdi, der ikke kan kategoriseres** vedr. vedvarende sygdomsforværring, fordi hverken den absolutte eller den relative værdi kan kategoriseres.

Bivirkninger (kritisk)

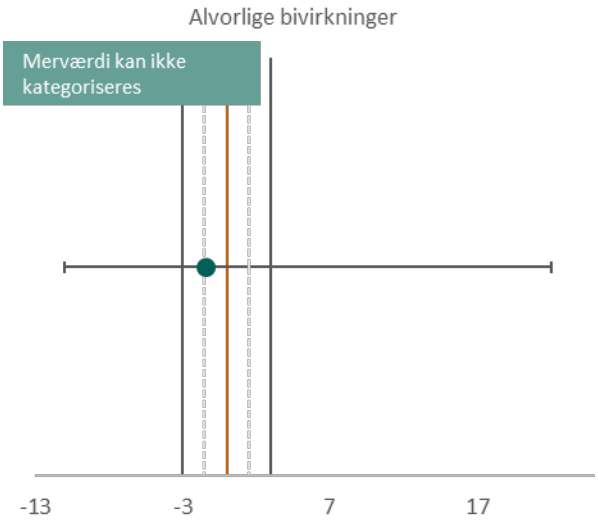
Alvorlige bivirkninger

Som beskrevet i protokollen er effektmålet *alvorlige bivirkninger* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi patienterne allerede er præget af mange alvorlige symptomer.

Grundlaget for kategorisering på dette effektmål er som tidligere beskrevet en NMA. Medicinrådet vurderer, at analysen er et acceptabelt valg og korrekt udført, men at der er væsentlige usikkerheder forbundet med den kvantitative sammenligning.

Ansøger har indsendt data for alvorlige uønskede hændelser i stedet for alvorlige bivirkninger. Som beskrevet i datagrundlag lægger fagudvalget mest vægt på en kvalitativ sammenligning af bivirkningsprofiler.

Ansøger estimerer på baggrund af sin NMA, at der en forskel på -1,48 %-point (95 % CrI -11; 22) af patienter behandlet med ozanimod og dimethylfumarat, der oplevede uønskede hændelser.



Figur 3. Punktestimat og 95 % CrI for den absolutte forskel for alvorlige bivirkninger. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Den absolutte forskel er vist i figur 3 ovenfor.
Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. CrI omfatter både positive og negative værdier. Derfor kan den foreløbige værdi af ozanimod vedr. alvorlige bivirkninger **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på den relative effektforskel, som er en HR på 0,92 (95 % CrI 0.37-2.23), har ozanimod foreløbigt en **værdi, der ikke kan kategoriseres** vedr. alvorlige bivirkninger. Det brede CrI omfatter både væsentlige positive og negative effekter af ozanimod i forhold til dimethylfumarat.

Ud fra de kvantitative data har ozanimod en **værdi, der ikke kan kategoriseres** vedr. bivirkninger, fordi hverken den absolutte eller den relative værdi kan kategoriseres.

Gennemgang af bivirkningsprofil

I tabel 4 nedenfor ses bivirkningsprofilerne fra de to lægemidlers produktresumeer.

Tabel 4. Bivirkningsprofiler fra produktresumeer

Hyppighed	Ozanimod	Dimethylfumarat
Meget almindelige	• Lymfopeni • Nasopharyngitis	• Abdominalsmerter, diarré, kvalme • Ketonstoffer i urinen • Flushing (rødme)
Almindelige	• Bradykardi • Luftvejsinfektion (viral) • Forhøjede levertransaminaser, forhøjet bilirubin, forhøjet gamma-glutamyltransferase – GGT • Urinvejsinfektion • Pharyngitis • Hypertension, ortostatisk hypotension	• Leukocytose, leukopeni, lymfocytose, lymfopeni • Dyspepsi, gastritis, gastroenteritis, opkastning, brændende fornemmelse • Forhøjede levertransaminaser (ALAT/ASAT) • Hyperæstesi • Albuminuri, proteinuria • Erytem, hudkløe, hududslæt • Hedeture, varmefølelse
Ikke almindelige		• Trombocytopeni • Anafylaktisk reaktion, hypersensitivitet
Ikke kendt	• Maculaødem • Hypersensitivitet (herunder udslæt og urticaria) • Herpes zoster	• Hypoxi • Hepatotoksicitet • Angioødem • Herpes zoster*, progressiv multifokal leukoencephalopati (PML) • Dyspnø • Hypotension

Øvrige forhold af betydning for fagudvalgets konklusion angående bivirkninger

Fagudvalget bad i protokollen om overvejelser angående *rebound* effekt og langtidsbivirkninger. Disse indgik i afsnittet "Andre overvejelser", men er præsenteret her, da de har indflydelse på fagudvalgets konklusion for effektmålet bivirkninger og det kliniske spørgsmål.

Graviditet og *rebound*-effekt

Ansøger oplyser, at der i de kliniske studier ikke var tegn på en *rebound*-effekt efter seponering af ozanimod. Ansøger oplyser også, at EMA har inkluderet en advarsel om

rebound-effekt efter seponering af ozanimod. Fagudvalget mener, at de samme overvejelser angående rebound-effekt gælder for ozanimod og fingolimod.
I produktresumeet står der, at ozanimod ikke må anvendes under graviditet, og at der er væsentlig teratogent potentiale ved terapeutiske doser. Derfor vurderer fagudvalget, at ozanimod ikke er en relevant behandling til kvinder, som har eller kan få graviditetsønske.

Overvejelser om forventningen til langtidsbivirkninger

Ansøger påpeger i sin endelige ansøgning, at ozanimods virkningsmekanisme er mere selektiv end fingolimods. Sammenholdt med kliniske data for uønskede hændelser skriver ansøger i sin endelige ansøgning, at ozanimod har en mere favorabel bivirkningsprofil end fingolimod angående kardielle effekter, infektioner, malignitet og makulært ødem. Ansøger kan ikke redegøre for, om en eventuel forskel skyldes receptorselektivitet eller forskelle i farmakokinetisk/farmakodynamisk profil.
Fagudvalget mener ikke, at ovenstående forhold er tilstrækkeligt til at se bort fra, at de potentielle langsigtede og alvorlige bivirkninger observeret hos patienter, der modtager fingolimod, måske også kan ses hos patienter, som behandles med ozanimod.

Konklusion angående sikkerhed

Fagudvalget finder det ikke dokumenteret ud fra det indleverede datagrundlag, at der er en forskel på de to lægemidler angående sikkerhed. Grundet analysens usikkerheder vælger fagudvalget at perspektivere ud fra klinisk erfaring.

Fagudvalget har stort kendskab til dimethylfumarat og finder, at bivirkningsprofilen og monitorering er håndterbar i klinisk praksis.
For ozanimod er fagudvalget især bekymret for levertoksicitet og bekymret for de alvorlige langtidsbivirkninger (deriblandt hudkræft, progressiv multifokal leuokoencephalopati og herpes-infektioner), der er kendt fra fingolimod, hvis virkningsmekanisme svarer til ozanimods. Fagudvalget vælger at inddrage klinisk erfaring med langtidsbivirkninger af fingolimod, da der ikke er data for patienter fulgt i lige så lang tid på ozanimod, og da fagudvalget ikke har erfaring med dette lægemiddel.

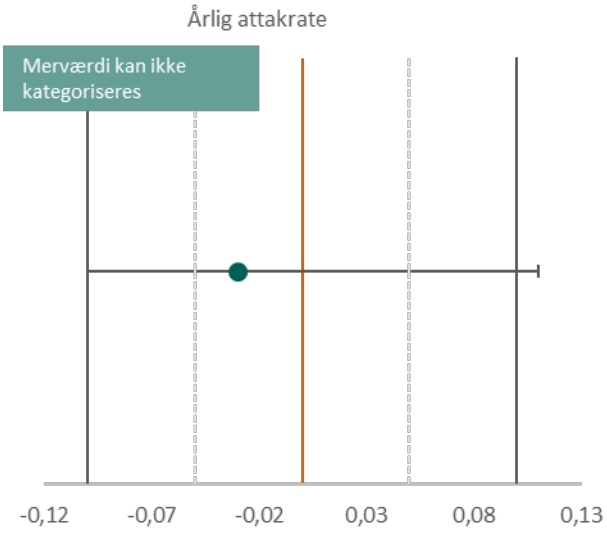
Samlet vurderer fagudvalget, at bivirkningsprofilerne ikke er sammenlignelige hvad angår langtidsbivirkninger. Fagudvalget har flere bekymringer for bivirkninger, heriblandt langvarige og alvorlige, for ozanimod end for dimethylfumarat.

Årlig attakrate (vigtigt)

Som beskrevet i protokollen er effektmålet *årlig attakrate* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi attakker medfører varige funktionstab hos patienter med RRMS. Effektmålet dækker over antal attakker pr år, hvorved en positiv ændring er et negativt resultat for patienterne.

Grundlaget for kategorisering på dette effektmål er som tidligere beskrevet en NMA. Medicinrådet vurderer, at analysen er et acceptabelt valg og korrekt udført, men at der er væsentlige usikkerheder forbundet med den kvantitative sammenligning.

Ansøger estimerer på baggrund af sin NMA, at der er en forskel på 0,03 (95 % CrI -0,10; 0,11) for patienter behandlet med ozanimod og dimethylfumarat, der oplevede uønskede hændelser



Figur 4. Punktestimat og 95 % CrI for den absolutte forskel for årlig attakrate. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Den absolutte forskel er vist i figur 4 ovenfor.
Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for CrI ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af ozanimod vedr. årlig attakrate **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på den relative effektforskel, som er en HR på 0,85 (95 % CrI 0,5-1,58), har ozanimod foreløbigt en **værdi, der ikke kan kategoriseres** vedr. årlig attakrate. Det brede CrI omfatter både væsentlige positive og negative effekter af ozanimod i forhold til dimethylfumarat.

Samlet har ozanimod en **værdi, der ikke kan kategoriseres** vedr. årlig attakrate, fordi hverken den absolutte eller den relative værdi kan kategoriseres.

Kognitiv funktion (vigtigt)
Som beskrevet i protokollen er effektmålet *kognitiv funktion* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienternes kognitive funktion har stor betydning for patienternes trivsel og funktionsniveau.

Ansøger har ikke indsendt data for dette effektmål, der kan bruges til en kvantitativ sammenligning af ozanimod mod dimethylfumarat på effektmålet kognitiv funktion.

Livskvalitet (vigtigt)
Som beskrevet i protokollen er effektmålet *livskvalitet* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi sygdommen i høj grad påvirker patienternes livskvalitet.

Ansøger har ikke indsendt data for dette effektmål, der kan bruges til en kvantitativ sammenligning af ozanimod mod dimethylfumarat på effektmålet livskvalitet.

Perspektivering af vurdering af klinisk effekt
Fagudvalget perspektiverer vurderingen på de relevante effektmål gennem en vurdering af effekten af ozanimod i de kliniske studier. Baggrunden er, at resultaterne fra NMA'en er forbundet med så brede CrI, at de principielt kunne dække over, at lægemidlet slet ikke har en klinisk effekt, hvis de vurderes isoleret. I registreringsstudiet af ozanimod var der ikke en signifikant forskel på sygdomsprogression mellem ozanimod og interferon-beta-1a [16]. Ozanimod havde i de kliniske studier en bedre effekt sammenlignet med interferon-beta-1a på effektmålet årlig attakrate, der var det primære endepunkt i studierne. Fagudvalget konkluderer ud fra de kliniske studier, at ozanimod har en effekt, som er mindst lige så god som en behandling, der indgår i Medicinrådets behandlingsvejledning for attakvis multipel sklerose (førstelinjebehandling), og betragtes dermed som effektiv i dansk klinisk praksis.

5.1.1 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af ozanimod sammenlignet med dimethylfumarat til patienter med attakvis multipel sklerose og gennemsnitlig sygdomsaktivitet ikke kan kategoriseres. På baggrund af det forelagte data og klinisk erfaring finder fagudvalget det sandsynligt, at sikkerhedsprofilen af ozanimod kan være dårligere end den for dimethylfumarat, grundet bekymring for langsigtede og alvorlige bivirkninger.

Det har ikke været muligt at kategorisere ozanimods værdi på noget effektmål. På to effektmål (det kritiske *vedvarende sygdomsforværring* og det vigtige *årlig attakrate*) er der et kvantitativt datagrundlag, men CrI er meget brede og omfatter både positive og negative effekter. Derfor kan retning eller størrelse på en eventuel effektforskel mellem de to lægemidler ikke estimeres. Ud fra de kliniske studier fremgår det, at lægemidlet har en effekt, som mindst svarer til interferon-beta-1a.

For de vigtige effektmål kognitiv funktion og livskvalitet er der ikke indleveret data.

For effektmålet *bivirkninger* har fagudvalget udført en narrativ sammenligning og inddraget klinisk erfaring.

Fagudvalget vurderer, at de to bivirkningsprofiler ikke er sammenlignelige, og at sikkerhedsprofilen for ozanimod risikerer at være dårligere end den for dimethylfumarat, især hvad angår langtidsbivirkninger. Fagudvalget har flere bekymringer for bivirkninger, heriblandt langvarige og alvorlige, for ozanimod.

5.2 Klinisk spørgsmål 2

5.2.1 Litteratur

Litteraturen for besvarelsen af klinisk spørgsmål 2 er den samme som for klinisk spørgsmål 1.

5.2.2 Databehandling og analyse

Fagudvalgets overvejelser omkring databehandling og analyse er beskrevet i afsnit 5.2.1.

5.2.3 Evidensens kvalitet

Evidensen kvalitet er meget lav. En uddybende forklaring er beskrevet i afsnit 5.1.3.

5.2.4 Effektestimater og kategorier

I tabel 5 fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.

Tabel 5. Resultater for kliniske spørgsmål 2

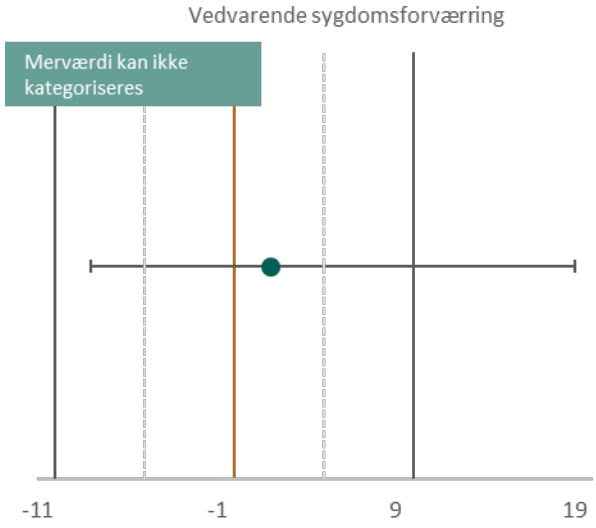
Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CrI)	Foreløbig værdi	Forskel (95 % CrI)	Foreløbig værdi	
Vedvarende sygdomsforværring bekræftet ved 3 måneder (CPD3)	Andel patienter, der oplever en ændring i CPD, der fastholdes over tre måneder (MKRF: 10 %)	Kritisk	2 % (-8; 19)	Kan ikke kategoriseres	HR: 1,11 (0,48; 2,44)	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel patienter, der oplever én eller flere alvorlige bivirkninger (MKRF: 3 %)	Kritisk	-2 % (-7; 8)	Kan ikke kategoriseres	RR: 0,81 (0,37; 1,73)	Kan ikke kategoriseres	Kan ikke kategoriseres
Årlig attakrate	Antal attakker pr. patient om året (MKRF: 0,1 attakker pr. patient om året)	Vigtig	0,00 (-0,07: 0,13)	Kan ikke kategoriseres	Rate ratio: 0,98 (0,61; 1,69)	Kan ikke kategoriseres	Kan ikke kategoriseres
Kognitiv funktion	Andel patienter, der undgår en 10 %'s forværring på SDMT (MKRF: 10 %)	Vigtig	Ikke opgjort	Kan ikke kategoriseres	Ikke opgjort	Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	Gennemsnit ændring på MSQOL54 (MKRF: 0,5 SMD)	Vigtig	Ikke opgjort	Kan ikke kategoriseres	Ikke opgjort	Kan ikke kategoriseres	Kan ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	Fagudvalget vurderer, at den samlede værdi af ozanimod sammenlignet med fingolimod til patienter med attakvis multipel sklerose og høj sygdomsaktivitet ikke kan kategoriseres. På baggrund af tilsvarende virkningsmekanismer for de to lægemidler forventer fagudvalget, at der ikke er væsentlige forskelle på effekt og sikkerhed af de to lægemidler. Der er dog større usikkerhed angående langtidseffekt og bivirkninger af ozanimod end fingolimod.
Kvalitet af den samlede evidens	Meget lav

Vedvarende sygdomsforværring (kritisk)
Som beskrevet i protokollen er effektmålet *vedvarende sygdomsforværring* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi et centralt mål med behandlingen er at forsinke progression af sygdommen. Effektmålet dækker over andelen af patienter, der oplever vedvarende sygdomsforværring, hvorved en positiv ændring er negativt for patienterne.

Grundlaget for kategorisering på dette effektmål er som tidligere beskrevet en NMA. Medicinrådet vurderer, at analysen er et acceptabelt valg og korrekt udført, men at der er væsentlige usikkerheder forbundet med den kvantitative sammenligning.

Ansøger estimerer på baggrund af sin NMA, at der en forskel på 2 %-point (95 % CrI -8; 19) for patienter behandlet med ozanimod og fingolimod.



Figur 5. Punktestimat og 95 % CrI for den absolutte forskel for vedvarende sygdomsforværring. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Den absolutte forskel er vist i figur 5 ovenfor.
Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af ozanimod vedr. vedvarende sygdomsforværring ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, som er en HR på 1,11 (95 % CrI 0,48-2,44), har ozanimod foreløbigt en **værdi, der ikke kan kategoriseres** vedr. vedvarende sygdomsforværring. Det brede CrI omfatter både væsentlige positive og negative effekter af ozanimod i forhold til fingolimod.

Samlet har ozanimod en **værdi, der ikke kan kategoriseres** vedr. vedvarende sygdomsforværring, fordi hverken den absolutte eller den relative værdi kan kategoriseres.

Bivirkninger (kritisk)

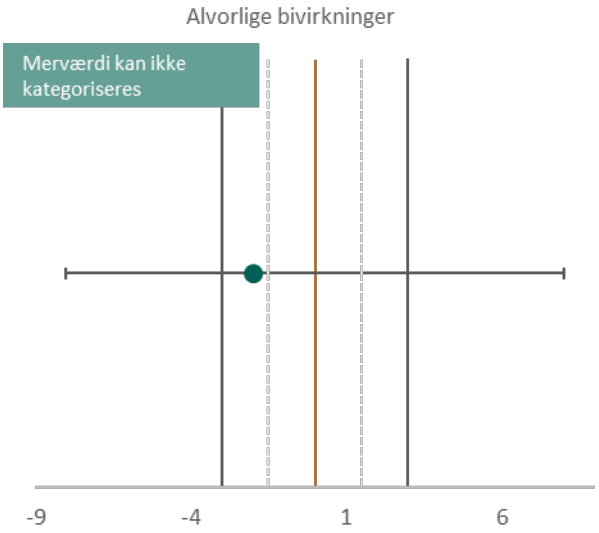
Alvorlige bivirkninger

Som beskrevet i protokollen er effektmålet *alvorlige bivirkninger* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi patienterne allerede er præget af mange alvorlige symptomer.

Grundlaget for kategorisering på dette effektmål er som tidligere beskrevet en NMA. Medicinrådet vurderer, at analysen er et acceptabelt valg og korrekt udført, men at der er væsentlige usikkerheder forbundet med den kvantitative sammenligning.

Ansøger har indsendt data for alvorlige uønskede hændelser i stedet for alvorlige bivirkninger. Som beskrevet i datagrundlag lægger fagudvalget mest vægt på en kvalitativ sammenligning af bivirkningsprofiler.

Ansøger estimerer på baggrund af sin NMA, at der en forskel på 2 %-point (95 % CrI -7; 8) for patienter behandlet med ozanimod og fingolimod.



Figur 6. Punktestimat og 95 % CrI for den absolutte forskel for alvorlige bivirkninger. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Den absolutte forskel er vist i figur 6 ovenfor.
Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af ozanimod vedr. alvorlige bivirkninger **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på den relative effektforskel, som er en RR på 0,81 (95 % CrI 0,37-1,73), har ozanimod foreløbigt en **værdi, der ikke kan kategoriseres** vedr. bivirkninger. Det brede CrI omfatter både væsentlige positive og negative effekter af ozanimod i forhold til fingolimod.

Gennemgang af bivirkningsprofil

I tabel 6 nedenfor ses beskrivelse af bivirkningsprofiler fra de to lægemidlers produktresuméer.

Tabel 6. Beskrivelse af bivirkningsprofiler for ozanimod og fingolimod

Hyppighed	Ozanimod	Fingolimod
Meget almindelige	• Lymfopeni • Nasopharyngitis	• Diarré • Influenzalignende symptomer • Forhøjede levertransaminaser • Rygsmerter • Hovedpine • Hoste, sinuitis
Almindelige	• Bradykardi • Luftvejsinfektion (viral) • Forhøjede levertransaminaser, forhøjet bilirubin, forhøjet gamma-glutamyltransferase – GGT • Urinvejsinfektion • Pharyngitis • Hypertension, ortostatisk hypotension	• Leukopeni, lymfopeni • AV-blok, bradykardi • Maculaødem, sløret syn, øjensmerter • Gastroenteritis Kraftesløshed, svimmelhed • Herpesvirusinfektioner, luftvejsinfektion, svampeinfektion i huden, svampeinfektioner • Vægttab • Hypertriglyceridæmi • Hudcancer • Migræne, paræstesier • Depression • Dyspnø • Alopeci, eksem, hudkløe • Hypertension
Ikke almindelige		• Neutropeni, trombocytopeni • Malignt melanom (inkl. pladecellekarcinom og merkelcellekarcinom) • Humørforstyrrelser • Pneumoni
Sjældne		• Lymfom* • Posterior reversibelt encefalopati-syndrom (PRES)
Meget sjældne		• Ekg-forandringer • Kaposis sarkom
Ikke kendt	• Maculaødem • Hypersensitivitet (herunder udslæt og urticaria) • Herpes zoster	• Hæmolytisk anæmi (autoimmun), lymfomlignende reaktion (B- og T-celle) • Hypersensitivitet • Kryptokokinfektion, progressiv multifokal leukoencephalopati (PML) • Perifere ødemer

Fagudvalget bemærker, at der kendes flere langtidsbivirkninger for fingolimod, fordi fingolimod har været benyttet i langt flere år i klinisk praksis. Baseret på den ensartede virkningsmekanisme for de to lægemidler forventer fagudvalget også, at bivirkningsprofilerne for langsigtede bivirkninger er tilsvarende ens. Fagudvalget vurderer ikke, at det er dokumenteret, at der er klinisk relevante forskelle på bivirkningsprofilerne for langsigtede bivirkninger for de to lægemidler (se overvejelser om langtidsbivirkninger og rebound-effekt i klinisk spørgsmål 1.

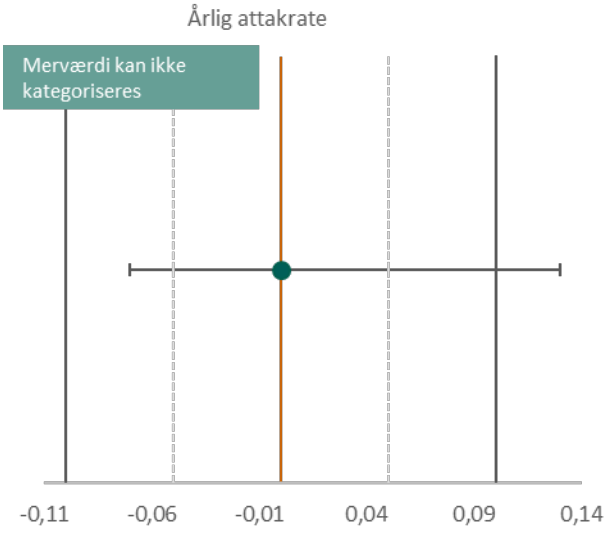
Samlet har ozanimod en **værdi, der ikke kan kategoriseres** vedr. bivirkninger, fordi hverken den absolutte eller den relative værdi kan kategoriseres. Fagudvalget vurderer, baseret på den kvalitative gennemgang og kendskab til virkningsmekanismer, at der ikke er noget, som tyder på, at bivirkningsprofilen er markant anderledes end den for fingolimod.

De samme overvejelser angående rebound-effekt og langtidsbivirkninger, som er nævnt under klinisk spørgsmål 1, gør sig også gældende for klinisk spørgsmål 2.

Årlig attakrate (vigtigt)
Som beskrevet i protokollen er effektmålet *årlig attakrate* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi attakker medfører varige funktionstab hos patienter med RRMS. Effektmålet dækker over antal attakker pr år, hvorved en positiv ændring er negativt for patienterne.

Grundlaget for kategorisering på dette effektmål er som tidligere beskrevet en NMA. Medicinrådet vurderer, at analysen er et acceptabelt valg og korrekt udført, men at der er væsentlige usikkerheder forbundet med den kvantitative sammenligning.

Ansøger estimerer på baggrund af sin NMA, at der en forskel på 0,00 (95 % CrI -0,7; 0,13) for patienter behandlet med ozanimod og fingolimod.



Figur 7. Punktestimat og 95% CrI for den absolutte forskel for årlig attakrate. De optrukne linjer indikerer den mindste klinisk relevante forskel.

Den absolutte forskel er vist i figur 7 ovenfor.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af ozanimod vedr. årlig attakrate **ikke kategoriseres** efter Medicinrådets metoder.

Baseret på den relative effektforskel, som er en RR på 0,99 (95 % CrI 0 0,61-1,69), har ozanimod foreløbigt en **værdi, der ikke kan kategoriseres** vedr. årlig attakrate. Det brede CrI omfatter både væsentlige positive og negative effekter af ozanimod i forhold til fingolimod.

Samlet har ozanimod en **værdi, der ikke kan kategoriseres** vedr. årlig attakrate, fordi hverken den absolutte eller den relative værdi kan kategoriseres.

Kognitiv funktion (vigtigt)
Som beskrevet i protokollen er effektmålet *kognitiv funktion* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienternes kognitive funktion har stor betydning for patienternes trivsel og funktionsniveau.

Ansøger har ikke indsendt data for dette effektmål, der kan bruges til en kvantitativ sammenligning af ozanimod mod fingolimod på effektmålet kognitiv funktion.

Livskvalitet (vigtigt)
Som beskrevet i protokollen er effektmålet *livskvalitet* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi sygdommen i høj grad påvirker patienternes livskvalitet.

Ansøger har ikke indsendt data for dette effektmål, der kan bruges til en kvantitativ sammenligning af ozanimod mod fingolimod på effektmålet livskvalitet.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af ozanimod sammenlignet med fingolimod til patienter med attakvis multipel sklerose og høj sygdomsaktivitet ikke kan kategoriseres. På baggrund af tilsvarende virkningsmekanismer for de to lægemidler forventer fagudvalget, at der ikke er væsentlige forskelle på effekt og sikkerhed af de to lægemidler. Der er dog større usikkerhed angående langtidseffekt og bivirkninger af ozanimod end fingolimod.

Det har ikke været muligt at kategorisere på noget effektmål. På to effektmål (det kritiske *vedvarende sygdomsforværring* og det vigtige *årlige attakrate*) er der et kvantitativ datagrundlag, men CrI er meget brede og omfatter både positive og negative effekter. Derfor kan retning eller størrelse på en eventuel effektforskel mellem de to lægemidler ikke estimeres. For de vigtige effektmål kognitiv funktion og livskvalitet er der ikke indleveret data.

6. Andre overvejelser

Da nedenstående overvejelser har væsentlig betydning for fagudvalgets konklusioner, er de også nævnt under klinisk spørgsmål 1.

Graviditet og *rebound*-effekt
Ansøger oplyser, at der i de kliniske studier ikke var tegn på en *rebound*-effekt efter seponering af ozanimod. Ansøger oplyser også, at EMA har inkluderet en advarsel om rebound-effekt efter seponering af ozanimod. Fagudvalget mener, at de samme overvejelser angående rebound-effekt gælder for ozanimod og fingolimod.
I produktresumeet står der, at ozanimod ikke må anvendes under graviditet, og at der er væsentlig teratogent potentiale ved terapeutiske doser. Derfor vurderer fagudvalget, at ozanimod ikke er en relevant behandling til kvinder, som har eller kan få graviditetsønske.
Disse overvejelser er medvirkende til, at fagudvalget ikke betragter ozanimod som et behandlingsalternativ til dimethylfumarat i første linje i nuværende dansk klinisk praksis. Risikoen for rebound-effekter er relevante for samtlige patienter, og en stor del af patienterne i dansk klinisk praksis er kvinder i den fertile alder.

Overvejelser omkring forventningen til langtidsbivirkninger
Ansøger påpeger, at ozanimods virkningsmekanisme er mere selektiv end fingolimods. Sammenholdt med kliniske data for uønskede hændelser skriver ansøger i sin endelige ansøgning, at ozanimod har en mere favorabel bivirkningsprofil end fingolimod angående kardielle effekter, infektioner, malignitet og makulært ødem. Ansøger kan ikke redegøre for, om en eventuel forskel skyldes receptorselektivitet eller forskelle i farmakokinetisk/farmakodynamisk profil.
Fagudvalget mener ikke, at overstående forhold er tilstrækkeligt til at se bort fra de potentielle langsigtede og alvorlige bivirkninger observeret hos patienter, der modtager fingolimod. Grundet forskellene i receptorselektivitet og farmakokinetisk/farmakodynamisk profil er der en usikkerhed på fagudvalgets forventninger til langtidsbivirkninger for ozanimod.

7. Relation til behandlingsvejledning

På baggrund af datagrundlaget kan Medicinrådet ikke foreløbigt indplacere ozanimod i Medicinrådets behandlingsvejledning for attakvis multipel sklerose.

Fagudvalget vil tage stilling til ozanimods indplacering i en ny behandlingsvejledning for attakvis multipel sklerose.

8. Referencer

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende multipel sklerose

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Kristian Storr Overlæge, speciallæge i neurologi	Lægevidenskabelige Selskaber og udpeget af Dansk Neurologisk Selskab
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Regionen ser sig repræsenteret af øvrige medlemmer og ønsker derfor ikke at udpege yderligere et medlem	Region Midtjylland
Thor Petersen Overlæge	Region Syddanmark
Said Nasim Ashna Overlæge	Region Sjælland
Jeppe Romme Christensen Afdelingslæge	Region Hovedstaden
Hilde Omestad Klinisk farmaceut	Dansk Selskab for Sygehusapotekledelse
Elisabeth Penninga Afdelingslæge	Dansk Selskab for Klinisk Farmakologi
Kan ikke opfylde Medicinrådets habilitetskrav	Sclerosebehandlingsregistret
Kan ikke opfylde Medicinrådets habilitetskrav	Dansk Neurologisk Selskab
Marie Lynning Patient/patientrepræsentant	Danske Patienter

Sammensætning af fagudvalg	
Malene Krüger Patient/patientrepræsentant	Danske Patienter
Preben Borring Andersen Overlæge	Inviteret af formanden
Matthias Kant Overlæge	Inviteret af formanden

Medicinrådets sekretariat

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

10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	27. januar 2021	Godkendt af Medicinrådet

11. Bilag 1: Evidensens kvalitet

11.1 Cochrane – risiko for bias

Tabel 1. Vurdering af risiko for bias ved Cochranes RoB 2.0 assessment tool

Studie	Risiko for bias i randomiserings-processen	Risiko for bias grundet afvigelser fra tilsigtet intervention (effekt af tildeling til intervention)	Manglende data for effektmål	Risiko for bias ved indsamlingen af data	Risiko for bias ved udvælgelse af resultater, der rapporteres	Overordnet risiko for bias
RADIANCE	Lav	Lav	Lav	Nogle bekymringer	Lav	Nogle bekymringer
SUNBEAM	Lav	Lav	Lav	Nogle bekymringer	Lav	Nogle bekymringer
CONFIRM	Lav	Lav	Lav	Lav	Lav	Lav
DEFINE	Lav	Lav	Lav	Lav	Lav	Lav
BRAVO	Lav	Lav	Lav	Nogle bekymringer	Lav	Nogle bekymringer
TRANSFORMS	Lav	Lav	Lav	Nogle bekymringer	Lav	Nogle bekymringer
FREEDOMS I	Lav	Lav	Lav	Lav	Lav	Lav
FREESOMS II	Lav	Lav	Lav	Lav	Lav	Lav

11.2 GRADE

Klinisk spørgsmål 1 – ozanimod sammenlignet med dimethylfumarat til behandling af RRMS

Direkte sammenligninger

Tabel 2. GRADE-evidensprofil for direkte sammenligning mellem ozanimod og interferon beta-1a (SUNBEAM og RADIANCE)

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Ozanimod	INF beta-1a	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Vedvarende sygdomsforværring												
2	RCT	Lav	Ingen	Ingen	Meget alvorlig[a]	Ingen	880	889	HR: 0,95 (0,68 – 1,33)		⨁⨁◯◯ LAV	Kritisk
Alvorlige uønskede hændelser												
2	RCT	Lav	Ingen	Alvorlig[b]	Ingen	Ingen					⨁⨁⨁◯ MODERAT	Kritisk
Årlig attakrate												
2	RCT	Lav	Ingen	Ingen	Ingen	Ingen					⨁⨁⨁⨁ HØJ	Vigtigt
Kvalitet af den samlede evidens	LAV											

[a] Konfidensintervallet er meget bredt.

[b] I protokollen blev der ønsket data på bivirkninger.

Tabel 3. GRADE-evidensprofil for direkte sammenligning mellem interferon beta-1a og placebo (BRAVO)

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	IFN beta-1a	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Vedvarende sygdomsforværring												
1	RCT	lav	Alvorlig[a]	Ingen	Meget alvorlig[b]	Ingen	447	450	HR: 0,74 (0,51 – 1,09)		⊕◯◯◯ MEGET LAV	Kritisk
Alvorlige uønskede hændelser												
1	RCT	lav	Alvorlig[a]	Alvorlig[c]	Ingen	Ingen	442	449	RR: 0,64 (0,43 – 0,96)		⊕⊕◯◯ LAV	Kritisk
Årlig attakrate												
1	RCT	lav	Alvorlig[a]	Ingen	Ingen	Ingen	447	450	Rate ratio: 0,74 (0,60 – 0,92)		⊕⊕⊕◯ MODERAT	Vigtigt
Kvalitet af den samlede evidens	MEGET LAV											

[a] Der var kun ét studie.

[b] Konfidensintervallet er meget bredt.

[c] I protokollen blev der ønsket data på bivirkninger.

Tabel 4. GRADE-evidensprofil for direkte sammenligning mellem dimethylfumarat og placebo (DEFINE og CONFIRM)

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	DMF	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Vedvarende sygdomsforværring												
2	RCT	Lav	Alvorlig	Ingen	Ingen	Ingen					⊕⊕⊕◯ MODERAT	Kritisk
Alvorlige uønskede hændelser												
2	RCT	Lav	Ingen	Alvorlig[a]	Ingen	Ingen			?		⊕⊕⊕◯ MODERAT	Kritisk
Årlig attakrate												
2	RCT	Lav	Ingen	Ingen	Ingen	Ingen			?		⊕⊕⊕⊕ HØJ	Vigtigt
Kvalitet af den samlede evidens	MODERAT											

[a] I protokollen blev der ønsket data på bivirkninger.

Indirekte sammenligninger

Tabel 5. GRADE-evidensprofil for direkte sammenligning mellem ozanimod og dimethylfumarat

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	**Studie-design**	**Risiko for bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Ozanimod**	**DMF**	**Relativ (95 % CrI)**	**Absolut (95 % CI)**	**Sikkerhed**	**Vigtighed**
Vedvarende sygdomsforværring												
5	RCT	lav	Meget alvorlig[a]	Ingen	Meget alvorlig[b]	Ingen			HR: 1,32 (0,48 – 3,25)		⨁◯◯◯ MEGET LAV	Kritisk
Alvorlige uønskede hændelser												
5	RCT	lav	Meget alvorlig[a]	Alvorlig[c]	Meget alvorlig[b]	Ingen			RR: 0,92 (0,37 – 2,23)		⨁◯◯◯ MEGET LAV	Kritisk
Årlig attakrate												
5	RCT	lav	Meget alvorlig[a]	Ingen	Meget alvorlig[b]	Ingen			rate ratio: 0,85 (0,5 – 1,58)		⨁◯◯◯ MEGET LAV	Vigtigt
Kvalitet af den samlede evidens	MEGET LAV											

[a] Studierne er udført med potentielt forskellige populationer. For en af de direkte sammenligninger, er der kun ét studie.

[b] Konfidensintervallerne er meget brede.

[c] I protokollen blev der ønsket data på bivirkninger.

Klinisk spørgsmål 2 – ozanimod sammenlignet med fingolimod til behandling af RRMS

Direkte sammenligninger

Tabel 6. GRADE-evidensprofil for direkte sammenligning mellem ozanimod og interferon beta-1a (SUNBEAM og RADIANCE)

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Ozanimod	INF beta-1a	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Vedvarende sygdomsforværring												
2	RCT	lav	Ingen	Ingen	Meget alvorlig[a]	Ingen	880	889	HR: 0,95 (0,68 – 1,33)		⨁⨁◯◯ LAV	Kritisk
Alvorlige uønskede hændelser												
2	RCT	lav	Ingen	Alvorlig[b]	Ingen	Ingen					⨁⨁⨁◯ MODERAT	Kritisk
Årlig attakrate												
2	RCT	lav	Ingen	Ingen	Ingen	Ingen					⨁⨁⨁⨁ HØJ	Vigtigt
Kvalitet af den samlede evidens	LAV											

[a] Konfidensintervallet er meget bredt.

[b] I protokollen blev der ønsket data på bivirkninger.

Tabel 7. GRADE-evidensprofil for direkte sammenligning mellem interferon beta-1a og placebo (BRAVO)

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	IFN beta-1a	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Vedvarende sygdomsforværring												
1	RCT	lav	Alvorlig[a]	Ingen	Meget alvorlig[b]	Ingen	447	450	HR: 0,74 (0,51 – 1,09)		⨁⨁◯◯ LAV	Kritisk
Alvorlige uønskede hændelser												
1	RCT	lav	Alvorlig[a]	Alvorlig[c]	Ingen	Ingen	442	449	RR: 0,64 (0,43-0,96)		⨁⨁◯◯ LAV	Kritisk
Årlig attakrate												
1	RCT	lav	Alvorlig[a]	Ingen	Ingen	Ingen	447	450	Rate ratio: 0,74 (0,60 – 0,92)		⨁⨁⨁◯ MODERAT	Vigtigt
Kvalitet af den samlede evidens	LAV											

[a] Der kun var ét studie.

[b] Konfidensintervallet er meget bredt.

[c] I protokollen blev der ønsket data på bivirkninger.

Tabel 8. GRADE-evidensprofil for direkte sammenligning mellem fingolimod og placebo (FREEDOMS I og FREEDOMS II)

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Fingolimod	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Vedvarende sygdomsforværring												
2	RCT	Lav	Alvorlig	Ingen	Ingen	Ingen					⨁⨁⨁◯ MODERAT	Kritisk
Alvorlige uønskede hændelser												
2	RCT	Lav	Ingen	Alvorlig[a]	Ingen	Ingen					⨁⨁⨁◯ MODERAT	Kritisk
Årlig attakrate												
2	RCT	Lav	Ingen	Ingen	Ingen	Ingen					⨁⨁⨁⨁ HØJ	Vigtigt
Kvalitet af den samlede evidens	MODERAT											

[a] I protokollen blev der ønsket data på bivirkninger.

Tabel 9. GRADE-evidensprofil for direkte sammenligning mellem fingolimod og interferon beta-1a (TRANSFORMS)

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Fingolimod	INF beta-1a	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Vedvarende sygdomsforværring												
1	RCT	Lav	Alvorlig[a]	Ingen	Ingen	Ingen	429	431	HR: 1,02 (0,99-1,06)		⊕⊕⊕◯ MODERAT	Kritisk
Alvorlige uønskede hændelser												
1	RCT	Lav	Alvorlig[a]	Alvorlig[b]	Alvorlig[c]	Ingen	429	431	RR: 1,21 (0,72-2,02)		⊕◯◯◯ MEGET LAV	Kritisk
Årlig attakrate												
1	RCT	Lav	Alvorlig[a]	Ingen	Ingen	Ingen	429	431	Rate ratio: 0,94 (0,90 – 0,98)		⊕⊕⊕◯ MODERAT	Vigtigt
Kvalitet af den samlede evidens	MEGET LAV											

[a] Der kun var ét studie.

[b] I protokollen blev der ønsket data på bivirkninger.

[c] Konfidensintervallet er meget bredt.

Indirekte sammenligninger

Tabel 10. GRADE-evidensprofil for direkte sammenligning mellem ozanimod og fingolimod

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	**Studie-design**	**Risiko for bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Ozanimod**	**Fingolimod**	**Relativ (95 % CrI)**	**Absolut (95 % CI)**	**Sikkerhed**	**Vigtighed**
Vedvarende sygdomsforværring												
6	RCT	lav	Meget alvorlig[a]	Ingen	Meget alvorlig[b]	Ingen			HR: 1,11 (0,48 – 2,44)		⨁◯◯◯ MEGET LAV	Kritisk
Alvorlige uønskede hændelser												
6	RCT	lav	Meget alvorlig[a]	Alvorlig[c]	Meget alvorlig[b]	Ingen			RR: 0,81 (0,37 – 1,73)		⨁◯◯◯ MEGET LAV	Kritisk
Årlig attakrate												
6	RCT	lav	Meget alvorlig[a]	Ingen	Meget alvorlig[b]	Ingen			Rate ratio: 0,98 (0,61 – 1,69)		⨁◯◯◯ MEGET LAV	Vigtigt
Kvalitet af den samlede evidens	MEGET LAV											

[a] Studierne er udført med potentielt forskellige populationer. For en af de direkte sammenligninger er der kun ét studie.

[b] Konfidensintervallerne er meget brede.

12. Bilag 2: Baselinekarakteristika

	RADIANCE		SUNBEAM		CONFIRM		DEFINE		FREEDOMS		FREEDOMS II		TRANSFORMS		BRAVO	
	INF	Ozanimod	INF	Ozanimod	Placebo	DMF	Placebo	DMF	INF	Ozanimod	INF	Ozanimod	Placebo	DMF	Placebo	DMF
Andel kvinder (%)	68,9	67,2	67,0	63,3	69	68	75	72	69,6	71,3	77	81	65,4	67,8	71,3	68,7
Alder (median)	35,1	36	35,9	34,8	36,9	37,8	38,5	38,1	36	37	41	40	37	36	37,5	38,5
Tid (år) siden symptomdebut (median)	Mean: 6,36	Mean: 6,92	Mean: 6,88	Mean: 6,85	-	-	-	-	6,6	7,0	8,6	9,2	6	6	4,7	5,3
Tid (år) fra diagnose (median)	Mean: 3,63	Mean: 3,97	Mean: 3,71	Mean: 3,60	4,8	4,9	5,8	5,6	-	-	-	-	-	-	1,2	1,4
Antal attakker i året op til studiestart (mean)	1,3	1,3	1,3	1,3	1,4	1,3	1,3	1,3	1,5	1,4	1,4	1,5	1,5	1,5	Median: 1	Median: 1
EDSS (mean)	2,49	2,55	2,62	2,61	2,6	2,6	2,5	2,4	2,3	2,5	2,4	2,4	2,24	2,19	Median: 2,5	Median: 2,5
Tidligere sygdomsmodificerende behandling (%)	28,6	28,4	33,7	28,6	31	28	42	40	42,6	40,4	74	73	55,2	53,3	6	9,4

Ozanimod: 1mg, Fingolimod: 0,5 mg, DMF: dimethylfumarat, to gange dagligt, INF: interferon beta-1a 30 µg

Application for the assessment of Zeposia® (ozanimod) for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.

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1 Basic information

Table 1 Contact information

Name	Lars Oddershede, Ph.d.
Title	Market Access Manager
Area of responsibility	Primary contact
Phone	+45 42 56 60 30
E-mail	Lars.oddershede@bms.com

Table 2 Overview of the pharmaceutical

Proprietary name	Zeposia®
Generic name	Ozanimod
Marketing authorization holder in Denmark	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Irland
ATC code	L04AA38
Pharmacotherapeutic group	Immunosuppressants, selective immunosuppressants
Active substance(s)	Ozanimod
Pharmaceutical form(s)	Hard capsules containing 0.23 mg, 0.46 mg and 0.92 mg respectively.
Mechanism of action	Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator, which binds selectively to sphingosine 1-phosphate receptor subtypes 1 and 5. Ozanimod causes lymphocyte retention in lymphoid tissues. The mechanism by which ozanimod exerts therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration into the central nervous system (CNS). Ozanimod is 10-fold more selective for $S1P_1$ relative to $S1P_5$ and has little activity on other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$). Ozanimod is extensively metabolised in humans to form a number of circulating active metabolites (see section 5.2). *In vitro*, ozanimod and its active metabolites demonstrated similar activity and selectivity for $S1P_1$ and $S1P_5$. In humans, approximately 94% of circulating total active drug exposure are represented by ozanimod (6%) and the two major metabolites CC112273 (73%), and CC1084037 (15%). [1]
Dosage regimen	The recommended dose of ozanimod is 0.92 mg taken orally once daily. An initial dose escalation from Day 1 to Day 7 is required: 0.23 mg once daily on days 1-4, 0.46 mg once daily on days 5-7, 0.92 mg once daily as maintenance dose thereafter. [1]

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features. [1]
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes - BEGR
Combination therapy and/or co-medication	None
Packaging – types, sizes/number of units, and concentrations	Treatment initiation pack: Zeposia 0.23 mg and 0.46 mg Pack size of 7 hard capsules (4 x 0.23 mg, 3 x 0.46 mg). [1] Maintenance pack: Zeposia 0.92 mg Pack size of 28 or 98 hard capsules. [1]
Orphan drug designation	No

2 Abbreviations

Acronym	Defintion
ADR	Adverse Drug Reaction
AE	Adverse events
ALC	Absolute lymphocyte count
ARR	Annualised relapse rates
AV	Atrioventricular
BG-12	Dimethyl fumarate (investigational name)
BID	Twice daily
BPM	Beats per minute
CBC	Complete blood count
CDP	Confirmed disability progression
CDP3	Confirmed disability progression 3 months (12 weeks)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CrI	Credible interval
DIC	Deviance information criterion
DMF	Dimethyl Fumarate
DMT	Disease modifying therapy
DSU	Decision Support Unit
EDSS	Expanded disability status scale
EMA	European medicines agency
EPAR	European public assessment report
EQ-5D	EuroQol five-dimension scale
GdH	Gadolinium enhancing
HPV	Human Papilloma Virus
HR	Hazard ratio
HRQoL	Health related quality of life
HSV	Herpes Simplex Virus
IFN	Interferon
ITC	Indirect Treatment Comparison

ITT	Intent-to-treat
JCV	John Cunningham virus
MAIC	Matching-adjusted indirect comparison
MFIS	Modified fatigue impact scale
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSQoL	Multiple Sclerosis Quality of Life
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
PBVC	Percent brain volume change
PICO	Population, Intervention, Comparator, Outcome
PML	Progressive multifocal leukoencephalopathy
PRIMUS	Patient Reported Indices for MS
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of life
QT	Measure of time between start of Q wave and end of T wave
RR	Risk ratio
RRMS	Relapsing Remitting Multiple Sclerosis
s.c.	Subcutaneous
S1P	Sphingosine 1-phosphate
SAE	Serious adverse events
SD	Standard deviation
SDMT	Symbol digit modalities test
SF-36	Short Form 36
SLR	Systematic literature review
TEAE	Treatment emergent adverse event
TID	Three times daily
ULN	Upper Limit of Normal
VZV	Varicella zoster virus

3 Summary

The European Commission approved ozanimod (Zeposia®) on 27th of May 2020: "Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features." [1]

Ozanimod was investigated in two phase III studies, the 2-year RADIANCE and the 1-year SUNBEAM both with interferon beta-1a as comparator. [2, 3]

Participants were aged 18–55 years, had multiple sclerosis according to 2010 McDonald criteria, a relapsing clinical course, brain MRI lesions consistent with multiple sclerosis, an expanded disability status scale score of 0·0–5·0, and either at least one relapse within 12 months before screening or at least one relapse within 24 months before screening plus at least one gadolinium-enhancing (GdH) lesion within 12 months before randomisation. [2, 3]

For the pooled data from the RADIANCE and SUNBEAM studies ozanimod 1 mg demonstrated a statistically significant and clinically meaningful reduction of the adjusted annualised relapse rate (ARR; the primary endpoint) compared to interferon beta-1a 30 µg once weekly (Rate Ratio 0.62 (0.51 to 0.77; p<0.0001)). Similar statistically significant effects were seen for the secondary endpoints, adjusted mean number of new or enlarging T2 lesions per scan over 24 months and adjusted mean number of GdH lesions at month 24. The proportion of participants with confirmed disability progression at 3 months (CDP3) was not significantly different between treatment groups. Fewer treatment emergent adverse events (TEAEs) were reported in the ozanimod group than in the interferon beta-1a group in both studies, while the frequency of serious TEAEs was similar between the groups. [2, 3]

As no head to head clinical studies comparing ozanimod with fingolimod and dimethyl fumarate (DMF) respectively, exists, a network meta-analysis (NMA) was conducted including studies with at least 12 months follow-up. The analysis was based on the DEFINE[4] and CONFIRM [5] studies for dimethyl fumarate and the FREEDOMS[6], FREEDOMS II [7] and TRANSFORMS [8] studies for fingolimod with inclusion of the BRAVO study (interferon beta 1a vs placebo) [9] to complete the network.

The NMA results for comparison between ozanimod and dimethyl fumarate showed no statistically significant difference with regard to ARR (rate ratio: 0.85; 95% credibility interval (CrI): 0.5-1.58), CDP3 (hazard ratio (HR): 1.32; 95% CrI: 0.48-3.25), frequency of serious adverse events (SAEs) (relative risk (RR): 0.92; 95% CrI: 0.37-2.23) and frequency of adverse events (AEs) (RR: 0.98; 95% CrI: 0.92-1.04).

The NMA results for comparison between ozanimod and fingolimod showed no statistically significant difference with regard to ARR (rate ratio: 0.98; 95% CrI: 0.61-1.69), CDP3 (HR: 1.11 95% CrI: 0.48-2.44), frequency of SAEs (RR: 0.81; 95% CrI: 0.37-1.73) and frequency of AEs (RR: 0.99; 95% CrI: 0.93-1.03)

A comprehensive review of the safety profile has been provided. Overall, the frequency of TEAEs is comparable between the ozanimod, dimethyl fumarate and fingolimod. However, ozanimod seems to have a favourable safety profile as compared to fingolimod regarding frequency of severe leukopenia and herpes virus infections, frequency of first dose cardiac AEs like bradycardia, skin malignancies and increases of liver enzymes.

Overall, ozanimod is a relevant new treatment option with efficacy and safety comparable to dimethyl fumarate and efficacy comparable to and safety profile more favourable than fingolimod.

4 Literature search

A systematic literature review was conducted to identify relevant publications to assess the clinical added value of ozanimod hydrochloride for the treatment of RRMS versus dimethyl fumarate and fingolimod.

The systematic literature review included the search string as defined in the protocol provided by the Danish Medicines Council. The results from the systematic search performed on 24 AUG 2020 in Medline and 27 AUG 2020 in CENTRAL are presented in Table 3 and Table 4, respectively.

Table 3. Search string and results of the systematic search in central (via Cochrane library)

#	Query	Search facet	No. of hits
#1	[mh ^"Multiple Sclerosis, Relapsing-Remitting"]	Population	870
#2	multiple sclerosis:kw and embase:an and relaps*:ti,ab,kw		2 191
#3	(RMS or RRMS):ti,ab		2 543
#4	relaps*:ti,ab and (multiple next sclerosis or MS):ti,ab		4 369
#5	#1 or #2 or #3 or #4		5 458
#6	(ozanimod or RPC1063 or "RPC 1063" or Zeposia*):ti,ab,kw	Intervention	100
#7	[mh "Dimethyl Fumarate"] or "fumaric acid dimethyl ester":kw	Comparators	281
#8	(dimethyl next fumarate or "FAG 201" or FAG201 or "BG 00012" or BG00012 or "BG 12" or BG12 or Tecfidera* or Fumaderm*):ti,ab		413
#9	[mh "Fingolimod Hydrochloride"]		147
#10	(fingolimod or "FTY 720" or FTY720 or Gilen*):ti,ab,kw		578
#11	#6 or #7 or #8 or #9 or #10		1 070
#12	#5 and #11	Combination population and treatment	770
#13	(clinicalstudies.gov or studiesearch):so	Exclusion of non-relevant publication types	331 618
#14	("conference abstract" or review):pt or (abstract or review):ti		189 045
#15	NCT*:au		194 684
#16	#13 or #14 or #15		520 724
#17	#12 not #16		206
#18	(Embase not Pubmed):an	Inclusion of ref-erences from Embase	348 438
#19	#17 and #18 in Studies	Final search (both clinical questions)	54

Table 4. Search string and results of the systematic search in Medline (via PubMed)

#	Query	Search facet	No. of hits
#1	Multiple Sclerosis, Relapsing-Remitting [mh:noexp]	Population	6 205
#2	RMS[tiab] OR RRMS[tiab]		16 677
#3	relaps*[tiab] AND (multiple sclerosis[tiab] OR MS[tiab])		15 151
#4	#1 OR #2 OR #3		29 988
#5	ozanimod[nm]	Intervention	29
#6	ozanimod[tiab] OR RPC1063[tiab] OR RPC-1063[tiab] OR Zeposia*[tiab]		61
#7	Dimethyl Fumarate[mh]	Comparators	687
#8	dimethyl fumarate[tiab] OR FAG-201[tiab] OR FAG201[tiab] OR BG-00012[tiab] OR BG00012[tiab] OR BG-12[tiab] OR BG12[tiab] OR Tecfidera*[tiab] OR Fumaderm*[tiab]		1 082
#9	Fingolimod Hydrochloride[mh]		2 148
#10	fingolimod[tiab] OR FTY-720[tiab] OR FTY720[tiab] OR Gilen*[tiab]		3 168
#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10		4 449
#12	#4 AND #11	Combination population and treatment	1 389
#13	(Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Studies as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans[mh])	Identification of randomised studies	1 249 731
#14	#12 AND #13		315
#15	(Review[pt] OR Comment[pt] OR Letter[pt] OR Case Reports[pt] OR case report[ti] OR review[ti]) NOT Randomized Controlled Trial[pt]	Exclusion of non-relevant publication types	6 132 661
#16	#14 NOT #15	Final search (both clinical questions)	192

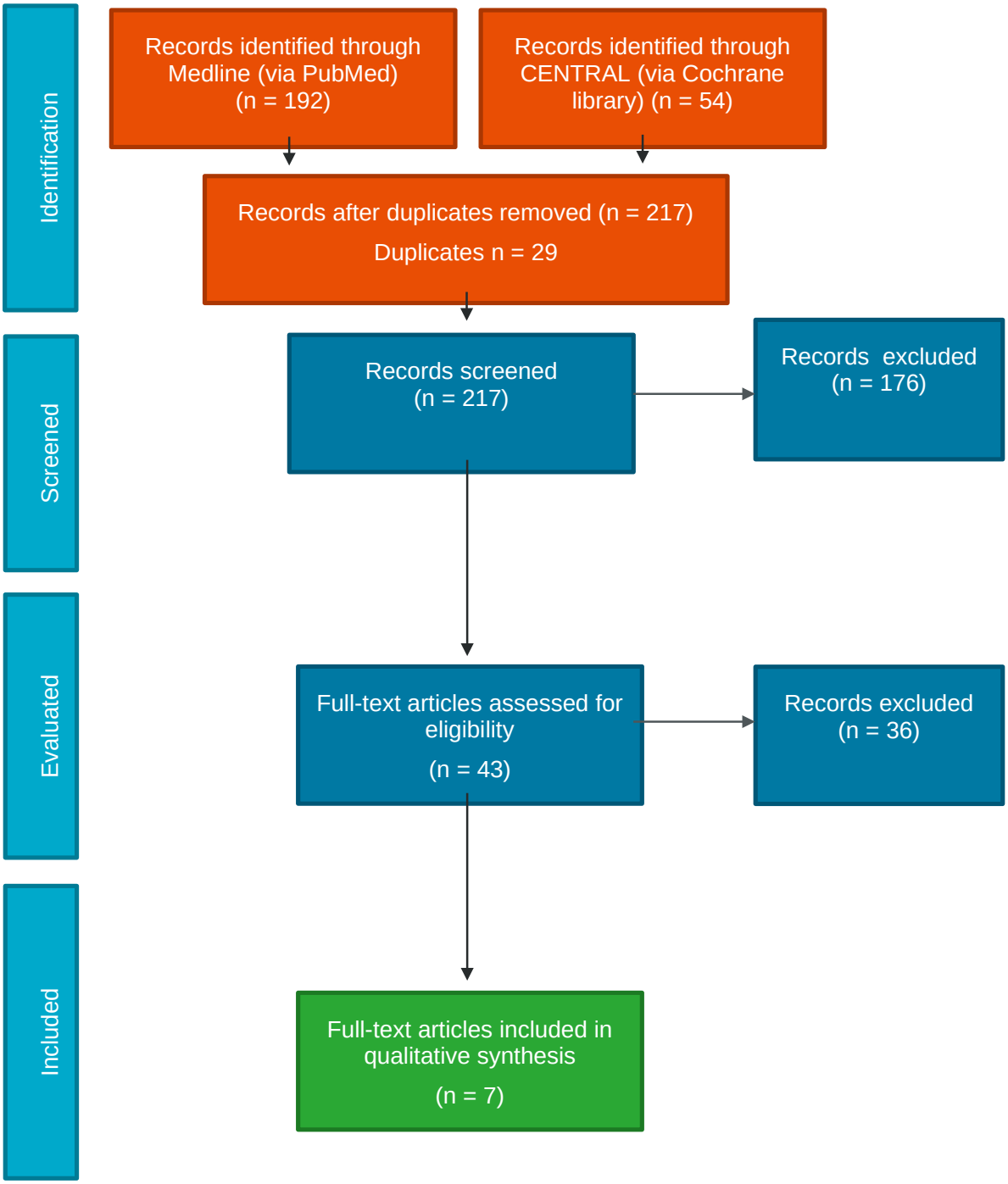
The eligibility criteria used for the systematic literature review are defined in terms of the Population, Interventions, Comparisons, Outcomes, and study design (PICOS) framework, as well as language and time frame (see Table 46 (p.72) and Table 47 (p.73) in section 7.1.1).

A total of 246 records were identified through CENTRAL and MEDLINE. With duplicates removed (n = 29), 217 records were left to be screened. Two reviewers, working independently, reviewed the identified records for inclusion by title or abstract according to the PICO selection criteria, resulting in 174 excluded records. The 43 full-text publications that passed the first screening underwent a more rigorous screening to assess any data of interest according to PICO. Of these, 7 publications corresponding to 7 clinical studies were found relevant, further described in section 4.2 (p. 16).

The process of study identification and selection is summarized in Figure 1 with a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1)

All records excluded after full text review are presented with reason for exclusion in Table 48 (p. 75).

Figure 1. Prisma flow diagram of Medline (via PubMed) and CENTRAL (via Cochrane library)



European Public Assessment Reports (EPARs) and Summary of Product Characteristics (SmPC) for ozanimod, fingolimod, and dimethyl fumarate were also reviewed.

During the data extraction stage, it became evident that ozanimod studies (versus interferon-beta 1 a) did not have the same comparator as the dimethyl fumarate studies (versus: placebo). In the DMC treatment guidelines[10], the BRAVO study for interferon beta-1a versus placebo[9] was identified and required to connect the network of evidence. As such, the BRAVO study was added as a link to support comparison between the ozanimod and dimethyl fumarate studies.

4.1 Relevant studies

Table 5 Relevant studies included in the assessment

Reference (title, author, journal, year)	Study name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Ozanimod				
Cohen JA, Comi G, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, Hartung HP, Montalban X, Kubala Havrdová E, Cree BAC, Sheffield JK, Minton N, Raghupathi K, Huang V, Kappos L; RADIANCE Trial Investigators. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. Lancet Neurol. 2019 Nov;18(11):1021-1033. doi: 10.1016/S1474-4422(19)30238-8. Epub 2019 Sep 3. PubMed PMID: 31492652.[2]	RADIANCE (phase III)	NCT02047734	03DEC2013-27MAR2017	1+2
Comi G, Kappos L, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, Hartung HP, Montalban X, Kubala Havrdová E, Cree BAC, Sheffield JK, Minton N, Raghupathi K, Ding N, Cohen JA; SUNBEAM Study Investigators. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol. 2019 Nov;18(11):1009-1020. doi: 10.1016/S1474-4422(19)30239-X. Epub 2019 Sep 3. PubMed PMID: 31492651. [3]	SUNBEAM	NCT02294058	03DEC2014—22DEC2016	1+2
Dimethyl fumarate				
Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012 Sep 20;367(12):1087-1097.[5]	CONFIRM	NCT00451451	JUNE2007-AUG2011	1
Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012 Sep 20;367(12):1098-1107. [4]	DEFINE	NCT00420212	JAN2007-AUG2011	1
Fingolimod				
Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387-401[6]	FREEDOMS	NCT00289978	JAN2006-JUL2009	2
Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Neurology. 2014;13(6):545-556.[7]	FREEDOMS II	NCT00355134	JUN2006-AUG2011	2
Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402-415.[8]	TRANSFORMS	NCT00340834	MAY2006-JUL2011	2
Additional study reference for the network meta-analysis, not captured in the structured literature search				
Vollmer et al.; A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol (2014) 261:773–783 doi: 10.1007/s00415-014-7264-4. [9]	BRAVO	NCT00605215	APR2008-DEC2011	1+2

4.2 Main characteristics of included studies

4.2.1 The RADIANCE phase III study (ozanimod)

The pivotal phase III RADIANCE study was a two-part study (Part A and B), phase II/III, with Part A (NCT01628393) consisting of a placebo-controlled phase (II) with an optional extension period and Part B (NCT02047734) as an active-controlled phase III study. RADIANCE Part B was a 24-month, multicentre, randomized, double-blind, double-dummy, active-controlled, three-arm, parallel group, phase III study comparing ozanimod 0.5 mg, 1.0 mg and interferon beta-1a. [2]

The purpose of the study was to determine whether ozanimod is effective in the treatment of relapsing multiple sclerosis (RMS). [2]

The primary endpoint was annualised relapse rate (ARR) over 24 months based on confirmed, protocol-defined relapses. [2]

Relapses were defined as new or worsening neurological symptoms persisting for more than 24 h, not attributable to confounding factors, and preceeded by stable or improving neurological status for at least 30 days. Relapses were confirmed when accompanied by objective neurological worsening measured on the Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating greater disability; EDSS increase ≥0.5 on overall score, 2 points on one functional system scale score, or 1 point on two or more functional system scale scores). [2]

Key secondary endpoints were a) number of new or enlarging T2 brain MRI lesions over 24 months, b) number of GdH brain MRI lesions at month 24 and c) time to onset of disability progression (EDSS worsening of ≥1-point increase, confirmed after 3 and 6 months). [2]

Disability progression was assessed as a prespecified pooled analysis with the SUNBEAM phase III study (treatment duration 12 months). [2, 3]

Eligible patients were aged 18–55 years with multiple sclerosis according to 2010 McDonald criteria, a relapsing clinical course (RRMS, progressive–relapsing, or secondary progressive), brain MRI lesions consistent with multiple sclerosis, an EDSS score of 0.0–5.0, either at least one relapse within 12 months before screening or at least one relapse within 24 months before screening, plus at least one GdH lesion within the 12 months. [2]

The main characteristics of the RADIANCE study are provided in Table 58 (p.102).

4.2.2 The SUNBEAM phase III study (ozanimod)

The pivotal SUNBEAM study was a 12-month, multicentre, randomized, double-blind, double-dummy, active-controlled, three-arm, parallel group, phase III study comparing ozanimod 0.5 mg, 1.0 mg and interferon beta-1a. [3]

The purpose of the study was to assess the safety and efficacy of ozanimod in patients with relapsing multiple sclerosis. [3]

The primary efficacy endpoint was ARR during the treatment period based on confirmed, protocol-defined relapses (i.e., new or worsening neurological symptoms attributable to multiple sclerosis persisting for >24 h, not attributable to confounding clinical factors, and immediately preceded by a mostly stable or improving neurological state for ≥30 days). Relapse was confirmed when accompanied by objective neurological worsening (i.e., EDSS score increase ≥0.5 on overall score, 2 points on one functional system scale score, or 1 point on two or more functional system scale scores). [3]

Key secondary efficacy endpoints were a) number of new or enlarging T2 brain lesions over 12 months, b) number of GdH brain lesions at month 12; and c) time to onset of disability progression (defined as a sustained worsening in EDSS ≥1-point increase) confirmed after 3 months and 6 months. [3]

Disability progression was assessed as a prespecified pooled analysis with the RADIANCE phase III study (treatment duration 24 months); the methods and results are reported with the RADIANCE phase III study. [2, 3]

Eligible patients were aged 18–55 years and diagnosed with multiple sclerosis per 2010 McDonald criteria, with a relapsing clinical course (RRMS, secondary progressive, or progressive–relapsing), history of brain MRI lesions consistent with multiple sclerosis, baseline EDSS score of 0.0–5.0, and either at least one relapse in the 12 months before screening or at least one relapse in the 24 months before screening, plus at least one GdH lesion in the 12 months before randomization. [3]

The main characteristics of the SUNBEAM study are provided in Table 60 (p.108).

4.2.3 The CONFIRM phase III study (dimethyl fumarate)

The CONFIRM study was a randomised, multicentre, placebo-controlled, and active reference phase III study in 1417 patients with RRMS according to the McDonald 2005 criteria. Patients were randomized to dimethyl fumarate 240 mg oral capsules twice daily (N=359), dimethyl fumarate 240 mg oral capsules three times daily (N=345), glatiramer acetate 20 mg s.c. once daily (N=350) or placebo (N=363). [5]

The primary efficacy endpoint was the ARR (defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days) at 2 years whilst secondary efficacy endpoints included the number of new or enlarging hyperintense lesions on T2-weighted images, the number of new hypointense lesions on T1-weighted images, the proportion of patients with a relapse, and the time to disability progression, each at 2 years. [5]

Key eligibility criteria were a diagnosis of RRMS (McDonald criteria 2005), an age of 18 to 55 years, a score of 0.0-5.0 on EDSS [10] and at least one clinically documented relapse in the previous 12 months or at least one GdH lesion 0 to 6 weeks before randomization. [5]

The main characteristics of the CONFIRM study are provided in Table 62 (p. 115).

4.2.4 The DEFINE phase III study (dimethyl fumarate)

DEFINE was a phase III randomized (1:1:1), multicentre, double-blind, placebo-controlled, dose-comparison study in 1237 patients with RRMS according to the McDonald 2005 criteria. Patients were randomized to dimethyl fumarate 240 mg oral capsules twice daily (N=410), dimethyl fumarate 240 mg oral capsules three times daily (N=416), or placebo (N=408).[4]

The primary endpoint was the proportion of patients who had a relapse by 2 years. Protocol defined relapses were new or recurrent neurologic symptoms, not associated with fever or infection, that lasted for at least 24 hours and that were accompanied by new objective neurologic findings according to the examining neurologist's evaluation, whilst secondary efficacy endpoints assessed were the number of GdH lesions and of new or enlarging hyperintense lesions on T2-weighted images, the ARR (the total number of relapses divided by the number of patient-years in the study, excluding data obtained after patients switched to alternative multiple sclerosis medications), and the time to progression of disability. [4]

Key eligibility criteria included an age of 18 to 55 years, a diagnosis of RRMS as defined according to the McDonald criteria, a baseline score of 0.0-5.0 on EDSS, and disease activity as evidenced by at least one clinically documented relapse within 12 months before randomization or a brain MRI scan, obtained within 6 weeks before randomization, that showed at least one GdH lesion. [4]

The main characteristics of the DEFINE study are provided in Table 64 (p. 117).

4.2.5 The FREEDOMS study (fingolimod)

FREEDOMS was a phase III, double-blind, placebo-controlled study. Patients were randomly assigned, in a 1:1:1 ratio, to receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg or matching placebo, once daily for 24 months. [6]

The primary endpoint was ARR, defined as the number of confirmed relapses per year. Relapses were verified by the examining neurologist within 7 days after the onset of symptoms. The symptoms must have been accompanied by an increase of at least half a point in the EDSS score, of one point in each of two EDSS functional system scores, or of two points in one EDSS functional-system score (excluding scores for the bowel–bladder or cerebral functional systems). [6]

Secondary endpoints included time to confirmed disability progression defined as an increase of one point in the EDSS score (or half a point (0.5) if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression. Other secondary endpoints were: time to a first relapse; time to disability progression (confirmed after 6 months); changes in the EDSS score z score between baseline and 24 months; number of GdH lesions; proportion

of patients free from GdH lesions; number of new or enlarged lesions on T2-weighted MRI scans; proportion of patients free from new or enlarged lesions on T2-weighted scans; volumes of hyperintense lesions on T2-weighted scans and hypointense lesions on T1-weighted scans; change in brain volume between baseline and 24 months; and safety and tolerability measures. [6]

Key eligibility criteria included an age of 18 to 55 years, a diagnosis of RRMS, and a baseline EDSS score of 0.0-5.5. [6]

The main study characteristics of the FREEDOMS study are summarized in Table 66, p. 120.

4.2.6 The FREEDOMS II study (fingolimod)

FREEDOMS II is a randomized, multicentre, parallel-group study consisting of 2 phases: a 24-month double-blind, randomized, multicentre, placebo-controlled, parallel-group study and an Extension phase which consisted of a dose-blinded period and an open-label period. In the Core phase—of concern for this document—patients were randomized to receive a fixed dose of fingolimod (0.5 mg/day), fingolimod (1.25 mg/day) or placebo for up to 24 months. [7]

The primary endpoint was ARR for up to 24 months (analysed by intention to treat). A relapse was confirmed when it was accompanied by an increase of at least half a step (0.5) on the EDSS, an increase of 1 point on two different functional systems of the EDSS, or 2 points on one of the functional systems (excluding bowel, bladder, or cerebral functional systems). [7]

Secondary endpoints included: percent brain-volume change from baseline and time to disability progression (1 point EDSS change [0.5 point if baseline EDSS was >5.0]) confirmed at 3 months for up to 24 months; safety and tolerability; time to first relapse and proportion of relapse free patients; time to disability progression confirmed at 6 months, as measured by EDSS; change from baseline to the end of study on the Multiple Sclerosis Functional Composite (MSFC) score; effect on MRI measurements of inflammatory disease activity; quality of life; and fatigue. [7]

Key eligibility criteria included an age of 18 to 55 years, a diagnosis of RRMS, and a baseline EDSS score of 0.0-5.5.

The main study characteristics of the FREEDOMS II study are summarized in Table 67, p. 122.

4.2.7 The TRANSFORMS study (fingolimod)

TRANSFORMS is a phase III, multicenter, randomized, double-blind, double-dummy, parallel group study. Patients were randomly assigned to 12 months of treatment with oral fingolimod, at a daily dose of either 1.25 or 0.5 mg, or intramuscular interferon beta-1a, at a weekly dose of 30 µg. The study included and optional extension phase. The core study is of interest to this document. [8]

The primary endpoint was ARR for 12 months (analysed by intention to treat), defined as the number of confirmed relapses in a year. A relapse is defined as the appearance of a new or worsening of a previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding relapse. The abnormality must be present for at least 24 hours and occur in the absence of fever or infection. The ARR for each treatment group was calculated using negative binomial regression adjusted by treatment, country, number of relapses in the previous 2 years, and the baseline EDSS. [8]

Secondary endpoints in the core study included: number of new or newly enlarged T2 lesions in comparison with baseline; percentage of participants free of 3-month disability progression assessed with the EDSS; and estimated annualised aggregate relapse rate. [8]

Key eligibility criteria included an age of 18 to 55 years, a diagnosis of RRMS, and a baseline EDSS score of 0.0-5.5. [8]

The main study characteristics of the TRANSFORMS study are summarized in Table 68, p. 126.

4.2.8 The BRAVO study (Interferon beta-1a)

BRAVO was a multinational, multicentre, randomized, parallel-group study performed in subjects with RRMS to assess the efficacy, safety, and tolerability of laquinimod over placebo in a double-blind design and a reference arm of Interferon beta-1a in a rater-blinded design. [9]

The primary endpoint was ARR over a 24-month period. A confirmed relapse was defined as the appearance of one or more new neurological abnormalities, or reappearance of one or more previously observed neurological abnormalities, in the absence of fever, persisting for ≥48 h, preceded by ≥30 days of a stable or improving condition, and accompanied

by at least one of the following: an increase of at least 0.5 point in EDSS score, an increase of one grade in the score of two of the seven functional systems (FS) on the EDSS, or an increase of two grades in one FS. Secondary endpoints included percent brain volume change (PBVC) and 3-month confirmed disability worsening. This definition is similar to the definitions of the FREEDOMS and TRANSFORMS studies (see Appendix 7.1.2). [9]

Key eligibility criteria included age 18–55 years, diagnosis of RRMS (revised McDonald criteria [11]), and EDSS scores of 0.0–5.5. Patients must have had at least one relapse in the previous 12 months, two relapses in the previous 24 months, or one relapse in the previous 12–24 months plus one Gadolinium enhancing (GdE) lesion in the previous 12 months. [9]

The main study characteristics of the BRAVO study are summarized in Table 69 (p. 129).

4.2.9 MS inclusion criteria across studies

The main inclusion criteria are shown in Table 6. Baseline characteristics and further study details are presented in the main study characteristics in section 4.2 and the tables in section 7.1.2.

Table 6 Inclusion criteria for MS

Study	Inclusion criteria MS	MS Criteria
RADIANCE[2]	EDSS 0.0-5.0 ≥1 relapse in the last 12 mo OR 1 relapse in the last 24 mo with ≥1 Gd+ lesion	McDonald 2010
SUNBEAM[3]	EDSS 0.0-5.0 ≥1 relapse past yr or ≥2 in past 2 yrs AND ≥1 Gd+ lesion MS duration ≥15 yrs with EDSS≤2 excluded	McDonald 2010
CONFIRM[4]	EDSS 0.0-5.0 ≥1 relapse in last yr OR ≥1 Gd+ lesion in past 6 wks	McDonald 2005
DEFINE[5]	EDSS 0.0-5.0 ≥1 relapse in past yr OR ≥1 Gd+ lesion within 6 mo	McDonald 2005
FREEDOMS[6]	EDSS 0.0-5.5 ≥1 relapse/yr for one or two yrs No relapse in last 30 days	McDonald 2005
FREEDOMS II[7]	EDSS 0.0-5.5 ≥1 relapse in past yr or ≥2 relapses in past 2 yr	McDonald 2005
TRANSFORMS[8]	EDSS 0.0-5.5 ≥1 relapse in past yr or ≥2 in the last 2 yr No relapse in last 30 days	McDonald 2005
BRAVO[9]	EDSS 0.0-5.5 ≥1 relapse in a 1 yr period within the last 2 yr	McDonald 2005

4.3 Evidence networks

A network of evidence was generated to connect the ozanimod data with that for dimethyl fumarate (clinical question 1) and fingolimod (clinical question 2), respectively. In order to connect the network, the BRAVO study comparing interferon beta-1a and placebo was hand searched outside of the DMC provided search string and added to the list of relevant studies. As outcomes were considered to be independent of follow-up time, 12- and 24-month data were pooled in the analysis. The proportion of patients with a history of prior disease modifying treatments varied between the trials

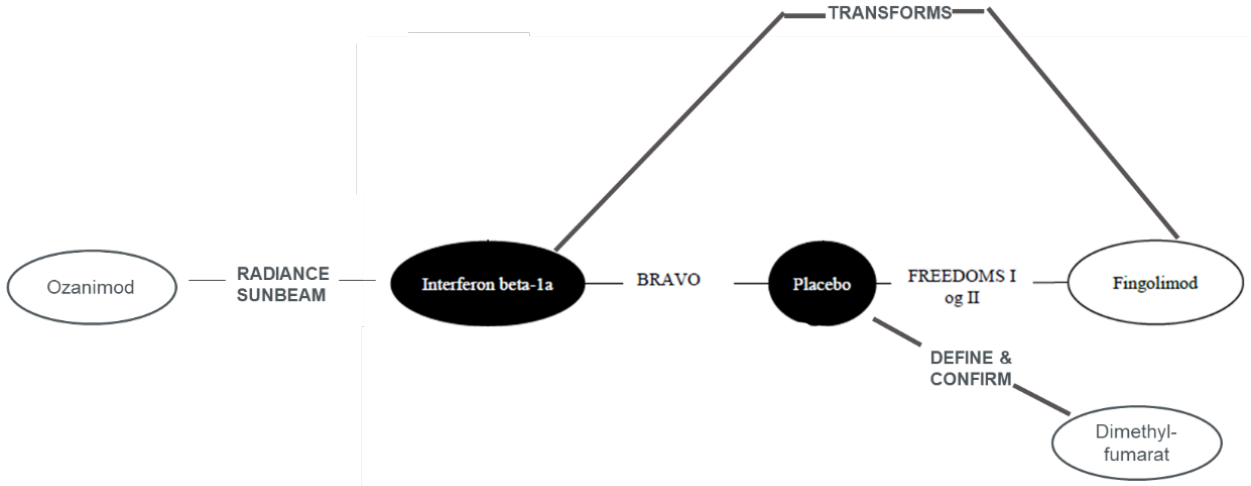
included in the network, and outcomes were in several trials not reported separately for the subgroups with prior treatment or not. Of note, the network relied on the inclusion of the BRAVO trial, in which >90 percent of patients had no prior treatment. Thus, the data did not allow for separate networks for the subgroups with prior or no prior treatment.

The network was connected for confirmed disability progression at 3 months (CDP3) and ARR. Definitions of ARR varied across studies but were considered sufficiently comparable to perform a statistical analysis. The definitions are explained in the Appendix 7.1.2.

For adverse drug reactions (ADR), the evidence network could not be connected. Instead, serious adverse events (SAE) and adverse events (AE) were used for which there was data available to allow the network to be connected. For cognitive function (SDMT) and quality of life (MSQOL-54), the evidence network could not be connected.

Figure 2 presents a general network of evidence for question 1 and 2 combined.

Figure 2: Network of evidence for question 1 and question 2



Note: The nodes represent the interventions in the network and the lines between the nodes represent the available direct comparisons between pairs of interventions.

4.4 Methodological approach

4.4.1 Network meta-analysis

For the analysis, a Bayesian network meta-analysis (NMA) approach was selected, as an indirect treatment comparison (ITC) requires a pairwise comparison one at a time. Bias in original studies may be magnified if the two sets of studies for the ITC are biased in opposite directions. For example, it is possible that the relative effect of a treatment versus the common comparator is over-estimated in one set of studies, and under-estimated in another set of studies. Under this circumstance, the ITC estimate will be biased, and the extent of such bias will be greater than the extent of bias in the original studies. The NMA approach is credited with the ability to conclude from both direct and indirect evidence by pooling results statistically across treatments to obtain the pooled estimate, a combined weighted average. When the simulated primary studies are not systematically biased, the ITC and NMA methods are not systematically biased, although the ITC method has the largest mean squared error and thus the lowest certainty.

The NMA was conducted using Bayesian approach, in order to meet the differing requirements of reimbursement and technology assessment organizations. The results were presented as rate ratio, hazard ratio (HR) and relative risk (RR).

The NMA was conducted within a generalized linear model framework, which has the flexibility to adapt to the structure of the data in line with the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) guidelines [12]. The actual estimation was undertaken utilizing Markov Chain Monte Carlo techniques using the statistical

package WinBUGS 1.4.3. This context requires the specification of prior distributions for parameters. The code for the comparison was based on that recommended by the NICE DSU.[13]

Both fixed and random effects models were considered as part of this analysis. In the fixed effects model, it is assumed that each study in the network is generating a common true effect, with between study variations in effect arising from sampling error. In the random effects model, the effect of treatment in each study is assumed to come from a common distribution of effects, with between study variation in effect arising from sampling error and heterogeneity between the studies. In the base case, vague prior distributions were used for all parameters in the model.

Three chains were run for each model. Convergence and lack of autocorrelation were confirmed with autocorrelation plots after a 100,000-simulation burn-in phase. DIC and residual deviance are comparable for fixed and random effects models. Both models generated equally plausible effect estimates based on residual deviance and DIC statistics, the simpler fixed effects model was preferred to a complex random effects model for parsimony and interpretability.

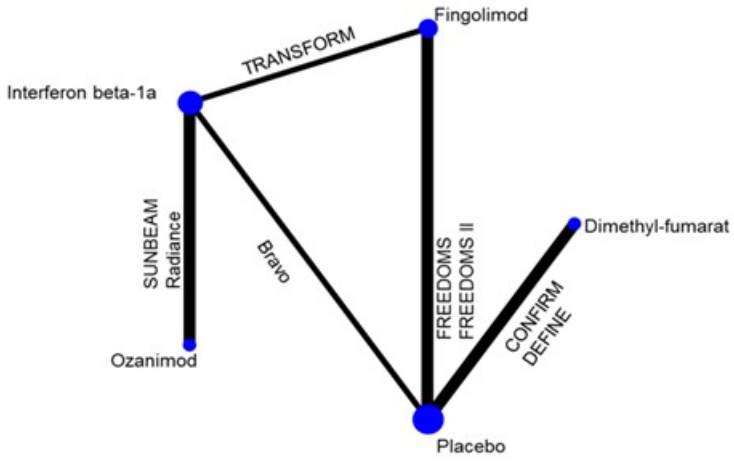
The NMA model estimates HR for CDP3 assuming a binomial likelihood and cloglog link function and relative ARR assuming a Poisson distribution for number of relapses within one study arm. For binary outcomes (AEs and SAEs), a generalized linear regression model with binomial likelihood and logit link was used. The data for each treatment in each study follows a binomial distribution.

$r_{j,k}$~ Binomial ($p_{j,k}$, $n_{j,k}$), where $p_{j,k}$ is the probability of experiencing the event during treatment k in study j, $r_{j,k}$ denotes the number of patients that experienced the event, and $n_{j,k}$ is the total number at risk. The WinBUGS models were based on recommendations from [13]. Placebo was taken as the reference treatment (coded as treatment 1) in all NMA models. The relative treatment effect between two interventions was expressed as relative risk with 95% credible intervals (CrI).

4.4.1.1 Assessment of consistency in the network meta-analysis

Consistency can be examined if direct and indirect evidence are available for comparison simultaneously. Hence, inconsistency tests are feasible only when at least a single loop is present in the network. In the evidence network, there is one closed loop, connecting the nodes interferon beta-1a, fingolimod and placebo (Figure 3).

Figure 3: Network of evidence



Bucher's method was used to evaluate the inconsistency in the evidence network as it provides a comparison of "direct" and "indirect" data in a closed loop. It compares the direct and indirect evidence within each loop with the null hypothesis of consistency. The test was repeated for each outcome of interest in the network (ARR, CPD3, Aes and SAEs). The inconsistency factor was calculated as the difference between direct and indirect estimates. Significant inconsistency was not found for any outcome of interest in the loop by direct and indirect evidence. Results for the inconsistency

evaluations are presented below in Appendix section 7.1.4, for each of the outcomes of interest (Table 54 to Table 57 and Figure 4 to Figure 7).

4.4.2 Comparative analyses methodology

The comparative analyses was based on the NMA described above. The assumed event rate used in the calculations for the absolute differences were based on the average event rate of the studies included in the NMA (see Appendix section 7.1.13 for detailed information on the comparative analyses).

The absolute differences between the comparators were calculated using the formula in the DMC methodology handbook, version 2.6, Appendix 5; $RD = ACR*RR-ACR$ [14]. For CDP3 the following formula from Appendix 6 was used; e^ln(ACR)$*HR-ACR$ [14]. The absolute differences for CDP3 are based on the proportion of patients without 3-month EDSS progression. Median rate ratios, median HRs or median risk ratios were used throughout the analyses.

In a Bayesian NMA the frequentist P-values are not applicable. Uncertainty around the effect estimate is based on the provided 95% CrI. The distinction between frequentist confidence interval (CI), and the Bayesian credibility interval (CrI), is therefore made throughout the document. Model fit can be evaluated with the deviance information criteria (DIC) and total residual deviance presented for each variable below.

Table 7 Total residual deviance and DIC

ARR (12/24 Months): Random effect model					
Parameter	Median	LCrI	UCrI	Mean	SD
Total residual deviance	15.04	7.16	27.62	15.62	5.21
DIC					
Total	136.61				
CDP3 (or 12) (12/24 Months): Random effect model					
Parameter	Median	LCrI	UCrI	Mean	SD
Total residual deviance	16.12	9.14	27.90	16.76	4.89
DIC					
Total	119.66				
AEs (12/24 Months): Random effect model					
Parameter	Median	LCrI	UCrI	Mean	SD
Total residual deviance	13.25	5.95	25.87	13.95	5.13
DIC					
Total	113.51				
SAEs (12/24 Months): Random effect model					
Parameter	Median	LCrI	UCrI	Mean	SD
Total residual deviance	14.33	6.61	27.02	15.00	5.24
DIC					
Total	114.91				

Abbreviations: AE, adverse event; ARR, annualised relapse rate; CDP3, confirmed disease progression at 3 months; DIC, deviance information criterion; LCrI, lower credibility interval; SAE, severe adverse events; SD, standard deviation; UCrI, upper credibility interval.

5 Clinical questions

5.1 Clinical question #1: What is the value of ozanimod compared to dimethyl fumarate for patients with RRMS and average disease activity (first line treatment)?

5.1.1 Presentation of relevant studies

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

For ozanimod

- RADIANCE (see section 4.2.1, p. 16, and Table 58, p. 102 for details)
- SUNBEAM (see section 4.2.2, p. 16, and Table 60 p. 108 for details)

For dimethyl fumarate

- CONFIRM (see section 4.2.3, p.17, and Table 62, p. 115 for details)
- DEFINE (see section 4.2.4, p. 17, and Table 58, p. 115 for details)

Interferon beta-1a

- BRAVO (see section 4.2.8, p 18, and Table 69 (p. 129).

5.1.2 Results per study

For a full listing of study results for the RADIANCE, SUNBEAM, DEFINE, CONFIRM and BRAVO studies, please refer to Table 71, Table 72, Table 73, Table 74 and Table 78, respectively.

Confirmed disability progression at 3 months

CDP3 was a secondary outcome in the ozanimod study, RADIANCE, and in the dimethyl fumarate studies, CONFIRM and DEFINE. In Cohen 2019 publication[2] for ozanimod, data for the pooled RADIANCE and SUNBEAM studies was also included. Study results are outlined in Table 8, Table 9 and Table 10, respectively.

Disability progression was assessed as a prespecified pooled analysis with data from both the RADIANCE and SUNBEAM studies, where studies were conducted concurrently and reported separately. Data for the RADIANCE studies alone is also available. CDP3 was defined as EDSS worsening of ≥1-point increase, confirmed after 3 months.

In the pooled analysis, 7.6% of patients in the ozanimod study arm (n=880) vs 7.8% for interferon beta-1a (n=889) achieved CDP3 (HR: 0.95; 95%CI 0.68 – 1.33; p=0.7651). [2] For RADIANCE alone, 12.5% of patients in the ozanimod study arm (n=433) vs 11.3% for interferon beta-1a (n=441) achieved CDP3 (HR: 1.05; 95%CI 0.71 – 1.54; p=0.8334). [2]

In CONFIRM and DEFINE, CDP3 was defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later. In CONFIRM, For CDP3, 13% of patients in the dimethyl fumarate 2x/daily study arm (n=359) vs 17% for placebo (n=363) achieved CDP3 (HR: 0.79; 95%CI 0.52 – 1.19; p=0.25). In DEFINE, for CDP3, 16 % of patients in the dimethyl fumarate 2x/daily study arm (n=409) vs 27% for placebo (n=408) achieved CDP3 (HR: 0.62; 95% CI 0.44 – 0.87; p=0.005). [4, 5]

As the ozanimod studies (versus: interferon-beta 1a) did not have the same comparator as the dimethyl fumarate studies (versus: placebo), the BRAVO study for interferon beta-1a versus placebo was identified through the DMC treatment guidelines and required to connect the network of evidence. In the BRAVO study, 10% of patients in the interferon beta-1a study arm (n=447) vs 13% for placebo (n=450) achieved CDP3 (HR: 0.74; 95%CI 0.51 – 1.09; p=0.13).[9]

Table 8: Confirmed Disability Progression at 3 months (CDP3) study data for ozanimod

	RADIANCE (24 month) [2]		**Pooled RADIANCE and SUNBEAM (pooled 12 and 24 month) [2]**	
	Ozanimod 1mg N=433	IFN beta-1a N=441	Ozanimod 1mg N=880	IFN beta-1a N=889
Persistent disease progression confirmed after 3 months (confirmed disease progression over 3 months, CDP3), n (%)	54 (12.5)	50 (11.3)	67 (7.6)	69 (7.8)
Estimated relative difference in effect, HR (95% CI, p-value)	1.05 (0.71 – 1.54; 0.8334)		0.95 (0.68 – 1.33; 0.7651)	

Abbreviations: CDP3, confirmed disability progression at 3 months; CI, confidence interval; HR, hazard ratio; IFN, interferon.

Table 9: Confirmed Disability Progression at 3 months (CDP3) study data for dimethyl fumarate

	DEFINE (24 month) [4]		**CONFIRM (24 month) [5]**	
	DMF 2x/daily N=409	Placebo N=408	DMF 2x/daily N=359	Placebo N=363
Persistent disease progression confirmed after 3 months (confirmed disease progression over 3 months, CDP3), n (%)	65 (16)	110 (27)	47 (13)	62 (17)
Estimated relative difference in effect, HR (95% CI, p-value)	0.62 (0.44 – 0.87; 0.005)		0.79 (0.52 – 1.19; 0.25)	

Abbreviations: CDP3, confirmed disability progression at 3 months; CI, confidence interval; DMF, dimethyl fumarate; HR, hazard ratio.

Table 10: Confirmed Disability Progression at 3 months (CDP3) for BRAVO

	BRAVO (24 month) [9]	
	IFN beta-1a N=447	Placebo N=450
Persistent disease progression confirmed after 3 months (confirmed disease progression over 3 months, CDP3), n (%)	47 (11)	60 (13)
Estimated relative difference in effect, HR (95% CI, p-value)	0.74 (0.51 – 1.09; 0.13)	

Abbreviations: CDP3, confirmed disability progression at 3 months; CI, confidence interval; HR, hazard ratio; IFN, interferon.

Lack of significant difference on CDP measures is not unprecedented in multiple sclerosis clinical studies of disease-modifying therapies (DMTs) versus interferons and likely reflects short duration of follow-up, low event rates, and lack of power for the CDP endpoint.

In both RADIANCE and SUNBEAM, rates of CDP, defined as worsening in EDSS of ≥1 point confirmed at 3 or 6 months, were low in each treatment group.

The low event rates may reflect patient characteristics in the ozanimod clinical studies. Patient characteristics in RRMS studies have changed over time, leading to patients with milder disease in more recent studies compared with historical populations.[15, 16]

Like in other recent studies in RRMS, patient baseline characteristics (mean age, 36 years; mean time since symptom onset, 6.7 years; mean EDSS, 2.6) reflected a population with mild to moderate disease. Moreover, approximately 70% of patients in the ozanimod clinical studies were treatment naive. These characteristics are consistent with a population with low likelihood of disability progression.

This phenomenon was previously shown in the CARE-MS studies of alemtuzumab, wherein rates of CDP-6M were lower in the treatment-naive patients in CARE-MS I[17] (alemtuzumab, 8.0%; interferon beta-1a, 10.7%) compared with previously treated patients in CARE-MS II (alemtuzumab, 12.7%; interferon beta-1a, 19.8%).[18] This was also

shown in a real-world study of fingolimod wherein CDP3 occurred in none of the treatment-naive patients versus 8.9% of patients who switched to fingolimod because of drug failure.[19]

The impact of low event rates is further evident when examining the powering assumptions for the pooled analysis. SUNBEAM and RADIANCE were powered for the primary endpoint of ARR, not for CDP3.[2, 3] The power analysis for CDP3 was based on historical rates of CDP in studies of interferon beta-1a (8% to 30%) [8, 9, 20-23] and an approximate minimum treatment difference in CDP of 6%, which suggested the proposed study sample size was adequate for CDP in the pooled analysis. However, this assumed 6% between-group difference in CDP-3 was not observed in the 1-year TRANSFORMS study of fingolimod 0.5 mg, a therapy with a similar mode of efficacy and study design to that of ozanimod. In the TRANSFORMS study, a 2% difference in CDP rates between fingolimod 0.5 mg (6% progression rate) and interferon beta-1a (8% progression rate) was observed.[8] Based on this 2% observed difference in CDP rates, a total of 5082 patients and 356 events would have been needed to achieve 80% power to detect a significant difference between ozanimod 1 mg and interferon beta-1a. In contrast, the total sample size in the ozanimod pooled analysis was 1769 patients, and the total number of events observed for CDP3 was 136.[2] As a result, the ozanimod pooled analysis had approximately 41% power to detect a significant difference in CDP-3M and was underpowered to show a benefit versus interferon beta-1a on this endpoint.

Serious adverse events and adverse events

As neither the ozanimod study nor the comparator studies for dimethyl fumarate reported on ADRs, comparisons of SAEs and AEs were reported to provide quantitative measures for the safety profile.

For a comprehensive qualitative review of the safety profile of ozanimod and dimethyl fumarate, see section 5.3 (p. 34).

In RADIANCE and SUNBEAM studies, 6.5% (of n=434) and 2.9% (of n=448) of ozanimod patients reported SAEs, respectively, while 6.4% (of n=440) and 2.5% (of n=445) of interferon beta-1a reported SAEs, respectively (RR: 1.01; 95% CI 0.611-1.683; p= 0.9576 and RR: 1.17; 95% CI 0.530-2.586; p=0.6957) (Table 11). [2, 3]

In DEFINE and CONFIRM studies, 18% (of n=410) and 17% (of n=359) of dimethyl fumarate 2x/daily patients reported SAEs, respectively, while 15% (of n=408) and 22% (of n=363) of placebo patients reported SAEs, respectively (RR: 0.86; 95% CI 0.648-1.132; p= 0.2755) (Table 12). [4, 5]

In the BRAVO study, 7.7% (of n=442) and 12.0% (of n=449) reported SAEs in the interferon beta-1a and placebo groups, respectively (RR: 0.64; 95% CI 0.425-0.962; p=0.0320) (Table 13). [9]

Table 11: Serious adverse events study data for ozanimod

	RADIANCE (24 month) [2]		**SUNBEAM (12 month) [3]**	
	Ozanimod 1mg N=434	IFN beta-1a N=440	Ozanimod 1mg N=448	IFN beta-1a N=445
Serious adverse events, n (%)	n=28 (6.5)	n=28 (6.4)	n=13 (2.9)	n=11 (2.5)
Estimated relative difference in effect, RR (95% CI, p-value)	1.01 (0.611-1.683; 0.9576)		1.17 (0.530-2.586; 0.6957)	

Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon.

Table 12: Serious adverse events study data for dimethyl fumarate

	DEFINE (24 month) [4]		**CONFIRM (24 month) [5]**	
	DMF 2x/daily N=410	Placebo N=408	DMF 2x/daily N=359	Placebo N=363
Serious adverse events, n (%)	n=74 (18)	n=86 (21)	n=61 (17)	n=79 (22)
Estimated relative difference in effect, RR (95% CI, p-value)	0.86 (0.648-1.132; 0.2755)		0.78 (0.578-1.055; 0.1065)	

Abbreviations: CI, confidence interval; DMF, dimethyl fumarate; RR, risk ratio.

Table 13: Serious adverse events the BRAVO study

	BRAVO (24 month) [9]	
	IFN beta-1a N=442	Placebo N=449
Serious adverse events, n (%)	n=34 (7.7)	n=54 (12)
Estimated relative difference in effect, RR (95% CI, p-value)	0.64 (0.425-0.962; 0.0320)	

Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon.

With respect to AEs observed in the RADIANCE and SUNBEAM studies, 75.1% (of n=434) and 60% (of n=448) of ozanimod patients reported AEs, respectively, while 83% (of n=440) and 75.5% (of n=445) of interferon beta-1a reported AEs, respectively (RR: 0.91; 95%CI 0.845-0.970; p= 0.0047 and RR: 0.79; 95%CI 0.722-0.869; p <0.0001) (Table 14). [2, 3]

In the DEFINE and CONFIRM studies, 96.3% (of n=410) and 94.2% (of n=359) of dimethyl fumarate 2x/daily patients reported AEs, respectively, while 94.9% (of n=408) and 91.7% (of n=363) of placebo patients reported AEs, respectively (RR: 1.02; 95%CI 0.986-1.046; p= 0.2999 and RR:1.03; 95%CI 0.986-1.069; p=0.2055)) (Table 15).[5] [4]

In the BRAVO study, 82% (of n=442) and 70% (of n=433) reported AEs in the interferon beta-1a and placebo groups, respectively (RR: 0.93; 95%CI 0.858-1.011; p=0.0886) (Table 16). [9]

Table 14: Adverse events study data for ozanimod

	RADIANCE (24 month) [2]		**SUNBEAM (12 month)[3]**	
	Ozanimod 1mg N=434	IFN beta-1a N=440	Ozanimod 1mg N=448	IFN beta-1a N=445
Adverse events, n (%)	326 (75.1)	365 (83.0)	268 (60.0)	336 (75.5)
Estimated relative difference in effect, RR (95% CI, p-value)	0.91 (0.845-0.970; 0.0047)		0.79 (0.722-0.869; <0.0001)	

Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon.

Table 15: Adverse events study data for dimethyl fumarate

	DEFINE (24 month) [4]		**CONFIRM (24 month) [5]**	
	DMF 2x/daily N=410	Placebo N=408	DMF 2x/daily N=359	Placebo N=363
Adverse events, n (%)	395 (96.3)	387 (94.9)	338 (94.2)	333 (91.7)
Estimated relative difference in effect, RR (95% CI, p-value)	1.02 (0.986-1.046; 0.2999)		1.03 (0.986-1.069; 0.2055)	

Abbreviations: CI, confidence interval; DMF, dimethyl fumarate; RR, risk ratio.

Table 16: Adverse events data for BRAVO

	BRAVO (24 month) [9]	
	IFN beta-1a N=442	Placebo N=433
Adverse events, n (%)	362 (82)	303 (70)
Estimated relative difference in effect, RR (95% CI, p-value)	0.93 (0.858-1.011; 0.0886)	

Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon.

Annualised relapse rate

ARR was a primary outcome in the ozanimod studies, RADIANCE and SUNBEAM, and the dimethyl fumarate studies, CONFIRM and DEFINE.

In RADIANCE, ARR was 0.17 (95%CI 0.14 – 0.21) for patients in the ozanimod study arm (n=433) vs 0.28 (95%CI 0.23 – 0.32) for interferon beta-1a (n=441) (rate ratio: 0.62; 95%CI 0.51-0.77; p<0.0001) (Table 17). [2] In SUNBEAM, ARR was 0.18 (95%CI 0.14 – 0.24) for patients in the ozanimod study arm (n=447) vs 0.35 (95%CI 0.28 –0.44) for interferon beta-1a (n=448) (rate ratio: 0.52; 95%CI 0.41-0.66; p <0.0001) (Table 17).[3]

In CONFIRM, ARR was 0.22 (95%CI 0.18 – 0.28) for patients in the dimethyl fumarate 2x/daily study arm (n=359) vs 0.40 (95% CI 0.33–0.49) for placebo (n=363) (rate ratio: 0.55; 95%CI 0.437-0.695; p<0.0001) (Table 18).[4]). In DEFINE, ARR was 0·17 (95%CI 0.14 – 0.21) for patients in the dimethyl fumarate 2x/daily study arm (n=410) vs 0.36 (0.30–0.44) for placebo (n=408) (rate ratio 0.47; 95%CI 0.37 – 0.61; p <0.001) (Table 18). [5]

In the BRAVO study, ARR was 0.26 (SD: 0.02) of patients in the interferon beta-1a study arm (n=447) vs 0.34 (SD:0.03) for placebo (n=450) (rate ratio: 0.74; 95%CI 0.60 – 0.92; p=0.007) (Table 19). [9]

Table 17: Annualised Relapse Rate study data for ozanimod

	RADIANCE (24 month) [2]		**SUNBEAM (12 month)[3]**	
	Ozanimod 1mg (N=433)	IFN beta-1a (N=441)	Ozanimod 1mg (N=447)	IFN beta-1a (N=448)
Annualised relapse rate, (95% CI)	0.17 (0.14 – 0.21)	0.28 (0.23 – 0.32)	0·18 (0.14 – 0.24)	0·35 (0.28 –0.44)
Estimated relative difference in effect, rate ratio (95% CI, p-value)	0.62 (0.51-0.77; <0.0001)		0.52 (0.41–0.66; <0.0001)	

Abbreviations: CI, confidence interval; IFN, interferon.

Table 18: Annualised Relapse Rate study data for dimethyl fumarate

	DEFINE (24 month) [4]		**CONFIRM (24 month) [5]**	
	DMF 2x/daily N=410	Placebo N=408	DMF 2x/daily N=359	Placebo N=363
Annualised relapse rate, (95% CI)	0.17 (0.14–0.21)	0.36 (0.30–0.44)	0.22 (0.18–0.28)	0.40 (0.33–0.49)
Estimated relative difference in effect, rate ratio (95% CI, p-value)	0.47 (0.37 – 0.61; <0.001)		0.55 (0.437-0.695; <0.0001)	

Abbreviations: CI, confidence interval; DMF, dimethyl fumarate.

Table 19: Annualised Relapse Rate data for BRAVO

	BRAVO (24 month) [9]	
	IFN beta-1a N=447	Placebo N=450
Annualised relapse rate, n (SD)	0.26 (0.02)	0.34 (0.03)
Estimated relative difference in effect, rate ratio (95% CI, p-value)	0.74 (0.60 – 0.92; 0.007)	

Abbreviations: CI, confidence interval; IFN, interferon; SD, standard deviation.

Cognitive function

While the evidence network for the SDMT could not be connected, the ozanimod study, SUNBEAM, has reported SDMT as a component of the multiple sclerosis functional composite for assessment of cognitive processing speed (secondary outcome); however, data for patients who avoided a 10% worsening was not available in the clinical study. [3] Further, SDMT was not an outcome of the dimethyl fumarate studies. [4, 5]

Data was available for mean change from baseline to month 12. The mean change from baseline to 12 months in SDMT for ozanimod (n=450) was 0.061 (SD: 0.552) vs - 0.029 (SD: 0.508) for interferon beta-1a (n=448) (Table 20). [3]

Table 20: Symbol Digital Modality Test for ozanimod in SUNBEAM

	SUNBEAM (12 month)[3]	
	Ozanimod 1mg (N=447)	IFN beta-1a (n=448)
Mean change from baseline to 12 months, n (SD)	0.073 (0.653)	–0.029 (0.508)
Estimated absolute difference in effect, difference (95% CI; p-value)	1.642 (0.104 to 3.180; 0.0024)	

Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon; SD, standard deviation.

Mean change in MSFC score from baseline to month 12 was similar across treatment groups, but mean change in SDMT Z score was greater for both ozanimod groups than in the interferon beta-1a group. [3]

Mean change in SDMT Z score was numerically greater (nominal p<0.05) in both ozanimod groups versus interferon beta-1a, suggesting potential beneficial effects on cognitive processing speed. Although the MSFC was originally designed to include the paced auditory serial addition test as an assessment of cognitive processing, the SDMT is considered an acceptable alternative that is at least as sensitive, if not more so.[24] SDMT has been used as an assessment of cognitive processing speed in studies of patients with multiple sclerosis versus healthy controls and in studies of other disease-modifying therapies for multiple sclerosis[25, 26].[3]

Quality of life

While the evidence network could not be connected for the 54-item Multiple Sclerosis Quality of Life (MSQOL-54), the ozanimod studies, RADIANCE and SUNBEAM, have reported MSQOL-54 as separate outcomes of the physical and mental health composite scores. [2, 3]

MSQOL-54 was not an outcome of the dimethyl fumarate studies. [4, 5] However, HRQoL was assessed by SF-36 and EQ-5D, and an integrated analysis of the data from the two studies was published by Kita et al in 2014.[27]

In the RADIANCE study, MSQOL-54 was mean change from baseline measured to 24-month change. For the physical health composite score, mean change from baselines for ozanimod (n=433) was 0.209 (SD: 12.321) vs -1.526 (SD: 12.319) for interferon beta-1a (n=441) (difference in effect: 1.345; –0.252 to 2.943; p=0.0988). For the mental health composite score, mean change from baselines for ozanimod (n=433) was -1.517 (SD: 15.544) vs -1.831 (SD: 16.422) for interferon beta-1a (n=441) (difference in effect: 0.380; -1.553 to 2.313; p=0.6997) (Table 21). [2]

In the SUNBEAM study, MSQOL-54 was mean change from baseline measured to 12-month change. For the physical health composite score, mean change from baselines for ozanimod (n=443) was 1.925 (SD: 11.870) vs 0.046 (SD: 12.578) for interferon beta-1a (n=445) (difference in effect: 1.642; 0.104 to 3.180; p=0.0364). For the mental health composite score, mean change from baselines for ozanimod (n=446) was 0.260 (SD: 15.800) vs -0.123 (SD: 15.240) for interferon beta-1a (n=448) (difference in effect: 1.642; 0.104 to 3.180; p=0.7104 (Table 21). [3]

Table 21: 54-item Multiple Sclerosis Quality of Life outcomes in the ozanimod studies

	RADIANCE (24 month) [2]				SUNBEAM (12 month) [3]			
	Physical health composite score		Mental health composite score		Physical health composite score		Mental health composite score	
	Ozanimod 1mg (N=433)	IFN beta-1a (N=441)	Ozanimod 1mg (N=433)	IFN beta-1a (N=441)	Ozanimod 1mg (N=443)	IFN beta-1a (n=445)	Ozanimod 1mg (N=446)	IFN beta-1a (N=448)
Mean change from baseline§, n (SD)	0.209 (12.321)	–1.526 (12.319)	–1.517 (15.544)	–1.831 (16.422)	1·925 (11·870)	0·046 (12·578)	0·260 (15·800)	–0·123 (15·240)
Estimated absolute difference in effect, difference (95% CI; p-value)	1.345 (–0.252 – 2.943; 0.0988)†		0.380 (–1.553 – 2.313; 0.6997) †		1.642 (0·104 – 3·180; 0.0364)		1.642 (0·104 – 3·180; 0.7104)	

§Missing data imputed using a mixed-effects regression model (random slope and intercept). †Difference in means and p values for comparison between ozanimod and interferon beta-1a are based on the analysis of covariance model, adjusted for region (eastern Europe *vs* rest of world), expanded disability status scale category at baseline, and baseline value of interest.
Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon; SD, standard deviation.

In the dimethyl fumarate studies, for SF-36, at 2 years, the delayed-release dimethyl fumarate BID and TID groups had significantly increased mean PCS and MCS scores, suggesting improvements in physical and mental functioning, whereas the placebo group had decreased mean PCS and MCS scores. [27]

At 2 years, the changes from baseline in mean PCS score were +0.47, +0.43, and -1.05 in delayed release dimethyl fumarate BID and TID and placebo groups, respectively (both, P<0.0001 vs placebo). The differences in PCS scores compared with placebo were significant at all time points over 2 years with delayed release dimethyl fumarate BID and at weeks 48 and 96 with delayed-release dimethyl fumarate TID. [27]

At 2 years, the changes from baseline in mean MCS score were +0.31, +0.63, and -0.60 in the delayed-release dimethyl fumarate BID or TID and placebo groups (P=0.0246 and P=0.0107 vs placebo, respectively). The mean changes in MCS score were numerically but not significantly higher with delayed-release dimethyl fumarate-treated compared with placebo at weeks 24 and 48. [27]

For EQ-5D the mean (SD) baseline EQ-5D index scores were 0.72 (0.22), 0.71 (0.23), and 0.71 (0.23) in the delayed-release dimethyl fumarate BID and TID and placebo groups, respectively. At 2 years, the delayed-release dimethyl fumarate groups had significantly improved mean EQ-5D index scores compared with the placebo group: The mean changes in EQ-5D index scores from baseline to 2 years were +0.01, +0.01, and -0.01 in the delayed-release dimethyl fumarate BID and TID and placebo groups (P=0.0239 and P=0.0141 vs placebo). The mean changes in EQ VAS score from baseline to 2 years were -0.90, - 0.31 and -3.37 in the delayed-release dimethyl fumarate BID and TID and placebo groups, respectively (P=0.0011 and P=0.0002 vs placebo) (data not reported). [27]

5.1.3 Comparative analyses of ozanimod and dimethyl fumarate

All results have been calculated according to the methodology described in section 4.4. See appendix in 7.1.13 for detailed information on the comparative analyses.

Confirmed Disability Progression at 3 months

The NMA did not show a statistically significant difference between ozanimod vs dimethyl fumarate on the CDP3 outcome (HR: 1.32; 95% CrI: 0.48 - 3.25). The absolute difference, with an assumed proportion of patients without 3-month EDSS progression of 86% for dimethyl fumarate, was 5% (CrI: -8% - 28%). HRs and absolute differences are presented in Table 79.

Serious adverse events and adverse events

The NMA did not show a statistically significant difference between ozanimod vs dimethyl fumarate on the SAE outcome (RR: 0.92; 95% CrI: 0.37 - 2.23). The absolute difference, with an assumed event rate of 18% for dimethyl fumarate, was -1.48% (CrI: -11% - 22%). RRs and absolute differences are presented in Table 79.

Comparably, the NMA did not show a statistically significant difference between ozanimod vs. dimethyl fumarate on the AE outcome (RR: 0.98; 95% CrI: 0.92 - 1.04). The absolute difference, with an assumed event rate of 14% for dimethyl fumarate, was -2% (CrI: -8% - 4%). RRs and absolute differences are presented in Table 79.

For a qualitative review of the safety profile of ozanimod and fingolimod, please refer to section 5.3 (p. 34).

Annualised Relapse Rate

The NMA did not show a statistically significant difference between ozanimod vs dimethyl fumarate on the ARR outcome (rate ratio: 0.85; 95% CrI: 0.5 - 1.58). The absolute difference, with an assumed event rate of 0.20, for dimethyl fumarate was -0.03 (CrI: -0.10 - 0.11). Rate ratios and absolute differences are presented in Table 79.

Cognitive function

Neither the dimethyl fumarate studies, DEFINE or CONFRIM, reported on SDMT as an outcome [4, 5]. Therefore, a formal comparative analysis is not possible.

Quality of life

MSQOL-54 was not an outcome in either dimethyl fumarate study, DEFINE or CONFIRM, but HRQoL data for dimethyl fumarate was reported as EQ-5D and SF-36 (see section 5.1.2 (p. 28)). [4, 5]. Therefore, a formal comparative analysis is not possible.

5.2 Clinical question #2: What is the value of ozanimod compared to fingolimod for patients with RRMS and high disease activity (second line treatment)?

5.2.1 Presentation of relevant studies

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

For ozanimod

- RADIANCE (see section 4.2.1, p. 16, and Table 58, p. 102 for details)
- SUNBEAM (see section 4.2.2, p. 16, and Table 60 p. 108 for details)

For fingolimod

- FREEDOMS (see section 4.2.5, p. 17, and Table 66, p. 120 for details)
- FREEDOMS II (see section 4.2.6, p. 18, and Table 67, p. 122for details)
- TRANSFORMS (see section 4.2.7, p. 18, and Table 68, p. 126 for details)

Interferon beta-1a

- BRAVO (see section 4.2.8, p 18, and Table 69 (p. 129).

5.2.2 Results per study

For a full listing of study results for the RADIANCE, SUNBEAM, FREEDOMS, FREEDOMS II, TRANSFORMS, and BRAVO studies, please refer to Table 71, Table 72, Table 66, Table 67, Table 68, and Table 78, respectively.

Confirmed disability progression at month 3

CDP3 was a secondary outcome in the fingolimod clinical studies, FREEDOMS, FREEDOMS II, and TRANSFORMS. Confirmed disease progression was defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.[6-8]

CDP3 events in FREEDOMS, FREEDOMS II, and TRANSFORMS are reported in table below (Table 22).

The RADIANCE, pooled RADIANCE and SUNBEAM and BRAVO studies are described in Table 8 and Table 10 in section 5.1.2.

Table 22: Confirmed Disability Progression at week 12 (CDP3) study data for fingolimod

	FREEDOMS (24 month) [6]		**FREEDOMS II (24 month) [7]**		**TRANSFORMS (12 month) [8]**	
	Fingolimod 0.5mg N=425	Placebo N=418	Fingolimod 0.5mg N=358	Placebo N=355	Fingolimod 0.5mg N=429	IFN beta-1a N=431
Persistent disease progression confirmed after 3 months (confirmed disease progression over 3 months, CDP3), n (%)	75 (17.7)	101 (24.1)	91 (25.3)	103 (29.0)	25 (5.9)	34 (7.9)
Estimated relative difference in effect, HR (95% CI, p-value)	HR: 0.70 (0.52 – 0.96; 0.02)		HR: 0.83 (0.61 – 1.12; <0.001)		HR: 1.02 (0.986-1.060; 0.2321)	

Abbreviations: CDP3, confirmed progressed disease at 3 months; CI, confidence interval; HR, hazard ratio; IFN, interferon.

Serious adverse events and adverse events

For fingolimod, in the FREEDOMS, FREEDOMS II, and TRANSFORMS studies, 10.1% (of n=425), 15% (of n=358), and 7% (of n=429) of fingolimod 0.5mg patients reported SAE, respectively. For the control groups, 12.4% (of n=418) and 13% (of n=355) of placebo patients in the FREEDOMS and FREEDOMS II studies reported SAEs, respectively, and 5.8% (of n=431) of interferon beta-1a reported SAEs in the TRANSFORMS study (Table 23). [6-8]

The RADIANCE, SUNBEAM and BRAVO studies are described in Table 11 and Table 13 in section 5.1.2.

Table 23: Serious adverse event study data for fingolimod

	FREEDOMS (24 month) [6]		**FREEDOMS II (24 month) [7]**		**TRANSFORMS (12 month) [8]**	
	Fingolimod 0.5mg N=425	Placebo N=418	Fingolimod 0.5mg N=358	Placebo N=355	Fingolimod 0.5mg N=429	IFN beta-1a N=431
Serious adverse events, n (%)	n=43 (10.1)	n=56 (13.4)	53 (15)	n=45 (13)	n=30 (7.0)	n=25(5.8)
Estimated relative difference in effect, RR (95% CI, p-value)	0.76 (0.520-1.098; 0.1410)		1.17 (0.807-1.689; 0.4099)		1.21 (0.721-2.015; 0.4756)	

Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon.

An overview of the most frequent types of serious TEAEs for ozanimod and fingolimod is provided in Table 30 (p. 39).

With respect to AEs observed in the fingolimod studies, FREEDOMS, FREEDOMS II, and TRANSFORMS, 94% (n=425), 98% (n=358), and 86% (n=429) of fingolimod 0.5mg patients reported AEs, respectively. For the control groups, 93% (n=418) and 97% (n=355) of placebo patients in the FREEDOMS and FREEDOMS II studies reported AEs, respectively, and 92% (n=431) of interferon beta-1a reported AEs in the TRANSFORMS study (Table 24).[6-8]

The RADIANCE, SUNBEAM and BRAVO studies are described in Table 14 and Table 16 in section 5.1.2.

Table 24: Adverse event study data for fingolimod

	FREEDOMS (24 month) [6]		**FREEDOMS II (24 month) [7]**		**TRANSFORMS (12 month) [8]**	
	Fingolimod 0.5mg N=425	Placebo N=418	Fingolimod 0.5mg N=358	Placebo N=355	Fingolimod 0.5mg N=429	IFN beta-1a N=431
Adverse events, n (%)	401 (94.3)	387 (92.6)	350 (98)	343 (97)	369 (86.0)	395 (91.6)
Estimated relative difference in effect, RR (95% CI, p-value)	1.02 (0.983-1.056; 0.2992)		1.01 (0.987-1.037; 0.3550)		0.94 (0.895-0.984; 0.0090)	

Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon.

For a qualitative review of the safety profile of ozanimod and fingolimod, please refer to section 5.3 (p. 34).

Annualised Relapse Rate

In FREEDOMS, the ARR was 0.18 (95% CI 0.15 - 0.22) of patients in the fingolimod 0.5mg study arm (n=425) vs 0.40 (95% CI 0.34 – 0.47) for placebo (n=418). In FREEDOMS II, the ARR was 0.21 (95% CI 0.17 to 0.25) of patients in the fingolimod 0.5mg study arm (n=358) vs 0.40 (95% CI 0.34 - 0.48) for placebo (n=355). In TRANSFORMS, the ARR was 0.16 (95% CI 0.12 - 0.21) of patients in the fingolimod 0.5mg study arm (n=429) vs 0.33 (95% CI 0.26 - 0.42) for interferon beta-1a (n=431) (Table 25). [3, 6, 7]

The RADIANCE, SUNBEAM and BRAVO studies are described in Table 17 and Table 19 in section 5.1.2.

Table 25: Annualised relapse rate study data for fingolimod

	FREEDOMS (24 month) [6]		FREEDOMS II (24 month) [7]		TRANSFORMS (12 month) [8]	
	Fingolimod 0.5mg N=425	Placebo N=418	Fingolimod 0.5mg N=358	IFN beta-1a N=355	Fingolimod 0.5mg N=429	IFN beta-1a N=431
Annualised relapse rate, n (95% CI)	0.18 (0.15-0.22)	0.40 (0.34 – 0.47)	0.21 (0.17 to 0.25)	0.40 (0.34-0.48)	0.16 (0.12- 0.21)	0.33 (0.26-0.42)
Estimated relative difference in effect, rate ratio (95% CI, p-value)	0.45 (0.359-0.573; <0.0001)		0.52 (0.40-0.66; <0.0001)		0.49 (0.378-0.630; <0.0001)	

Abbreviations: CI, confidence interval; RR, risk ratio; IFN, interferon.

Cognitive function

Fingolimod studies did not report on SDMT as a cognitive function outcome. Therefore, a formal comparative analysis is not possible.

Quality of life

Data for quality of life in the fingolimod studies were reported only in the FREEDOMS II study. [7] Mean changes from baseline in EQ-5D utility score at 24 months were –0.014 (SD 0.179, p=0.290 vs placebo) in the fingolimod 1.25 mg group, –0.016 (0.199, p=0.328 vs placebo) in the fingolimod 0.5 mg group, and –0.004 (0.230) in the placebo group. Mean changes from baseline in EQ-5D Visual Analogue Scale score at month 24 were 1.11 (13.02, p=0.462 vs placebo) in the fingolimod 1.25 mg group, 0.04 (15.04, p=0.143 vs placebo) in the fingolimod 0.5 mg group, and –0·67 (15.21) in the placebo group. No statistically significant between-group differences for PRIMUS and MFIS measures were detected (data not shown). [7]

5.2.3 Comparative analyses of ozanimod and fingolimod

5.2.4 Baseline characteristics

The main inclusion criteria for the ozanimod, dimethyl fumarate and fingolimod studies are shown in Table 6 (p. 19). Baseline characteristics and further study details are presented in the main study characteristics in section 4.2 and the tables in section 7.1.2.

5.2.5 Results per outcome

All results have been calculated according to the methodology described in section 4.4. See appendices in section 7.1.13 for detailed information on the comparative analyses.

Confirmed disability progression at month 3

The NMA analysis did not show a statistically significant difference between ozanimod vs fingolimod on the CDP3 outcome (HR: 1.11; 95% CrI: 0.48 - 2.44). The absolute difference, with an assumed proportion of patients without 3-month EDSS progressionof 84% for fingolimod, was 2% (CrI: -8% - 19%). HRs and absolute differences are presented in Table 80.

Serious adverse events and adverse events

As mentioned in clinical question 1, the ozanimod studies did not report on ADR, as neither did the fingolimod studies. Thus, a comparison of SAEs has been conducted to present the safety profile.

The NMA did not show a statistically significant difference between ozanimod vs fingolimod on the SAE outcome (RR: 0.81; 95% CrI: 0.37 - 1.73). The absolute difference, with an assumed event rate of 11% for fingolimod, was -2% (95% CrI: -7% – 8%). RRs and absolute differences are presented in Table 80.

Comparably, the NMA did not show a statistically significant difference between ozanimod vs. fingolimod on the AE outcome (RR: 0.99; 95% CrI: 0.93 - 1.03). The absolute difference, with an assumed event rate of 93% for fingolimod, was -1% (95% CrI: -6% – 3%). RRs and absolute differences are presented in Table 80.

For a qualitative review of the safety profile of ozanimod and fingolimod, please refer to section 5.3 (p. 34).

Annualised Relapse Rate

The NMA did not show a statistically significant difference between ozanimod vs dimethyl fumarate on the ARR outcome (rate ratio: 0.98; 95% CrI: 0.61 – 1.69). The absolute difference, with an assumed event rate of 0.18 for fingolimod, was 0.00 (CrI: --0.07 - 0.13). Rate ratios and absolute differences are presented in Table 80.

Cognitive function

Neither of the fingolimod studies reported on SDMT as an outcome. [6-8] Therefore, a formal comparative analysis is not possible.

Quality of life

MSQOL-54 was not an outcome in either fingolimod study, FREEDOM, FREEDOM II or TRANSFORMS, although EQ-5D data was reported in the FREEDOMS II study. [6-8] Therefore, a formal comparative analysis is not possible.

5.3 Qualitative review of safety

In this section a review of the adverse drug reactions and adverse events for ozanimod, fingolimod and dimethyl fumarate is provided.

The section contains the following subsections

- Overall incidence of TEAEs, subdivided into all TEAEs, serious TEAEs, TEAEs leading to discontinuation, and death (p.34)
- Incidence of TEAEs per preferred term (MedDRA) (p. 34)
- Review of AE of special interest including
    - lymphopenia (p. 44)
    - infections (including opportunistic infections, HPV and PML) (p. 45)
    - macular oedema (p. 50)
    - malignancies (p. 51)
    - cardiac effects (p. 52)
    - hypertension (p. 55)
    - hepatic function (p. 56)
- Requirements and recommendations for monitoring before, during and after treatment initiation (p. 57)
- Frequency of Adverse Drug Reactions (p. 62)

In addition to data from the respective SmPCs and publications, findings from a matching-adjusted indirect comparison (MAIC) analysis published by Swallow has been included. [28]

Swallow et al conducted a matching-adjusted indirect comparison (MAIC) based on individual patient data from the RADIANCE and SUNBEAM studies for ozanimod and published summary level data, pooled safety data and study data reported at clinicalstudies.gov from the FREEDOMS, FREEDOMS II and TRANSFORMS studies. Comparisons were made for first dose cardiac monitoring outcomes, 1-year outcomes and 2 years outcomes for both efficacy and safety parameters.[28]

5.3.1 Overall incidence of TEAEs

Data for the overall incidence of TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to discontinuation for ozanimod, dimethyl fumarate and fingolimod are listed in Table 26, Table 27 and Table 28.

Table 26 Incidence of TEAEs for ozanimod in the RADIANCE and SUNBEAM studies

	RADIANCE[2]		SUNBEAM[3]	
	Ozanimod 1.0 mg (N=434) n (%)	**IFN beta-1a (N=440) n (%)**	**Ozanimod 1.0 mg (N=445) n (%)**	**IFN beta-1a (N=445) n (%)**
At least 1 TEAE	324 (74.7)	365 (83.0)	268 (59.8)	336 (75.5)
At least 1 severe TEAE	15 (3.5)	19 (4.3)	7 (1.6)	10 (2.2)
At least 1 serious TEAE	28 (6.5)	28 (6.4)	13 (2.9)	11 (2.5)
Any TEAE leading to permanent discontinuation of study drug	13 (3.0)	18 (4.1)	13 (2.9)	16 (3.6)
Death*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* During the controlled period, there was 1 death (accidental drowning) in the ozanimod 0.5 mg treatment group (not reported in the table); there was 1 additional death (chronic kidney failure) in the ozanimod 1 mg treatment group that occurred ~10 months after discontinuation of study drug. Neither death was considered by the investigator or the Sponsor to be related to ozanimod.[29]

The difference in overall incidence of TEAEs for ozanimod compared to interferon ß-1a was mainly driven by the high rate of influenza-like illness seen with interferon beta-1a.[29]

In the RADIANCE study the reasons for discontinuation of study drug in the ozanimod 1.0 mg group were invasive breast cancer carcinoma (1), keratoacanthoma (1), drug hypersensitivity (1), Guillain-Barré syndrome (1), hypertransaminasaemia (1), urticaria (2), pyrexia (1), and increased liver function tests (6). [2] In the SUNBEAM study the reasons for discontinuation of study drug in the ozanimod 1.0 mg group were subcutaneous abscess (1 case), anxiety disorder (1), irritability (1), headache (2), macular oedema (1), supraventricular tachycardia (1), hepatitis toxic, back pain (2), increased liver function tests (5) and abnormal cervix smear (1). [3]

Table 27 Incidence of TEAEs for dimethyl fumarate in the CONFIRM and DEFINE studies

	CONFIRM [5]		DEFINE[4]	
	240 mg BID (N=359) n (%)	**Placebo (N=363) n (%)**	**240 mg BID (N=410) n (%)**	**Placebo (N=408) n (%)**
At least 1 TEAE	338 (94.2)	333 (91.7)	395 (96.3)	387 (94.9)
At least 1 serious TEAE incl. MS relapse[a]	61 (17.0)	79 (21.8)	74 (18.0)	86 (21.1)
At least 1 serious TEAE excl. MS relapse[a]	22 (6.1)	28 (7.7)	35 (8.5)	26 (6.4)
Any TEAE incl. MS relapse leading to permanent discontinuation of study drug	44 (12.3)	38 (10.5)	65 (15.9)	55 (13.5)
Any TEAE excl. MS relapse leading to permanent discontinuation of study drug	38 (10.6)	21 (5.8)[‡]	61 (14.9)	24 (5.9)
Death	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)

[a]In the studies MS relapse was reported as a TEAE. To provide data for a relevant comparison, the numbers for TEAEs have been shown without MS relapse included as well.
BID – twice daily

The difference in overall incidence of TEAEs and TEAEs leading to discontinuation for dimethyl fumarate was mainly driven by flushing and gastrointestinal AEs.[4, 5]

In the CONFIRM study the reasons for discontinuation of dimethyl fumarate 240 mg BID were flushing in 14 (4%) patients, diarrhoea (2 (<1%)), nausea (1 (<1%)), vomiting (3 (<1%)), upper abdominal pain (1 (<1%)), headache (4 (1%)) and increased alanine aminotransferase (3 (1%)). [5] In the DEFINE study the reasons for discontinuation of dimethyl fumarate 240 mg BID were gastrointestinal adverse event in 21 (5%) patients, flushing (10 (2%)), diarrhoea (5 (1%)), upper abdominal pain (5 (1%)), nausea (5 (1%)), vomiting (5 (1%)), and abdominal pain (3 (<1%)). [4]

Reasons for death was stroke and road accident in the CONFIRM and DEFINE studies, respectively. [4, 5]

Table 28 Incidence of TEAEs for fingolimod in the FREEDOMS, FREEDOMS II and TRANSFORMS studies

	FREEDOMS [6]		FREEDOMS II [7]		TRANSFORMS [8]	
	Fingolimod 0.5 mg (N=425) n (%)	**Placebo (N=418) n (%)**	**Fingolimod 0.5 mg (N=358) n (%)**	**Placebo (N=355) n (%)**	**Fingolimod 0.5 mg (N=429) n (%)**	**IFN beta-1a (N=431) n (%)**
At least 1 TEAE	401 (94.4)	387 (92.6)	350 (98)	343 (97)	369 (86.0)	395 (91.6)
At least 1 severe TEAE	NR	NR	NR	NR	NR	NR
At least 1 serious TEAE	43 (10.1)	56 (13.4)	53 (15)	45 (13)	30 (7.0)	25 (5.8)
Any TEAE leading to permanent discontinuation of study drug	32 (7.5)	32 (7.7)	66 (18)	37 (10)	24 (5.6)	16 (3.7)
Death	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

IFN – Interferom; NR – Not reported; TEAE – Treatement emergent adverse evenet

In the FREEDOMS and TRANSFORMS publications the incidence of specific TEAEs leading to discontinuation is not listed. In the FREEDOMS study causes of study discontinuation and adverse events related to fingolimod included bradycardia and atrioventricular conduction block at the time of fingolimod initiation, macular oedema, elevated liver-enzyme levels, and mild hypertension. [6] In the FREEDOMS II study, the incidence of specific TEAEs leading to discontinuation is not listed. However, study drug was discontinued amongst other in patients with lymphopenia, increased liver enzymes, 2nd degree AV-block, and macular oedema. [7] In the TRANSFORMS study drug was discontinued amongst other in patients with varicella zoster, herpes simplex, and macular oedema. [8]

Tabulations of types and frequency of TEAEs reported in the ozanimod and fingolimod studies

Type and frequency of TEAEs and for serious TEAEs reported for ozanimod and fingolimod in the included studies are listed in Table 29 and Table 30, respectively and for ozanimod and dimethyl fumarate in Table 31 and Table 32, respectively.

Only data for approved dosages has been included. For ease of comparison the data for ozanimod has been included in both tables.

In the publications the reporting of the frequency of TEAEs has been done with different selection criteria as detailed in the table footers.

Table 29 Types and frequency of TEAEs reported in the RADIANCE, SUNBEAM, FREEDOMS, FREEDOMS II and TRANSFORMS studies

	RADIANCE [2]		SUNBEAM [3]		FREEDOMS [6]		FREEDOMS II [7]		TRANSFORMS [8]	
	Ozanimod 1.0 mg OD (N=434) n (%)	IFN beta-1a 30 µg/wk (N=440) n (%)	Ozanimod 1.0 mg OD (N=445) n (%)	IFN beta-1a 30 µg/wk (N=445) n (%)	Fingolimod 0.5 mg OD (N=425) n (%)	Placebo (N=418) n (%)	Fingolimod 0.5 mg OD (N=358) n (%)	Placebo (N=355) n (%)	Fingolimod 0.5 mg (N=429) n (%)	IFN beta-1a 30 µg/wk (N=431) n (%)
Infections (please refer to Table 35 for details)										
Nervous system disorders										
Headache			34 (7.6)	25 (5.6)	107 (25.2)	96 (23.0)	83 (23)	77 (22)	99 (23.1)	88 (20.4)
Dizziness	8 (1.8)	5 (1.1)			31 (7.3)	23 (5.5)	37 (10)	42 (12)	24 (5.6)	21 (4.9)
Paraesthesia					23 (5.4)	18 (4.3)	19 (5)	18 (5)		
Migraine							25 (7)	21 (6)		
Abnormal liver function test					67 (15.8)	21 (5.0)				
Alanine aminotransferase increased	26 (6.0)	20 (4.5)	21 (4.7)	8 (1.8)			29 (8)	6 (2)	28 (6.5)	8 (1.9)
Gamma glutamyl transfer-ase increased	25 (5.8)	9 (2.0)	15 (3.3)	2 (0.4)			23 (6)	2 (1)		
Aspartate aminotransfer-ase increased							11 (3)	5 (1)		
Hepatic enzyme increased							10 (3)	0		
General disorder										
Fatigue	16 (3.7)	12 (2.7)			48 (11.3)	45 (10.8)			44 (10.3)	45 (10.4)
Pyrexia									18 (4.2)	77 (17.9)
Influenza like ill ness									15 (3.5)	159 (36.9))
Musculoskeletal disorders							136 (38)	148 (42)		
Back pain	18 (4.1)	14 (3.2)	17 (3.8)	9 (2.0)	50 (11.8)	29 (6.9)	29 (8)	39 (11)	26 (6.1)	23 (5.3)
Arthralgia	15 (3.5)	6 (1.4)			30 (7.1)	33 (7.9)	30 (8)	39 (11)	12 (2.8)	24 (5.6)
Pain in extremity/limb pain					28 (6.6)	28 (6.7)	44 (12)	27 (8)	21 (4.9)	28 (6.5)
Neck pain							14 (4)	16 (5)		
Myalgia									14 (3.3)	44 (10.2)
Gastrointestinal disorders							155 (43)	143 (40)		
Diarrhoea	8 (1.8)	8 (1.8)			50 (11.8)	31 (7.4)	49 (14)	43 (12)	32 (7.5)	21 (4.9)
Upper abdominal pain	14 (3.2)	6 (1.4)	6 (1.3)	3 (0.7)						

Vomiting							22 (6)	27 (8)		
Dyspepsia							12 (3)	18 (5)		
Nausea					38 (8.9)	36 (8.6)	63 (18)	54 (15)	40 (9.3)	29 (6.7)
Respiratory disorders										
Cough					43 (10.1)	34 (8.1)	52 (15)	53 (15)	20 (4.7)	16 (3.7)
Dyspnoea					30 (7.1)	19 (4.5)	35 (10)	33 (9)	8 (1.9)	7 (1.6)
Oropharyngeal pain					29 (6.8)	29 (6.9)	29 (8)	32 (9)		
Nasal congestion							17 (5)	21 (6)		
Blood and lymphatic system disorders										
Leukopenia					12 (2.8)	1 (0.2)				
Lymphopenia/lymphocyto-penia					15 (3.5)	2 (0.5)	27 (8)	0 (0)	1 (0.2)	0 (0)
Lymphadenopathy							8 (2)	15 (4)		
Cardiovascular disorders										
Hypertension	24 (5.5)	14 (3.2)	6 (1.3)	4 (0.9)	26 (6.1)	16 (3.8)	32 (9)	11(3)	16 (3.7)	8 (1.9)
Bradycardia, bradyarrhyth-mia, sinus bradycardia					9 (2.1)	3 (0.7)	3 (1)	3 (1)		
Atrioventricular block										
First degree					2 (0.5)	2 (0.5)	2 (1)	2 (1)		
Second degree					0 (0.0)	1 (0.2)	0 (0)	1 (<0.5)		
Psychiatric disorders										
Depression					33 (7.8)	28 (6.7)	29 (8)	34 (10)	21 (4.9)	32 (7.4)
Insomnia					21 (4.9)	25 (6.0)	31 (9)	24 (7)		
Anxiety							18 (5)	18 (5)		
Melanocytic naevus									28 (6.5)	24 (5.6)
Hypercholesterolaemia			11 (2.5)	5 (1.1)	24 (5.6)	26 (6.2)				
Weight increase					14 (3.3)	22 (5.3)				
Vertigo					18 (4.2)	21 (5.0)				
Macular oedema					0 (0.0)	0 (0.0)	3 (1)	2 (1)		
Only data for approved dos-ages included	Source: Table 4. Adverse events occurring in at least 2% of ozanimod-treated		Source: Table 4 Adverse events occurring in at least 2% of ozanimod-treated		Source: Table 3 and text. Listed are all adverse events that occurred in more than 5% of patients in any study group (with the exception of		Source: Table 3. Listed are all adverse events that occurred in more than 5% of patients in any study group (with the exception of		Source: Table 3 and text Listed are all adverse events that occurred in more than 5% of patients in any study	

	participants and with an incidence of at least 1% higher than in the interferon group.	participants and with an incidence of at least 1% higher than in the interferon group.	lymphocytopenia), in decreasing order of total frequency.	lymphocytopenia), in decreasing order of total frequency.	group (with the exception of lymphocytopenia), in decreasing order of total frequency.

Table 30 Serious TEAEs occurring in more than one patient for ozanimod and fingolimod

	RADIANCE [2]		**SUNBEAM [3]**		**FREEDOMS [6]**		**FREEDOMS II [7]**		**TRANSFORMS [8]**	
	Ozanimod 1.0 mg OD (N=434) n (%)	**IFN beta-1a 30 µg/wk (N=440) n (%)**	**Ozanimod 1.0 mg OD (N=448) n (%)**	**IFN beta-1a 30 µg/wk (N=445) n (%)**	**Fingolimod 0.5 mg OD (N=425) n (%)**	**Placebo (N=418) n (%)**	**Fingolimod 0.5 mg OD (N=358) n (%)**	**Placebo (N=355) n (%)**	**Fingolimod 0.5 mg (N=429) n (%)**	**IFN beta-1a 30 µg/wk (N=431) n (%)**
Serious adverse events total	28 (6.5)	28 (6.4)	13 (2.9)	11 (2.5)	43 (10.1)	56 (13.4)	53 (15)	45 (13)	30 (7.0)	25 (5.8)
Cardiovascular disorders							3 (1)	2 (1)		
Bradycardia					4 (0.9)	1 (0.2)	0 (0)	1 (<0.5)	2 (0.5)	0 (0)
AV-block, 1st degree							0 (0)	0 (0)	1 (0.2)	0 (0)
AV-block, 2nd degree							0 (0)	0 (0)	1 (0.2)	0 (0)
Angina pectoris							0 (0)	2 (1)		
Myocardial infarction					0 (0.0)	2 (0.5))				
Neoplasms							13 (4)	8 (2)		
Basal-cell carcinoma					4 (0.9)	3 (0.7)	10 (3)	2 (1)	3 (0.7)	1 (0.2)
Squamous cell carcinoma							1 (<0.5)	2 (1)		
Breast cancer	1 (0.2)	0 (0.0)			0 (0.0)	3 (0.7)				
Invasive breast carcinoma	1 (0.2)	0 (0.0)								
Breast cancer incl. in situ									2 (0.5)	0 (0)
Keratoacanthoma	1 (0.2)	0 (0.0)								
Melanoma incl. in situ					0 (0.0)	1 (0.2)			3 (0.7)	0 (0)
Bowen's disease					0 (0.0)	0 (0.0)				
Testicular seminoma			1 (0.2)	0 (0.0)						
Cervical carcinoma, stage 0)					0 (0.0)	1 (0.2))				
Endometrial cancer					0 (0.0)	1 (0.2)				
Uterine leiomyoma			1 (0.2)	0 (0.0)			0	2 (1)		
Benign uterine tumour			0 (0.0)	1 (0.2)						
Thyroid cancer							1 (<0.5)	1 (<0.5)		
Chronic lymphatic leukaemia	0 (0.0)	1 (0.2)								

	RADIANCE [2]		SUNBEAM [3]		FREEDOMS [6]		FREEDOMS II [7]		TRANSFORMS [8]	
	Ozanimod 1.0 mg OD (N=434) n (%)	**IFN beta-1a 30 µg/wk (N=440) n (%)**	**Ozanimod 1.0 mg OD (N=448) n (%)**	**IFN beta-1a 30 µg/wk (N=445) n (%)**	**Fingolimod 0.5 mg OD (N=425) n (%)**	**Placebo (N=418) n (%)**	**Fingolimod 0.5 mg OD (N=358) n (%)**	**Placebo (N=355) n (%)**	**Fingolimod 0.5 mg (N=429) n (%)**	**IFN beta-1a 30 µg/wk (N=431) n (%)**
Ovarian cyst	2 (0.5)	0 (0.0)								
Prostate cancer					0 (0.0)	1 (0.2)				
Chest pain					4 (0.9)	2 (0.5)				
Non-cardiac chest pain							2 (1)	0 (0)		
Abdominal pain							2 (1)	2 (1)		
Abnormal liver function test					0 (0.0)	1 (0.2)				
Central nervous system										
Migraine							1 (<0.5)	2 (1)		
Convulsions							3 (1)	1(<0.5)		
Syncope							2 (1)	1 (<0.5)		
Major depression							1 (<0.5)	3 (1)		
Depression					0 (0.0)	1 (0.2)	0 (0)	2 (1)		
Epilepsy	1 (0.2)	1 (0.2)								
MS Relapse					4 (0.9)	1 (0.2)	1 (<0.5)	3 (1)		
Macular oedema							1 (<0.5)	1 (<0.5)		
Back pain					2 (0.5)	1 (0.2)				
Intervertebral disk protrusion					0 (0.0)	2 (0.5)				
Abortion					0 (0.0)	3 (0.7)	1 (<0.5)	2 (1)		
Urinary tract infection					2 (0.5)	0 (0.0)				
Herpes virus infection									1 (0.2)	1 (0.2)
Appendicitis	2 (0.5)	2 (0.5)							0 (0.0)	2 (0.5)
Only data for approved dosages included	Source Cohen 2019, Table S4 and text, p. 9. Serious TEAEs occurring in more than one patient plus all neoplasms regardless of incidence.		Source Comi 2019, table S4 and text. Serious TEAEs occurring in more than one patient plus all neoplasms regardless of incidence.		Kappos 2010, table 3 and text. "Serious adverse events" include those reported in two or more patients in any group or of special interest.		Source Calabresi 2014, table 3 Serious adverse events include those reported in at least two patientsin any group or of special interest		Source Cohen 2010, Table 3 and text Listed serious adverse events occurred in at least two patients in any study group.	

Table 31 Types and frequency of TEAEs reported in the RADIANCE, SUNBEAM, DEFINE and CONFIRM studies

	RADIANCE[2]		SUNBEAM[3]		CONFIRM [5]		DEFINE[4]	
	Ozanimod 1.0 mg OD (N=434) n (%)	**IFN beta-1a 30 µg/wk (N=440) n (%)**	**Ozanimod 1.0 mg OD (N=445) n (%)**	**IFN beta-1a 30 µg/wk (N=445) n (%)**	**DMF 240 mg BID (N=359) n (%)**	**Placebo (N=363) n (%)**	**DMF 240 mg BID (N=410) n (%)**	**Placebo (N=408) n (%)**
Infections (please refer to Table 35 for details)								
Nervous system disorders								
Headache			34 (7.6)	25 (5.6)	52 (14)	49 (13)		
Dizziness	8 (1.8)	5 (1.1)						
Alanine aminotransferase increased	26 (6.0)	20 (4.5)	21 (4.7)	8 (1.8)				
Gamma glutamyl transferase increased	25 (5.8)	9 (2.0)	15 (3.3)	2 (0.4)				
General disorder								
Fatigue	16 (3.7)	12 (2.7)			37 (10)	33 (9)		
Flushing					110 (31)‡	13 (4)	154 (38)‡	20 (5)
Pruritus							42 (10)	19 (5)
Musculoskeletal disorders								
Back pain	18 (4.1)	14 (3.2)	17 (3.8)	9 (2.0)	35 (10)	33 (9)		
Arthralgia	15 (3.5)	6 (1.4)						
Gastrointestinal disorders								
Diarrhoea	8 (1.8)	8 (1.8)			45 (13)‡	28 (8)	62 (15)‡	55 (13)
Upper abdominal pain	14 (3.2)	6 (1.4)	6 (1.3)	3 (0.7)	36 (10)‡	17 (5)	40 (10)‡	28 (7)
Abdominal pain							46 (11)	22 (5)
Vomiting							40 (10)	24 (6)
Nausea					40 (11)‡	29 (8)	53 (13)‡	38 (9)
Cardiovascular disorders								
Hypertension	24 (5.5)	14 (3.2)	6 (1.3)	4 (0.9)				
Psychiatric disorders								
Depression					24 (7)	35 (10)		
Hypercholesterolaemia			11 (2.5)	5 (1.1)				
Proteinuria					29 (8)	25 (7)	38 (9)	34 (8)

Only data for approved dosages included OD-once daily, BID – twice daily, wk – week, DMF – dimethyl fumarate	Source Cohen 2019, Table 4. Adverse events occurring in at least 2% of ozanimod-treated participants and with an incidence of at least 1% higher than in the interferon group.	Source: Comi 2019, table 4 Adverse events occurring in at least 2% of ozanimod-treated participants and with an incidence of at least 1% higher than in the interferon group.	Source: Fox 2012, Table 3 and text. Events were reported by at least 10% of patients in any group, except for ‡ These events had a reported incidence of at least 5 percentage points higher in the active group than in the placebo group.	Source: Gold 2012, table 3. Events were reported by at least 10% of patients in any group, except for ‡ These events had a reported incidence of at least 5 percentage points higher in the active group than in the placebo group.

Table 32 Serious TEAEs occurring in more than one patient for ozanimod and dimethyl fumarate

	RADIANCE[2]		**SUNBEAM[3]**		**CONFIRM [5]**		**DEFINE[4]**	
	Ozanimod 1.0 mg OD (N=434) n (%)	**IFN beta-1a 30 µg/wk (N=440) n (%)**	**Ozanimod 1.0 mg OD (N=448) n (%)**	**IFN beta-1a 30 µg/wk (N=445) n (%)**	**DMF 240 mg BID (N=359) n (%)**	**Placebo (N=363) n (%)**	**DMF 240 mg BID (N=410) n (%)**	**Placebo (N=408) n (%)**
Serious adverse events total	28 (6.5)	28 (6.4)	13 (2.9)	11 (2.5)	61 (17)	79 (22)	74 (18)	86 (21)
Multiple sclerosis relapse			0 (0.0)	2 (0.4)	39 (11)	51 (14)	39 (10)	60 (15)
Neoplasms								
Basal-cell carcinoma							1 (<1)	1 (<1)
Transitional cell carcinoma							1 (<1)	0 (0)
Breast cancer	1 (0.2)	0 (0.0)					0 (0)	1 (<1)
Invasive breast carcinoma	1 (0.2)	0 (0.0)						
Keratoacanthoma	1 (0.2)	0 (0.0)						
Testicular seminoma			1 (0.2)	0 (0.0)				
Endometrial cancer								
Uterine leiomyoma			1 (0.2)	0 (0.0)			0 (0.0)	2 (<1)
Benign uterine tumour			0 (0.0)	1 (0.2)				
Chronic lymphatic leukaemia	0 (0.0)	1 (0.2)						
Gastroenteritis					2 (<1)	0 (0)	4 (<1)	0 (0)
Appendicitis	2 (0.5)	2 (0.5)						
Abdominal pain					2 (<1)	0 (0)		
Central nervous system								
Convulsions					0 (0)	2 (<1)		
Back pain					2 (<1)	0 (0)		
Cellulitis					2 (<1)	0 (0)		

Abortion					0 (0)	2 (<1)		
Ovarian cyst	2 (0.5)	0 (0.0)					1 (<1)	1 (<1)
Depression							2 (<1)	1 (<1)
Pneumonia					0 (0)	1 (<1)	2 (<1)	1 (<1)
Tendon rupture							0 (0.0)	2 (<1)
Only data for approved dosages included DMF – dimethyl fumarate, OD – once daily, BID – twice daily, wk - week	Source Cohen Table S4 and text, p. 9 Serious TEAEs occurring in more than one patient plus all neoplasms regardless of incidence.		Source Cohen table S4 and text Serious TEAEs occurring in more than one patient in plus all neoplasms regardless of incidence.		Source: Fox table 3 [5] These events were reported by at least two patients in any group.		Source: Gold, table 3 and S6, S7 and S8 These events were reported by at least two patients in the DMF group	

5.3.2 Adverse events of special interest

Lymphopenia (ALC)

The main general lymphocyte parameters for ozanimod, dimethyl fumarate and fingolimod are listed in Table 33. Results from the individual studies are described below.

Table 33 Main lymphocyte parameters for ozanimod, fingolimod and dimethyl fumarate

Parameter	**Ozanimod** [1]	**Fingolimod** [30]	**Dimethyl fumarate**
Lymphocyte reduction from baseline	55%	70%	30 %[31]
Approximate ALC, nadir	800 x 10^6/L (mean)	500 x 10^6/L (median)	1.200 x 10^6/L (median) [32]
Patients with ALC <0.2x10^9/L	3.3 %	18 %	<1 %[31]
Time to lymphocyte recovery	Median time 30 days 90% within 3 months	1-2 months	7 weeks[33]

ALC=Absolute lymphocyte count

Ozanimod

Expectedly, reductions in lymphocyte counts were reported, based on the mode of action of ozanimod.

In the RADIANCE study among the participants who received ozanimod, mean absolute lymphocyte count (ALC) decreased from baseline to month 3 and remained stable through month 24. [2]

Mean ALC at month 24 was 0.753 (SD 0.454) x 10^9 cells per L (43.2% of baseline) in the ozanimod 1.0 mg group, 1.012 (0.536) x 10^9 cells per L (54.2% of baseline) in the ozanimod 0.5 mg group, and 1.833 (1.138) x 10^9 cells per L (98.9% of baseline) in the interferon beta-1a group. [2]

Mean minimum ALC at any time point during the study was 0.525 (SD 0.295) x 10^9 cells per L in the ozanimod 1.0 mg group, 0.750 (0.387) x 10^9 cells per L in the ozanimod 0.5 mg group, and 1.284 (0.503) x 10^9 cells per L in the interferon beta-1a group. [2]

At least one post baseline ALC less than 0.2 x 10^9 cells per L was recorded in 18 (4.2%) participants in the ozanimod 1.0 mg group, four (0.9%) in the ozanimod 0.5 mg group, and none in the interferon beta-1a group. [2]

A total of 249 (57.8%) participants in the ozanimod 1.0 mg group, 108 (24.7%) in the ozanimod 0.5 mg group, and six (1.4%) in the interferon beta-1a group had at least one ALC less than 0.5 × 10^9 cells per L. No participant had serious infections when lymphocyte counts were less than 0.2 x 10^9 cells per L.[2]

In the SUNBEAM study mean absolute lymphocyte count (ALC) decreased from baseline at month 3 and remained stable through month 12 in both ozanimod groups. [3]

Mean ALC at month 12 was 0.759 × 10^9 cells per L (SD 0.427; 42.8% of baseline) in the ozanimod 1.0 mg group, 0.963 × 10^9 cells per L (0.461; 54.1% of baseline) in the ozanimod 0.5 mg group, and 1.764 × 10^9 cells per L (0.641; 97.7% of baseline) in the interferon beta-1a group.

Mean minimum ALC at any time point was 0.557 × 10^9 cells per L (SD 0.290) in the ozanimod 1.0 mg group, 0.755 × 10^9 cells per L (0.351) in the ozanimod 0.5 mg group, and 1.324 × 10^9 cells per L (0.498) in the interferon beta-1a group.

Eleven (2.5%) participants, all treated with ozanimod 1.0 mg, had an ALC of less than 0.2 × 10^9 cells per L after baseline; none were associated with serious or opportunistic infections.

In the overall pool of MS subjects treated with ozanimod 1 mg (N = 2631) reviewed in the EPAR, with up to ~75 months of exposure as of 31 Jan 2019, the mean reduction in ALC of ~55% from baseline observed within 3 months was generally maintained through the data cut-off date.[29] There was no increase in the overall incidence of infections, serious infections, or other opportunistic infections with longer exposure.[29]

Dimethyl fumarate

In the CONFIRM study mean lymphocyte counts in both dimethyl fumarate groups (240 mg BID and TID, respectively) decreased during the first year and then plateaued, remaining within the normal range.

Mean percentage reductions from baseline in lymphocyte counts were approximately 32% in the twice-daily dimethyl fumarate group at 1 year. Lymphocyte counts of less than 0.5×10^9 cells per L was seen in 5% of patients in the twice daily dimethyl fumarate group and in less than 1% of patients in the placebo group. [5]

In the DEFINE study mean percentage reductions from baseline in lymphocyte counts were approximately 28% in the combined dimethyl fumarate groups at 1 year. Lymphocyte counts of less than 0.5×10^9 cells per L was seen in 4% of patients in the dimethyl fumarate groups and in 1% or less of patients in the placebo group. There were no serious infections in patients with lymphocyte counts $<0.5\times10^9$/L. [4]

Fox et al reported data for long-term follow up for the dimethyl phase IIb, III and long-term safety studies with a follow-up up to 90.5 months confirming the data from the initial experience in the phase III program. [32]

Fingolimod

In the FREEDOMS study mean ALC at month 24 was 0.49 (SD 0.26) x 10^9 cells per L (26.6% of baseline) in the fingolimod 0.5 mg group, and 1.76 (0.57) x 10^9 cells per L (96.7% of baseline) in the placebo group. [6]

In the TRANSFORMS study mean ALC at month 12 was 0.5 (SD 0.31) x 10^9 cells per L (28% of baseline) in the fingolimod 0.5 mg group, and 1.7 (0.57) x 10^9 cells per L (100% of baseline) in the interferon beta-1a group. [8]

In the FREEDOMS II study, the mean ALC in the fingolimod 0.5 mg group was reduced at the end of 2 weeks to 0.48 × 10^9/L (baseline values not reported) and remained stable on chronic treatment up to month 24. [7]

For the pooled data, the SmPC states with continued daily dosing, the lymphocyte count continues to decrease over a two-week period, reaching a minimal count of approximately 500 cells/microlitre or approximately 30% of baseline. Eighteen percent of patients reached a minimal count below 0.2 x 10^9 cells per L on at least one occasion.[30]

ALC comparison between ozanimod and fingolimod

The MAIC analysis conducted by Swallow et al (see the study description on p. 34 reported a statistically significant adjusted risk difference for ozanimod HCl 1 mg vs fingolimod 0.5 mg mean (difference in means) ALC at year one of 0.4 (95% CI 0.3, 0.5; P<0.001) in favour of ozanimod. [28]

Similarly, a statistically significant adjusted risk difference for patients with ALC < 0.2 x 10^9 cell per L at year one of -13.8 (95%CI -17.3, - 10.3; p<0.001) was reported. [28]

A statistically significant adjusted mean difference in mean absolute lymphocyte count of 0.4 (0.3, 0.5; P<0.001) at year 1 was seen in favour of ozanimod. [28]

Serious and/or uncommon infection related TEAEs

Please refer to Table 35 (ozanimod and fingolimod) and Table 36 (ozanimod and dimethyl fumarate) below for a complete overview of infection related TEAEs reported for ozanimod, fingolimod and dimethyl fumarate. For ease of comparison, the data for ozanimod has been included in both tables.

In the RADIANCE study, serious infections were infrequent, and no serious opportunistic infections occurred. The incidence of herpes infections (oral herpes, herpes zoster, herpes simplex, or herpes virus infection) was low and similar across treatment groups (9 [2.1%] with ozanimod 1.0 mg; 11 [2.5%] with ozanimod 0.5 mg; and 12 [2.7%] with interferon beta-1a). Of these, Herpes zoster cases were few in number (four [0.9%] with ozanimod 1.0 mg; two [0.5%] with ozanimod 0.5 mg; and one [0.2%] with interferon beta-1a), affected a single dermatome, were non-serious, not associated with ALC less than $0.2\text{x}10^9$ cells per L, and resolved with oral acyclovir. [2]

In the SUNBEAM study the proportion of participants with an infection was similar across treatment groups (range 26.7–28.9%). The incidence of herpes infections (oral herpes, herpes zoster, herpes simplex, or herpes virus infection) was low and similar across treatment groups (four [0.9%] with ozanimod 1.0 mg; three [0.7%] with ozanimod 0.5 mg; and five [1.1%] with interferon beta-1a). The herpes zoster cases were in a single dermatome and mild (one case in each ozanimod group) or moderate (one case in the interferon beta-1a group); all cases resolved on treatment and all participants completed the study. No serious opportunistic infections were reported in participants treated with ozanimod. [3]

No systemic opportunistic infections were reported with long-term exposure of ozanimod in clinical studies. [29]

In the CONFIRM study the incidence of serious infections was low and similar (1 to 2%) across groups; no opportunistic infections were reported in any group. [5]

In the DEFINE study the incidence of serious infections was 2% in all the groups; no opportunistic infections were observed in the dimethyl fumarate groups, and no serious infections were reported in patients with lymphocyte counts of less than 0.5×10^9 per L. [4]

In the FREEDOMS study the overall incidence of herpes virus infections were reported in similar proportions of patients across the three study groups. Of these infections, herpes zoster was reported in seven patients receiving 0.5 mg of fingolimod, three receiving 1.25 mg of fingolimod, and four receiving placebo. Two cases of herpes virus infection were classified as serious adverse events: one case of genital herpes (in a patient receiving 1.25 mg of fingolimod) and one case of herpes simplex labialis (in a patient receiving 0.5 mg of fingolimod). Data from the open label extension of the FREEDOMS study shows an incidence of herpes virus infections in 12.1 percent of the patients continuing fingolimod 0.5 mg and 9.0% of the patients shifting from placebo to fingolimod 0.5 mg. [34]

Lower respiratory tract infections (including bronchitis and pneumonia) were more common with fingolimod than with placebo (occurring in 41 patients [9.6%] receiving 0.5 mg of fingolimod and 49 patients [11.4%] receiving 1.25 mg of fingolimod vs. 25 patients [6.0%] receiving placebo). [6]

In the FREEDOMS II study, bronchitis, influenza, and herpes viral infections occurred in slightly higher percentages of patients in the fingolimod groups, whereas urinary tract infections were more common in the placebo group. Herpes zoster was more common in the fingolimod groups (in 12 [3%] patients in the 1.25 mg group and nine [3%] patients in the 0.5 mg group) compared with placebo (three [1%] patients). [7]

One case of asymptomatic cryptococcal infection was seen 5 months after stopping treatment and one case of tuberculosis was seen during the extension phase of the study. [7]

In the TRANSFORMS study serious infections occurred in 0.2 to 1.7% of patients. The only serious infections that were reported in more than one patient were appendicitis and herpes virus infections. Among patients assigned to receive fingolimod, herpes virus infections were diagnosed in 23 (5.5%) patients in the 1.25-mg group and 9 (2.1%) patients in the 0.5-mg group, as well as in 12 (2.8%) patients in the interferon group. In 41 of these 44 patients (93%), the infections were mild. [8]

In the open label extension of the TRANSFORMS study with up to 4.5 years follow-up herpes viral infections were reported in 36 (10.1%) patients in the continuous-fingolimod group and 25 (15%) patients in the interferon-switch group. [35]

In the post-marketing setting of patients treated with fingolimod, cases of infections with opportunistic pathogens, such as viral (e.g. varicella zoster virus [VZV], John Cunningham virus [JCV] causing Progressive Multifocal Leukoencephalopathy, herpes simplex virus [HSV]), fungal (e.g. cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal. [30]

Comparison between ozanimod and fingolimod – herpes virus infections

The results of the MAIC comparison by Swallow et al is shown in Table 34. [28]

Table 34 Herpes infection - Adjusted risk difference for ozanimod 1.0 mg vs fingolimod 0.5 mg

	Δ[a]	95% CI	p-value
Year 1			
Any AE – herpetic infection	2.2	(-1.6, 6.0)	0.25
Serious AE -herpetic infection	0.0	(-0.6, 0.6)	1.0
Year 2			
Any AE – herpetic infection	-4.9	(-8.9, -0.9)	<0.05
Serious AE - herpetic infection	-0.3	(-0.7, 0.1)	0.12

[a] Difference in proportion of events unless otherwise noted

Source: [28]

Progressive Multifocal Leukoencephalopathy

PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised and may lead to death or severe disability. JCV infection resulting in PML has been observed in patients treated with MS therapies (e.g. dimethyl fumarate, fingolimod, natalizumab, ocrelizumab) and has been associated with some risk factors (e.g., polytherapy with immunosuppressants, severely immunocompromised patients). [29]

No cases of PML were identified in the ozanimod clinical program up to the data cut-off (30 June 2019). [29] On 24 February 2020, EMA became aware of a possible first case of PML under ozanimod treatment in the ongoing OLE Study RPC01-3001. However, the diagnosis of PML could not be verified. A detailed case description is available in the ozanimod EPAR (p. 129). [29]

Though no confirmed cases of PML have been reported for ozanimod, guidance on PML has been included in the section on special warnings and precautions in the ozanimod SmPC due to the potential PML risk seen with MS therapies in general. The ADR term PML has not been included in the section on undesirable effects in the SmPC. [1]

PML cases have occurred with dimethyl fumarate and other medicinal products containing fumarates in the setting of moderate to severe prolonged lymphopenia. [31]

The ADR term is included in the section on undesirable effects with the frequency “not known” and guidance on PML is listed in the section on special warnings and precautions in the dimethyl fumarate SmPC. [31]

No cases of PML were reported in the phase III studies for fingolimod. However during post marketing surveillance a number of cases have been reported why the ADR term PML has been included in the section on undesirable effects with the frequency “not known” and guidance on PML is listed in the section on special warnings and precautions in the dimethyl fumarate SmPC. [30]

Infection with Human Papilloma Virus

In the ozanimod safety population (pool A) for the phase II and phase III studies no cases of HPV-infection, genital warts or cervical dysplasia/cancer were reported. In the expanded safety pool (B) including data from the long-term safety study, one case of cervix carcinoma was reported. [29]

The SmPC for ozanimod contains a statement on general precautions related to the immunosuppressive effects as well as the increased risk of infections due to reduced lymphocyte count, but HPV and related disease are not mentioned. [1] In the dimethyl fumarate phase III program one case of cervix carcinoma was reported. However, no relationship to HPV infection is reported. [4] [36]

The SmPC for dimethyl fumarate contains a statement on general precautions related to previous immunosuppressive treatment as well as the risk of infections due to reduced lymphocyte count, but HPV and related disease is not mentioned. [31]

According to special warnings and precautions section in the SmPC for fingolimod human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with fingolimod in the post-marketing setting. Due to the immunosuppressive properties of fingolimod, vaccination against HPV should be considered prior to treatment initiation with fingolimod taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care. [30]

The inclusion of the above section into the fingolimod SmPC was based on a CHMP review of safety data due to identification of 414 cases of HPV and related cancers. The majority of cases were HPV infection, papilloma, dysplasia and warts. Given the pharmacological properties of fingolimod on immunity and cases of reactivation (in some cases after several years of latency) with close temporal association with fingolimod, these data strongly support possible HPV infection reactivation upon fingolimod treatment.[37]

Table 35 Types and frequency of infection related TEAEs reported in the RADIANCE, SUNBEAM, FREEDOMS, FREEDOMS II and TRANSFORMS studies

	RADIANCE [2]		**SUNBEAM [3]**		**FREEDOMS [6]**		**FREEDOMS II [7]**		**TRANSFORMS [8]**	
	Ozanimod 1.0 mg OD (N=434) n (%)	**IFN beta-1a 30 µg/wk (N=440) n (%)**	**Ozanimod 1.0 mg OD (N=445) n (%)**	**IFN beta-1a 30 µg/wk (N=445) n (%)**	**Fingolimod 0.5 mg OD (N=425) n (%)**	**Placebo (N=418) n (%)**	**Fingolimod 0.5 mg OD (N=358) n (%)**	**Placebo (N=355) n (%)**	**Fingolimod 0.5 mg (N=429) n (%)**	**IFN beta-1a 30 µg/wk (N=431) n (%)**
Infections reported as Serious TEAEs	4 (0.9)	4 (0.9)	5 (1.1)	3 (0.7)	2 (0.5)	0 (0.0)	11 (3)	4 (1)	1 (0.2)	3 (0.7)
All infections										
Nasopharyngitis	68 (15.7)	48 (10.9)	30 (6.7)	36 (8.1)	115 (27.1)	115 (27.5)	84 (24)	85 (24)	88 (20.5)	88 (20.4)
Pharyngitis	17 (3.9)	15 (3.4)	11 (2.5)	5 (1.1)	27 (6.4)	24 (5.7)				
Urinary tract infection	19 (4.4)	17 (3.9)	17 (3.8)	10 (2.2)	34 (8.0)	47 (11.2)	53 (15)	59 (17)	26 (6.1)	22 (5.1)
Upper respiratory tract infection	-	-	18 (4.0)	24 (5.4)	-	-	87 (24)	86 (24)	31 (7.2)	27 (6.3)
Respiratory tract infection viral	-	-	15 (3.3)	3 (0.7)	-	-				
Rhinitis	-	-	9 (2.0)	3 (0.7)	25 (5.9)	26 (6.0)				
Sinusitis					28 (6.6)	19 (4.5)	57 (16)	45 (13)		
Lower respiratory tract/lung infection	-	-	-	-	41 (9.6)	25 (6.0)	38 (11)	30 (9)		
Herpes virus infection	9 (2.1)	12 (2.7)	4 (0.9)	5 (1.1)	37 (8.7)	33 (7.9)	30 (8)	19 (5)	9 (2.1)	12 (2.8)
Influenza viral infections					55 (12.9)	41 (9.8)	35 (10)	24 (7)	29 (6.8)	32 (7.4)
Only data for approved dosages included	Source: Tables 4, S4 and S8		Source: Table 4 and text		Source: Table 3 and text		Source: table 3		Source: Table 3 and text	

Table 36 Types and frequency of infection related TEAEs reported in the RADIANCE, SUNBEAM, CONFIRM and DEFINE studies

	RADIANCE [2]		SUNBEAM [3]		CONFIRM[5]		DEFINE[4]	
	Ozanimod 1.0 mg OD (N=434) n (%)	**IFN beta-1a 30 µg/wk (N=440) n (%)**	**Ozanimod 1.0 mg OD (N=445) n (%)**	**IFN beta-1a 30 µg/wk (N=445) n (%)**	**DMF 240 mg BID (N=359) n (%)**	**Placebo (N=363) n (%)**	**DMF 240 mg BID (N=410) n (%)**	**Placebo (N=408) n (%)**
Infections reported as Serious TEAEs	4 (0.9)	4 (0.9)	5 (1.1)	3 (0.7)	NR[a]	NR[a]	10 (2.4)	7 (1.7)
Nasopharyngitis	68 (15.7)	48 (10.9)	30 (6.7)	36 (8.1)	62 (17)	58 (16)	NR[b]	NR[b]
Pharyngitis	17 (3.9)	15 (3.4)	11 (2.5)	5 (1.1)			NR[b]	NR[b]
Urinary tract infection	19 (4.4)	17 (3.9)	17 (3.8)	10 (2.2)	52 (14)	42 (12)	NR[b]	NR[b]
Upper respiratory tract infection	-	-	18 (4.0)	24 (5.4)	36 (10)	34 (9)	NR[b]	NR[b]
Respiratory tract infection viral	-	-	15 (3.3)	3 (0.7)			NR[b]	NR[b]
Rhinitis	-	-	9 (2.0)	3 (0.7)			NR[b]	NR[b]
Sinusitis							NR[b]	NR[b]
Lower respiratory tract/lung infection	-	-	-	-			NR[b]	NR[b]
Herpes virus infection	4 (0.9)	1 (0.2)	4 (0.9)	5 (1.1)-			NR[b]	NR[b]
Influenza viral infections							NR[b]	NR[b]
Only data for approved dosages included OD-once daily, BID – twice daily, wk - week, DMF dimethyl fumarate; NR – not reported	Source: Tables 4, S4 and S8		Source: Table 4 and text		Source: Table 3 and text [a] Narratively stated to be 1-2% in each group.		Source: Table 3. A listing of serious infections is available in table S7. [b] Numbers for infections in general are not reported in the publication.	

Macular oedema

Macular oedema was included as a safety topic of interest in the ozanimod development program because of the effect of S1P receptor modulation on vascular endothelial cells.

The incidence of macular oedema in the phase III programs for ozanimod and fingolimod was low and numerically comparable. As expected, due to the different mode of action no cases have been reported for dimethyl fumarate.

Ozanimod

In the ozanimod RMS program Optical Coherence Tomography was used as a standard screening tool at baseline and Months 6, 12, and (in Study RPC01-201B) 24 in the controlled studies, at the end of the 6-month Study RPC01-201A Extension, and every 12 months in the open label extension study RPC01-3001.

Minor mean increases in central foveal thickness were observed across treatment groups but lacking a dose-dependency or a time effect. Abnormal values in subjects with normal values at baseline were highest around Month 6 in any group not exceeding an incidence of 5%.

The incidence of confirmed macular oedema cases in the controlled Phase III RMS studies (Pool A1) was 1/882 (0.1%) in the ozanimod 1 mg treatment group and 3/892 (0.3%) in the ozanimod 0.5 mg treatment group (there were none in the interferon beta-1a treatment group). An additional 3 confirmed cases were identified in the OLE Study RPC01-3001, for a total of 7/2787 (0.3%) in the RMS clinical program.

All cases of macular oedema were associated with pre-existing risk factors or comorbid conditions that are known to cause macular oedema. Eight of the 9 subjects recovered following discontinuation of study drug; the remaining case (secondary to ocular trauma) was reported to be stable as of the last available follow-up. [29]

In the SmPC macula oedema is described in the warnings and precautions section and listed as an ADR with the incidence “uncommon” in the undesirable effects section with a footnote indicating “for patients with pre-existing factors”. [1]

Dimethyl fumarate

In the dimethyl fumarate phase III studies DEFINE and CONFIRM no events of macular oedema have been reported. [4, 5] Macular oedema is not listed in the SmPC. [31]

Fingolimod

In the fingolimod phase III program total of 5 cases (0.4%) of macular oedema in 1212 patients were seen in the 0.5 mg treatment groups. [6-8] Generally, the reported macular oedema improved or resolved spontaneously after discontinuation of fingolimod. [EPAR p. 96]

In the SmPC macula oedema is described in the warnings and precautions section and listed as an ADR with the incidence “uncommon” in the undesirable effects section. [30]

Comparison between ozanimod and fingolimod – Macular oedema

The incidence of macular oedema in the ozanimod 1.0 mg groups of the RADIANCE and SUNBEAM studies was 0 and 1 events, respectively, while the incidence in the 0.5 mg groups of fingolimod in the FREEDOMS, FREEDOMS II and TRANSFORMS studies was 0, 3 and 2, respectively.

In the MAIC by Swallow et al the adjusted risk difference for macular oedema between ozanimod and fingolimod at year 2 was -0.4 (-0.8, 0.0; p=0.08). [28]

Malignancies, in particular skin cancers

In the SmPC the listing of adverse drug reactions for ozanimod and dimethyl fumarate does not include skin cancers or other malignancies, while several types of malignancies (basal cell carcinoma, malignant melanoma, lymphoma, squamous cell carcinoma, Kaposi's sarcoma, and Merkel cell carcinoma) are listed for fingolimod (Table 44).

Data for malignancies reported as TEAEs in the clinical studies are summarized below.

Ozanimod

In the RADIANCE study, malignancies were reported for four (0.9%) of 434 participants in the ozanimod 1.0 mg group (breast cancer, invasive breast carcinoma, keratoacanthoma, and basal cell carcinoma); three (0.7%) of 439 in the ozanimod 0.5 mg group (malignant melanoma in situ [pre-existing], medulloblastoma [pre-existing], and basal cell carcinoma), and two (0.5%) of 440 in the interferon beta-1a group (chronic lymphocytic leukaemia and basal cell carcinoma). [2]

In the SUNBEAM study malignancies occurred in one (0.2%) participant in the ozanimod 1.0 mg group (testicular seminoma; diagnosed on study day 51), two (0.4%) in the ozanimod 0.5 mg group (invasive breast cancer and basal cell carcinoma), and none in the interferon beta-1a group. [3]

In the ozanimod open label long term study (DAYBREAK) 1.2 % of the participants developed malignancies (Incidence Rate 320.8/100,000 Person Years) as presented at the joint ACTRIMS/ECTRIMS meeting in September 2020.[38] This Incidence Rate is consistent with the malignancy rates seen in MS patients treated with other DMTs. [39]

Increased cutaneous neoplasms have been identified in MS patients treated with other S1P receptor modulators prompting recent amendments of their SmPCs. With respect to the established role of the S1P1 receptor in tumorigenesis, the lack of experience from long-term clinical ozanimod therapy and the generally wide tissue distribution of ozanimod including the eyes and skin, the potential risk for skin neoplasms has been included as a warning in section 4.4 of the SmPC. [1, 29]

The SmPC for ozanimod includes the following paragraph under special warnings and precautions:

> *Half of the neoplasms reported with ozanimod in the controlled Phase 3 studies consisted of non-melanoma skin malignancies, with basal cell carcinoma presenting as the most common skin neoplasm and reported with similar incidence rates in the combined ozanimod (0.2%, 3 patients) and IFN beta-1a (0.1 %, 1 patient) groups. Since there is a potential risk of malignant skin growths, patients treated with ozanimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy. [1]*

Dimethyl fumarate

In the CONFIRM study no malignant neoplasms were reported in the dimethyl fumarate groups. [5]

In the DEFINE study there were two cases of malignant neoplasms (one basal cell carcinoma, one transitional cell carcinoma) in the dimethyl fumarate BID group and two cases (breast cancer, cervix carcinoma) in the dimethyl fumarate TID group. [4]

The SmPC for dimethyl fumarate does not include any warnings or precautions related to malignancies. [31]

Fingolimod

In the FREEDOMS study malignant neoplasms were reported in 4 patients receiving 0.5 mg of fingolimod, 4 receiving 1.25 mg of fingolimod, and 10 receiving placebo. Of these 11 were skin cancers (basal-cell carcinoma, malignant melanoma, or Bowen's disease) of which 3 cases were with 1.25-mg fingolimod, 4 with 0.5-mg fingolimod, and 4 with placebo. [6]

In the FREEDOMS II study 31 cases of malignancies were reported across the three treatment arms, most of them involving the skin. Basal cell carcinoma was reported in 6 (2%) patients in the 1.25 mg fingolimod group, 10 (3%) patients in the 0.5 mg fingolimod group, and 2 (1%) patients in the placebo group; other malignancies occurred with a similarly low frequency in the fingolimod and placebo groups. [7] In the TRANSFORMS study, 10 localized skin cancers were reported: 5 basal-cell carcinomas in the fingolimod groups (2 in the 1.25-mg group and 3 in the 0.5-mg group) and 1 in the interferon group; 3 melanomas (all limited to the epidermis) in the group receiving the 0.5-mg dose of

fingolimod; and 1 squamous cell carcinoma in the interferon group. Breast cancer was reported in 2 patients in each of the fingolimod groups. [2]

During post marketing surveillance cases of malignant melanoma, lymphoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma have been reported. [30]

The SmPC for fingolimod includes the following paragraph under special warnings and precautions:

Cutaneous malignancies

Basal cell carcinoma (BCC) and other cutaneous neoplasms, including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported in patients receiving Gilenya. Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected.

Since there is a potential risk of malignant skin growths, patients treated with fingolimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy. [30]

Comparison of ozanimod and fingolimod

The results of the MAIC comparison by Swallow et al is shown in (Table 37). [28]

Table 37 Malignancies - Adjusted risk difference for ozanimod 1.0 mg vs fingolimod 0.5 mg

	Δ[a]	95% CI	p-value
Year 1			
Basal cell carcinoma	-0.5	(-1.4, 0.4)	0.27
Melanoma (incl. in situ)	-0.7	(-1.5, 0.3)	0.08
Breast cancer (incl. in situ)	-0.5	(-1.2, 0.2)	0.14
Year 2			
Basal cell carcinoma	-1.8	(-2.7, -0.9)	<0.001
Melanoma (incl. in situ)	-0.1	(-0.3, 0.1)	0.38
Breast cancer (incl. in situ)	0	(-0.3, 0.3)	0.96

[a] Difference in proportion of events unless otherwise noted; negative delta favours ozanimod.

Source: [28]

Cardiac and cardiovascular effects

Based on the known biology of S1P modulators special attention was directed at assessing cardiac effects both at first dose and during long-term treatment.

The S1P1 receptor is highly expressed in atrial, septal, and ventricular cardiomyocytes. After initial agonism, continuous dosing results in functional antagonism and down-regulation of S1P. Activation of S1P receptors on cardiac cells provides an explanation for the transient effects on heart rate (bradycardia) and atrioventricular conduction. The S1P1 receptor is expressed on all endothelial and vascular smooth muscle cells, where it appears to contribute to the regulation of endothelial barrier function and peripheral vascular tone. Modulation of S1P1 on these cells may result in blood pressure effects. [29]

S1P modulators, initiated at the full dose, result in a transient reduction in heart rate (of 8 bpm) on Day 1 and, less commonly, a temporary delay in atrioventricular (AV) conduction observed in some patients.[40] High-grade AV conduction abnormalities occurred in some patients, treated with non-selective S1P modulators. First dose effects resulted in the regulatory requirement for first-dose observation when initiating treatment with S1P non-selective modulators. [29]

First dose experience and monitoring

First dose effects like decrease in heart rate, blood pressure reduction and conduction abnormalities are seen with SP1 modulators.

In the ozanimod phase III program the incidence of blood pressure reduction and decrease in heart rate was low and not clinically meaningful. No cases of 2nd or 3rd degree conduction abnormalities were seen. [2, 3]

In the fingolimod phase III program higher incidence of clinically meaningful blood pressure reduction and decrease in heart rate as well as conduction abnormalities were seen. [6-8]

In the MAIC by Swallow et al the incidence of first dose cardiac complications was statistically significantly lower with ozanimod than with fingolimod. [28]

Due to the different mode of action for dimethyl fumarate, the effect on heart rate, blood pressure and heart conduction is minimal and will not be described in this context.

Ozanimod

In the ozanimod Phase II and 3 clinical programs a 7-day dose-escalation approach was implemented to reduce the risk of adverse events at first dose administration.

The dose escalation approach consisted of treatment with ozanimod 0.25 mg on Days 1 to 4 and ozanimod 0.5 mg on Days 5 to 7, and from day 8 the maintenance dose of 1 mg. [29]

This dose regimen was shown to be successful in mitigating chronotropic and dromotropic effects observed after initiation at the full (maintenance) dose due to the initial S1P1 agonism. [29]

In the active-controlled Phase III studies including approximately 1,774 subjects treated with ozanimod, the 6-hour monitoring data on Day 1 demonstrated that ozanimod was associated with only a modest and not clinically meaningful reduction in mean HR on Day 1 (mean HR reduction from baseline of 1.2 bpm with a nadir at Hour 5, with return towards baseline by Hour 6). 'Symptomatic bradycardia' was reported in two subjects belonging to the ozanimod 0.5 mg group during the dose escalation period (with 0.25 mg) in Pool A1. [29]

Second- or third-degree AV block were not reported in the active-controlled Phase III RMS studies and no patient was reported with a HR < 40 bpm. It should be noted that patients with clinically significant cardiovascular history were excluded from these studies as were patients taking medications that reduce HR or affect cardiac conduction. [29]

In the open label extension study RPC01-3001 (ozanimod 1 mg), consistent results were demonstrated at the time of ozanimod dose escalation initiation. A non-clinically meaningful reduction in mean HR (-1.2 bpm) was observed in subjects who switched from interferon beta-1a. No conduction abnormalities were identified. Moreover, ozanimod did not affect cardiac repolarization. [29]

In the EPAR EMA states, that *"at this moment, scientific and clinical data appear to support the balance between mainly beneficial effects from S1P1/S1P5 modulation and mainly adverse effects from the S1P3/S1P4 receptors. Specifically, evidence appears to suggest that S1P1 agonism might be more related to an acute effect in bradycardia induction compared to a S1P3-mediated chronic effect on heart rate and conductivity"*.

"This might explain, at least in part, the different effect profile of ozanimod in heart conductivity compared to fingolimod. The lesser bradycardic effect in therapy initiation of ozanimod might be related to a combination of the dose-escalation protocol with the modulation of S1P1 rather than S1P3". [29]

As for fingolimod it was found for ozanimod that cardiovascular medical history (such as bradycardia and 1st degree AV-block) as well as concomitant cardiovascular medication increased the incidence of cardiovascular events. [1, 30]

Thus, it is reco mmended in the SmPCs for both fingolimod and ozanimod that patients at cardiovascular risk should be monitored and in certain cases obtain advice from a cardiologist prior to initiation of treatment. [1, 30]

Fingolimod

DiMarco et al published a safety analysis of the cardiac first dose effects of fingolimod based on data for the safety populations in the FREEDOMS, FREEDOMS II and TRANSFORMS studies.[40]

Initiation of fingolimod treatment was associated with a transient, mostly asymptomatic, dose-dependent reduction in heart rate. [40]

Monitoring of sitting heart rate revealed a drop from baseline following the administration of the first dose of fingolimod (0.5mg or 1.25mg), with the lowest mean heart rates noted at the 4-and 5-h time points. [40]

At nadir, the mean (standard deviation [SD]) decreases from baseline in the mean sitting heart rates were 8.1 (8.1) bpm in the fingolimod 0.5mg group (n=1212) and 11.3 (8.2) bpm in the fingolimod 1.25mg (n=1219) group. [40]

At 6h, heart rate was increased in the interferon beta-1a group by 8.3 (11.4) bpm and was unchanged in the placebo group, but was decreased from baseline by 7.4 (8.0) bpm in the fingolimod 0.5 mg group and by 10.2 (8.0) bpm in the fingolimod 1.25 mg group. [40]

After 1 month of daily dosing with fingolimod, the mean sitting heart rates in all study groups were stable at pre-dose levels. [40]

On ECG readings at 6h post-dose, AV node conduction delays were more common in both fingolimod-treated groups than in the interferon beta-1a and placebo groups. In fingolimod-treated groups, the incidence of AV node conduction delays was higher in the 1.25mg group than in the 0.5mg group. [40]

A lower incidence of Wenckebach (Mobitz type I) 2nd degree AV-block was observed with fingolimod 0.5mg (0.2%) than with 1.25mg (1%). However, the incidence in both fingolimod groups was higher than that seen with placebo (0%). There were no cases of 2:1 AV-block with fingolimod 0.5mg. Mobitz type II 2nd degree AV-block and higher grades of AV-block were not seen during treatment in any patient group during TRANSFORMS, FREEDOMS or FREEDOMS II. Fingolimod had no significant effect on QTcI. [40]

Symptomatic bradycardia on initiation of treatment was reported in 0.6% of patients in the fingolimod 0.5 mg group and 2.1% in the fingolimod 1.25 mg group. Events were mild or moderate in severity in most patients (30/32) and resolved spontaneously without additional pharmacological treatment in the majority of participants. In the fingolimod 0.5 mg group the most common symptom was dizziness. Two patients (0.2%) in the fingolimod 1.25mg group had symptoms during bradycardia that were classified as severe. [40]

A small decrease in blood pressure (BP) was observed in fingolimod-treated patients on day 1 that was maximal 4–5 h after the first dose. [40]

At the 4-h time point, changes from the pre-dose level in mean ±SD sitting systolic BP were: fingolimod 0.5mg, -3.1 ±10.5 mmHg; fingolimod 1.25mg, -3.7 ±10.9 mmHg; placebo, -0.8 ±10.4 mmHg and interferon beta-1a, -0.1 ±9.9 mmHg. For mean sitting diastolic BP, changes from baseline were: fingolimod 0.5mg, -3.9 ±8.4 mmHg; fingolimod 1.25mg, -5.5 ±8.8 mmHg; placebo, -2.1 ±8.1 mmHg and interferon beta-1a, -1.7 ±7.7 mmHg. By the 6-h timepoint, the decline in BP in the fingolimod-treated groups had started to attenuate. [40]

Comparison between ozanimod and fingolimod

The results of the MAIC comparison by Swallow et al is shown in Table 38. [28]

Compared with ozanimod, the adjusted absolute increases in the percentages of patients whose lowest hourly recorded heart rate was <45 bpm (45–54 bpm) in the first 6 h were +1.4% (+12.1%) for fingolimod 0.5 mg ($p < 0.001$), indicating that the adjusted risk difference (RD) was more favourable for ozanimod. [28]

The rates of the studied safety outcomes during first-dose cardiac monitoring were generally lower with ozanimod than with fingolimod. [28]

Compared with fingolimod, ozanimod was associated with significantly lower rates of conduction abnormalities (RD: −3.5%) and first-degree atrioventricular block (RD: −3.0%), as well as a lower risk of requiring monitoring beyond 6 h (RD −8.3%) and of requiring Day 2 monitoring (RD −2.6%; all $p < 0.001$) (Table 38). [28]

Ozanimod was associated with significantly less reduction in systolic (difference in means: 2.2 mm Hg) and diastolic (difference in means: 5.0 mm Hg) BP compared with fingolimod at first dose (both $p < 0.001$) (Table 38). [28]

Table 38 Comparison of first-dose cardiac monitoring outcomes for ozanimod HCl 1 mg versus fingolimod 0.5 mg: assessment of risk differences

	Δ[a]	95% CI	p-value
Heart rate, bpm			
<45	-1.4	(-2.0, -0.7)	<0.001[c]
45-54	-12.1	(-14.7, -9.5)	<0.001[c]
54-64	-3.5	(-7.9, 0.9)	0.12
≥65	17.2	(13.0, 21.3)	<0.001[c]
Decrease in heart rate from baseline, hour 5[b]	6.6	(5.8, 7.5)	<0.001[c]
Decrease in heart rate from baseline, hour 6[b]	7.5	(6.7, 8.3)	<0.001[c]
ECG findings			
Any conduction abnormality	-3.5	(-5.3, -1.8)	<0.001[c]
Atrioventricular block			
1st degree atrioventricular block	-3.0	(-4.4, 1.7)	<0.001[c]
2nd degree atrioventricular block (Wenckebach/Mobitz type I, Mobitz type II, 2:1)	-0.2	(-0.5, 0.1)	0.12
Received extended monitoring beyond 6 hours	-8.3	(-10.6, -6.0)	<0.001[c]
Received day 2 monitoring	-2.6	(-3.5, -1.7)	<0.001[c]
Discontinued on day 1	0.1	(-0.3, 0.4)	0.72
BP, mm HG			
Change in mean sitting systolic BP	2.2	(1.3, 3.1)	<0.001[c]
Change in mean sitting diastolic BP	5.0	(4.3, 5.7)	<0.001[c]

First-dose cardiac monitoring outcomes for both fingolimod arms were extracted from the pooled analysis reported in DiMarco *et al.* [29]. Patient characteristics for ozanimod were extracted from the patient-level data from the RADIANCE-B and SUNBEAM studies; data for the 0.5 mg arm and the 1 mg arm were pooled for this analysis.

[a] represents the change in risk between the two arms.

[b] Decrease in heart rate from baseline to nadir for both fingolimod arms was compared with decrease in heart rate from baseline to hours 5 and 6 for ozanimod. Hour 5 represents the nadir for ozanimod, whereas hour 6 represents the end of the monitoring period.

[c] Denotes a statistically significant difference.

Source: [28]

Long term cardiac experience

Ozanimod

Chronic treatment with ozanimod resulted in a slightly increased mean HR over baseline level in all treatment groups at Week 24 (phase II study) and Month 24 (controlled part of phase III studies), respectively. The increases were of approximately 2 bpm or less. [29] No clinically significant changes in ECG parameters were observed with chronic treatment in either treatment group. Specifically, there were no 2nd - or 3rd-degree AV blocks observed in the phase III studies. [29]

In OLE Study RPC01-3001, the incidence of AEs in the Cardiac Disorders and Vascular Disorders category did not increase with longer-term exposure with ozanimod 1 mg. [29]

Dimethyl fumarate

In the DEFINE study no clinically relevant changes in the corrected QT interval or any other electrocardiographic variable.[4] In the CONFIRM study the incidence of cardiovascular events was similar across the four study groups. [5]

Fingolimod

In the FREEDOMS study starting during month 2, the mean sitting systolic and diastolic blood pressures increased from the baseline values; at month 24, they had increased by 1.9 and 0.7 mm Hg, respectively, with 0.5 mg of fingolimod and had decreased by 0.4 and 0.5 mm Hg, respectively, in the placebo group.[6] Whilst conduction abnormalities were

infrequently reported as and AE, no clinically notable effect on heart rate or atrioventricular conduction was seen with continued use of fingolimod. [6] In the FREEDOMS II study no long-term data for cardiovascular AEs are reported. [7]

In the TRANSFORMs study no significant effect on heart rate or atrioventricular conduction was observed with continued administration of the drug. Increases in mean arterial pressure occurred in both fingolimod groups (3 mm Hg in the 1.25-mg group and 2 mm Hg in the 0.5-mg group) during the first 6 months and remained stable between 6 and 12 months. [8]

Key cardiac safety parameters for ozanimod, fingolimod and dimethyl fumarate sourced from the respective SmPCs are listed in Table 39.

Table 39 Key cardiac safety parameters for ozanimod, fingolimod and dimethyl fumarate

	Ozanimod [1]	**Fingolimod** [30]	**Dimethyl fumarate** [36]
Blood pressure			
Increase SBP/DBP	1-2 mmHg/1 mmHg	~3mmHg/~1 mmHg	No clinically significant change
Hypertension incidence	4,5% vs 2,3% (IFN)	6.5% vs. 3.3% (Pbo)	No clinically significant change
QT-prolongation	No	Yes	No relevant changes
AV-block (1st degree)	0.6% vs 2% (IFN)	4.7% vs 2.8% (IFN)	Not reported
AV-block (≥2nd degree)	None	<0.2%	Not reported
IFN – interferon; Pbo - placebo			

Comparison of ozanimod and fingolimod

In the MAIC analysis conducted by Swallow et al [28], the adjusted risk difference for ozanimod 1 mg vs fingolimod 0.5 mg for serious cardiac AEs is listed in Table 40. [28]

Table 40 Cardiac SAEs - Adjusted risk difference for ozanimod 1.0 mg vs fingolimod 0.5 mg

	Δ[a]	**95% CI**	**p-value**
Year 1			
Bradycardia or sinus bradycardia	-0.4	(-1.1, 0.3)	0.23
AV-block, 1st degree	-0.2	(-0.6, 0.2)	0.35
AV-block, 2nd degree	-0.2	(-0.6, 0.2)	0.35
Myocardial infarction	-0.2	(-0.5, 0.2)	0.32
Year 2			
Bradycardia or sinus bradycardia	-0.5	-1.0, 0.0	<0.05
AV-block, 1st degree	0	(0.0, 0.0)	-
AV-block, 2nd degree	0	(0.0, 0.0)	-
Myocardial infarction	0	(0.0, 0.0)	-

Negative delta favours ozanimod

[a] Difference in proportion of events unless otherwise noted;
Source: [28]

Hepatic function

In the ozanimod, fingolimod and dimethyl fumarate phase III program increases in liver parameters were seen more frequently in the intervention groups than in the comparator groups. [2-8]

Ozanimod

In the RADIANCE study alanine aminotransferase increases of at least three times the ULN occurred in 29 (6.7%) of 431 participants in the ozanimod 1.0 mg group, 26 (5.9%) of 438 in the ozanimod 0.5 mg group, and 17 (3.9%) of 434 participants in the interferon beta-1a group. Most were transient and resolved without study drug discontinuation. [2] Seven (1.6%) participants treated with ozanimod 1.0 mg, 3 (0.7%) treated with ozanimod 0.5 mg, and 6 (1.4%) treated with interferon beta-1a had TEAEs of hepatobiliary dysfunction or related investigations that led to treatment discontinuation. [2]

In the SUNBEAM study alanine aminotransferase increase to at least three times the ULN occurred in 19 (4.3%) of 447 participants treated with ozanimod 1.0 mg, 8 (1.8%) of 453 treated with ozanimod 0.5 mg, and 10 (2.2%) of 445 treated with interferon beta-1a. Most TEAEs related to alanine aminotransferase increase were transient and resolved without study drug discontinuation. [3] Four (0.9%) participants treated with ozanimod 1.0 mg, 1 (0.2%) treated with ozanimod 0.5 mg, and 1 (0.2%) treated with interferon beta-1a had TEAEs of hepatobiliary dysfunction or related investigations that led to discontinuation of study drug. [3]

Liver function tests should be performed prior to treatment initiation with ozanimod and at months 1, 3, 6, 9, 12 and periodically thereafter. [1]

Dimethyl fumarate

In the CONFIRM study the incidence of liver aminotransferase levels that were at least three times the ULN range was similar across the study groups; none of these elevations were concurrent with bilirubin levels that were more than two times the ULN range. increases in the alanine aminotransferase level to three times the ULN range occurred in 20 (6%) of 359 patients in the dimethyl fumarate 240 mg BID group and 23 (6%) of 363 patients in the placebo group. [5] In the DEFINE study alanine aminotransferase levels, that were three or more times the ULN range, were seen in 6% of the patients in each dimethyl fumarate group and in 3% of the patients in the placebo group. [4]

Liver function tests should be performed prior to treatment initiation with dimethyl fumarate and during treatment as clinically indicated. [31]

Fingolimod

In the FREEDOMS study increases in the alanine aminotransferase level to three times the ULN range or more were more frequent in the fingolimod groups (reported in 8.5% of patients in the 0.5-mg group and 12.5% in the 1.25-mg group) than in the placebo group (1.7%) and occurred predominantly in men. One patient receiving 0.5 mg of fingolimod had an increase in the alanine aminotransferase level to more than 10 times the ULN range. Elevated liver enzyme levels returned to normal in all patients, even in the few who continued the study treatment. In all three groups, bilirubin levels remained stable, with no clinically relevant changes during the study. In the FREEDOMS II study increases in the alanine aminotransferase level to three times ULN range or more were more frequent in the fingolimod groups (reported in 7% of patients in the 0.5-mg group and 10.0% in the 1.25-mg group) than in the placebo group (2%). Increases in liver enzymes improved once therapy was discontinued, and no patient developed liver failure.[7] In the TRANSFORMS study alanine aminotransferase levels that were three times the ULN range were more frequent in the fingolimod groups (occurring in 29 patients in the 1.25-mg group [7%] and 36 patients in the 0.5-mg group [8%]) than in the interferon group (10 patients [2%]). Alanine aminotransferase levels that were 10 times the ULN range occurred in 2 patients in the interferon group. [8]

Liver function tests should be performed prior to treatment initiation with fingolimod and at months 1, 3, 6, 9, 12 and periodically thereafter. [30]

Comparison of ozanimod and fingolimod

In the MAIC analysis conducted by Swallow et al [28] the adjusted risk difference for ozanimod 1 mg vs fingolimod 0.5 mg of an increase in liver enzymes (ALT ≥3x ULN %) was -6.8 (-10.6, -3-1; P<0.001) at year 1 and -3.0 (-5.8, -0.1; p<0.05) at year 2 in favour of ozanimod. [28]

Monitoring requirements and recommendations

For all three treatment options requirements and recommendations for tests, assessments, and monitoring prior to (Table 41) and during treatment initiation (Table 42), as well as during maintenance treatment and discontinuation (Table 43) have been described in this section.

Table 41 Tests and assessments prior to initiation of treatment

Test/Assessment	**Ozanimod** [1]	**Fingolimod** [30]	**Dimethyl fumarate** [31]
Baseline ECG	Yes	Yes	NR
Blood pressure	Yes	Yes	-
Liver function test (< 6 months prior)	Yes	Yes	Yes
Renal function test	-	-	Yes (creatinine, blood urea nitrogen, urine analysis)
Complete blood cell count	Yes (<6 months prior)	Yes (<6 months prior)	Yes
Ophthalmological exam	Yes (if diabetes, uveitis, retinal disease)	Yes (if diabetes, uveitis)	NR
Negative pregnancy test	Yes	Yes	Recommended
Varicella vaccine	Recommended, if no documented immunity	VZV antibody test; if negative, then vaccination	NR
HPV vaccination	-	To be considered	NR
Skin assessment for malignancies	Caution for exposure to sunlight	Recommended prior to treatment initiation, caution for exposure to sunlight	NR
Cardiological assessment	In patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnoea, history of recurrent syncope or symptomatic bradycardia; pre-existing significant QT interval prolongation (QTc greater than 500 msec) or other risks for QT prolongation, and patients on medicinal products other than beta-blockers and calcium channel blockers that may potentiate bradycardia; Patients on class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products, which have been associated with cases of torsades de pointes in patients with bradycardia have not been studied with ozanimod.	Risk patients (see SmPC for a full description): patients with sino-atrial heart block, a history of symptomatic bradycardia, recurrent syncope or cardiac arrest, or in patients with significant QT prolongation (QTc>470 msec [adult female], QTc >460 msec [paediatric female] or >450 msec [adult and paediatric male]), uncontrolled hypertension or severe sleep apnoea. patients with arrhythmias requiring treatment with class Ia or class III antiarrhythmic medicinal products. patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers, or other substances which may decrease heart rate.	NR

MRI scanning	-	Yes	Yes (< 3 months prior)
NR – not required/recommended			

Table 42 Monitoring requirements and recommendations during initiation of treatment

Parameter	**Ozanimod** [1]	**Fingolimod** [30]	**Dimethyl fumarate** [31]
Dose escalation recommended	Yes	No	Yes
ECG	All patients – before first dose; in risk patients[a] also after 6 hours)	Before and 6h after first dose	-
Blood pressure	In risk patients[a]: hourly for 6 hours	All patients: hourly for 6 hours	-
Continuous ECG		Recommended for the initial 6 hours In risk patients[b]: Cardiologist assessment, extended overnight monitoring	-
Heart rate	In risk patients[a]: - hourly for 6 hours	All patients: hourly for 6 hours	-
Monitoring after 6 hours, if	In patients with HR<45 bpm, lowest recorded HR at 6h, new onset 2nd degree AV-block, QTc interval ≥500msec	Monitoring should be continued in patents with bradyarrhythmia related symptoms If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), monitoring should be extended by at least 2 hours and until heart rate increases again. Additionally, if after 6 hours, the heart rate is <45 bpm in adults, <55 bpm in paediatric patients aged 12 years and above, or <60 bpm in paediatric patients aged 10 to below 12 years, or the ECG shows new onset second degree or higher grade AV block or a QTc interval ≥500 msec, extended monitoring (at least overnight monitoring),	

		should be performed, and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring (at least overnight monitoring).	
	[a] Risk patients: resting HR <55 bpm, second-degree [Mobitz type I] AV block or a history of myocardial infarction or heart failure	[b] Risk patients: sino-atrial heart block, a history of symptomatic bradycardia, recurrent syncope or cardiac arrest, or in patients with significant QT prolongation (QTc>470 msec [adult female], QTc >460 msec [paediatric female] or >450 msec [adult and paediatric male]), uncontrolled hypertension or severe sleep apnoea	

Table 43 Monitoring requirements and recommendations during maintenance treatment

Test	**Ozanimod** [1]	**Fingolimod** [30]	**Dimethyl fumarate** [31]
Liver test (transaminases and bilirubin)	At months 1, 3, 6, 9, 12 and periodically thereafter	At months 1, 3, 6, 9, 12 and periodically thereafter	During treatment as clinically indicated
Complete blood cell count	Periodically	Periodically (at month 3 and at least yearly thereafter, and in case of infection)	Every 3 months
Renal function test	-	-	X (creatinine, blood urea nitrogen, urinalysis) after 3 and 6 months, every 6 to 12 months thereafter
Monitoring for infections	Ongoing and until 3 months after discontinuation	Ongoing and until 2 months after discontinuation	Not specified
Ophthalmological exam	Follow up evaluations during therapy (frequency not specified)	Recommended at 3-4 months after treatment initiation. Follow up evaluations during therapy for patients with diabetes and uveitis (frequency not specified)	-
Blood pressure	Regularly (no frequency specified)	Regularly (no frequency specified)	-
Monitoring for rebound after discontinuation	3 months	Yes, no duration specified	-
MRI	If PML suspected	If PML suspected	If PML suspected

Treatment shift	Not specified	Shift from dimethyl fumarate to fingolimod requires CBC recovery before initiation	CBC recommended
Skin assessment for malignancies	Yes	Recommended prior to treatment initiation, and every 6 to 12 months thereafter	-
Monitor for immunosuppressive effects	Yes	Yes	

5.3.3 Adverse drug reactions

In the pivotal studies and the respective EPARs adverse events have been reported as TEAES only. The most comprehensive source of the incidence of ADRs is therefore section 4.8 of the respective SmPCs.

For ozanimod the most commonly reported adverse reactions are nasopharyngitis (11%), alanine aminotransferase increased (5%), and gamma-glutamyl transferase increased (5%). The most common adverse reactions leading to discontinuation were related to liver enzyme elevations (1.1%). [1]

For dimethyl fumarate the most common adverse reactions (incidence ≥ 10%) for patients treated with dimethyl fumarate were flushing and gastrointestinal events (i.e. diarrhoea, nausea, abdominal pain, abdominal pain upper). The most commonly reported adverse reactions leading to discontinuation (incidence > 1%) were flushing (3%) and gastrointestinal events (4%). [31]

For fingolimod the most common adverse reactions (≥ 10%) are influenza, sinusitis, headache, cough, diarrhoea, back pain, and increased liver enzymes.[30]

An overview of adverse drug reactions by frequency in the SmPCs has been tabulated in Table 44.

No numeric values are indicated in the SmPC. The ADR frequency is thus reported as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 44 Adverse Drug Reactions by frequency for ozanimod, fingolimod and dimethyl fumarate

System Organ Class Adverse reaction	**Ozanimod** [1]	**Fingolimod** [30]	**Dimethyl fumarate** [31]
Infections and infestations			
Nasopharyngitis	Very common		
Pharyngitis,	Common		
Respiratory tract infection viral,	Common		
Urinary tract infection*	Common		
Herpes zoster	Uncommon		
Influenza		Very common	
Sinusitis		Very common	
Herpes viral infections		Common	
Bronchitis		Common	
Tinea versicolor		Common	
Pneumonia		Uncommon	
Progressive multifocal leukoencephalopathy		Not known**	Not known [1]
Cryptococcal infections		Not known**	
Gastroenteritis			Common
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma		Common	
Malignant melanoma		Uncommon****	
Lymphoma		Rare****	
Squamous cell carcinoma		Rare****	
Kaposi's sarcoma		Very rare****	
Merkel cell carcinoma		Not known****	
Blood and lymphatic system disorders			

Lymphopenia	Very common	Common	Common
Leucopenia		Common	Common
Thrombocytopenia		Uncommon	Uncommon
Autoimmune haemolytic anaemia		Not known***	
Peripheral oedema		Not known***	
Immune system disorders			
Hypersensitivity (including rash and urticaria*)	Uncommon		
Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation		Not known***	
Hypersensitivity			Uncommon
Anaphylaxis			Not known[1]
Hypoxia			Not known[1]
Angioedema			Not known[1]
Psychiatric disorders			
Depression		Common	
Depressed mood		Uncommon	
Nervous system disorders			
Headache		Very common	
Dizziness		Common	
Migraine		Common	
Seizure		Uncommon	
Posterior reversible encephalopathy syndrome (PRES)		Rare*	
Severe exacerbation of disease after Gilenya discontinuation		Not known*	
Burning sensation			Common
Eye disorders			
Macular oedema	Uncommon**	Uncommon	
Vision blurred		Common	
Cardiac disorders			
Bradycardia*	Common	Common	
Atrioventricular block		Common	
T-wave inversion		Very rare***	
Vascular disorders			
Hypertension*†	Common	Common	
Orthostatic hypotension	Common		
Hypotension			Not known[1]
Flushing			Very common
Hot flush			Common
Respiratory, thoracic, and mediastinal disorders			
Cough		Very common	
Dyspnoea		Common	Not known[1]

Gastrointestinal disorders			
Diarrhoea		Very common	Very common
Nausea		Uncommon***	Very common
Abdominal pain upper			Very common
Abdominal pain			Very common
Vomiting			Common
Dyspepsia			Common
Gastritis			Common
Gastrointestinal disorder			Common
Hepato-biliary disorders			
Drug induced liver injury			Not known[1]
Skin and subcutaneous tissue disorders			
Eczema		Common	
Alopecia		Common	
Pruritus		Common	Common
Rash			Common
Erythema			Common
Renal and urinary disorders			
Proteinuria			Common
Musculoskeletal and connective tissue disorders			
Back pain		Very common	
Myalgia		Common	
Arthralgia		Common	
General disorders and administration site conditions			
Asthenia		Common	
Feeling hot			Common
Investigations			
Alanine aminotransferase increased	Common		Common
Gamma-glutamyl transferase increased	Common		
Aspartate aminotransferase increased			Common
Blood bilirubin increased	Common		
Pulmonary function test abnormal***	Common		
Hepatic enzyme increased (increased ALT, Gamma glutamyl transferase, Aspartate transaminase)		Very common	
Weight decreased		Common***	
Blood triglycerides increased		Common	
Neutrophil count decreased		Uncommon	
Ketones measured in urine			Very common
Albumin urine present			Common
White blood cell decreased			Common

[a] Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000); not known (cannot be estimated from the available data).	*At least one of these adverse reactions was reported as serious † Includes hypertension, essential hypertension, and blood pressure increased (see section 4.4). ** for patients with pre-existing factors (see section 4.4) ***including pulmonary function test decreased, spirometry abnormal, forced vital capacity decreased, carbon monoxide diffusing capacity decreased, forced expiratory volume decreased	* Not reported in Studies FREEDOMS, FREEDOMS II and TRANSFORMS. The frequency category was based on an estimated exposure of approximately 10,000 patients to fingolimod in all clinical studies. ** PML and cryptococcal infections (including cases of cryptococcal meningitis) have been reported in the post-marketing setting (see section 4.4). *** Adverse drug reactions from spontaneous reports and literature **** The frequency category and risk assessment were based on an estimated exposure of more than 24,000 patients to fingolimod 0.5 mg in all clinical studies.	[1] Adverse reactions derived only during post marketing experience

5.4 Other considerations

5.4.1 Women with intention of pregnancy

Question

The Scientific Committee notices that the indication for ozanimod encompasses women using effective contraceptives but may have a future desire to become pregnant. The EMA EPAR recommends that women use effective contraceptives at least three months after termination of ozanimod treatment.
The Scientific Committee is concerned about any possible rebound effect, with treatment with ozanimod is terminated due to a desire to become pregnant and requests the applicant to describe the options for so-called bridging therapy, that is, treatment of women with a desire to become pregnant, after the discontinuation of ozanimod treatment.

Answer

No formal clinical studies have been performed to define a relevant treatment sequence following discontinuation of ozanimod. This lack of formal study is also the case for other S1P receptor modulators (fingolimod and siponimod).

In the clinical program for ozanimod there were also no specific recommendations for bridging therapy with MS DMT treatment following ozanimod discontinuation due to any reason including pregnancy. However, a number of treatments were allowed per the protocols and choice of specific treatment, including bridging therapy, was at the discretion of the treating physician.

Rebound in MS has been defined as exceptionally high disease activity with a severe increase in disability and multiple new MRI brain lesions following discontinuation of therapy. [41, 42] Return of severe disease activity has been observed rarely after fingolimod discontinuation. The EMA reviewed data submitted by Celgene regarding rebound and the review indicated no evidence of rebound effect associated with the cessation of ozanimod.[29] However, additional wording on “Return of disease activity (rebound) after ozanimod discontinuation” has been included in SmPC section 4.4 to reflect this concern together with the class effect known for S1P receptor modulators. [1]

In addition to no evidence of rebound in the active-controlled Phase III RMS studies, there is also none observed in the open label extension (OLE) after subjects discontinued treatment with ozanimod. Safety follow-ups have been extended to 90 days following discontinuation of ozanimod in the OLE. Data beyond 90 days after discontinuation has not been captured as would be expected once a subject exits a clinical trial.

In case of discontinuation of treatment with ozanimod, the treating physician should observe the following guidance as described in the SmPC:

> *Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of another S1P receptor modulator (fingolimod).*
>
> *The possibility of severe exacerbation of disease after stopping ozanimod treatment should be considered. Patients should be observed for relevant signs of possible severe exacerbation or return of high disease activity upon ozanimod discontinuation and appropriate treatment should be instituted as required.* [1]

As neither formal studies nor relevant data are available, treatment of patients following discontinuation of treatment with ozanimod, including any bridging therapy, should be decided by the treating clinician based on the needs of the individual patient, and the potential benefits of treatment must outweigh the risks.

5.4.2 Long term safety profile compared to fingolimod

Question:

Due to the pharmacological similarity between the two pharmaceuticals, the Scientific Committee is requesting the applicant's considerations regarding the expectation regarding the long-term safety profile, as compared to Gilenya. Specifically, the Scientific Committee is interested in knowing whether there are pharmacodynamics or pharmacokinetic qualities of ozanimod that would cause an expectation that the more rare and serious side effects of Gilenya would be seen less frequently with ozanimod.

Answer

Please refer to section 5.3 (p. 34) for a comprehensive overview of the general safety profile including long term safety of ozanimod and fingolimod.

Selectivity for the S1P receptor family

Ozanimod, similar to fingolimod, causes internalization of S1P1 and retention of lymphocytes in the lymphoid tissues, as evidenced by a dose-dependent reduction in peripheral lymphocyte count and therefore ameliorating the pathological processes through inhibition of lymphocyte migration into the central nervous system.

Ozanimod is active selectively at the $S1P_1$ and $S1P_5$. This pharmacology, its pharmacodynamic profile and dosing regimen differentiate it from non-selective S1P receptor modulators like fingolimod. [43]

In contrast, fingolimod is a nonselective S1P receptor modulator acting on S1P1, S1P3, S1P4 and S1P5 receptors. [43]

Differences in PKPD between ozanimod and fingolimod

The main PKPD characteristics of ozanimod and fingolimod are tabulated in Table 45.

Table 45 Main differences in pharmacokinetic and pharmacodynamic properties between ozanimod and fingolimod

Parameter	Ozanimod	Fingolimod
Selectivity profile	S1P1, S1P5	S1P1, S1P3, S1P4, S1P5
Median time to C_{max}	6-8 hours [29]	12-16 hours[30]
Mean half-life (effective)	11 days[1]	6-9 days [44, 45]
Elimination half-life, mean	21 hours [1]	6-9 days[30]
Lymphocyte reduction from baseline	45% [1]	70%[30]
Approximate ALC, nadir	800 x 10^6/L (mean) [1]	500 x 10^6/L (median) [30]
Patients with ALC <0.2x10^9/L	3.3 % [1]	18%[30]
Time to lymphocyte recovery	Median time 30 days 90% within 3 months [1]	1-2 months[30]
Monitoring post discontinuation	3 months[1]	2 months[30]

ALC=Absolute lymphocyte count;

The safety profile of ozanimod and fingolimod differ primarily in the following areas:

Cardiac effects

The cardiac effects including extent of bradycardia, appearance of conduction abnormalities (e.g. 2nd degree AV-block), and blood pressure decrease in connection with administration of first dose is less marked with ozanimod than with fingolimod. This observation is in part, likely caused by dose escalation when initiating treatment with ozanimod compared to no escalation with fingolimod. Please refer to p. 52 for further details.

Effect on lymphocyte levels

One of the concerns surrounding the use of immunomodulatory therapies is the potential for increased risks of infection In consideration of the risks of long-term immunosuppression with ozanimod, based on a review of the clinical trial data, there is no association between absolute ALC reduction and the overall risk of infections, including serious or opportunistic infections, or malignancies. The mean ~55% reduction from baseline in ALC observed with ozanimod in the Phase III program is less than that reported with fingolimod (~70%).[30]

The effect on lymphocyte levels differ markedly between ozanimod and fingolimod (see Table 33 (p. 44)).

- lymphocyte reduction from baseline with ozanimod is less pronounced than with fingolimod
- the approximate nadir for ALC is higher for ozanimod than for fingolimod
- the percentage of patients with very low ALC levels is lower for ozanimod than for fingolimod

Phase III clinical trials of ozanimod showed infection rates that were comparable with patients treated with intramuscular interferon beta-1a, and infrequent serious infections, no serious opportunistic infections, and low (<1%) rates of malignancy among patients with RMS receiving ozanimod.[2, 3]

The extent to which these data have implications for a distinction between ozanimod and fingolimod remains to be proven.

Please refer to p. 44 for further details.

Hepatic effects

The frequency of increased liver enzymes, particularly ALT> 3 and > 5 times the upper limit of normal is less for ozanimod than that reported in Phase III controlled trials of fingolimod in MS. To which extent this difference is caused a difference in the PKPD profile is not known. (see p. 56 for further details)

Skin malignancies

There is a lower incidence of skin malignancies in patients treated with ozanimod than with fingolimod. The underlying mechanism is not known. (see p. 51 for further details)

Macular oedema

In multiple sclerosis clinical studies with fingolimod, macular oedema occurred in a clear dose-dependent fashion and was seen in 0.5% of patients treated with the recommended dose of 0.5 mg and 1.1% of patients treated with the higher dose of 1.25 mg (SmPC). The incidence of ME in both doses of the phase III ozanimod clinical program in MS (0.3%) and 0.2% in the ozanimod 1 mg treatment group and 0.3% in the ozanimod 0.5 mg treatment group; lower than the reported in controlled studies with fingolimod. Fingolimod may cause macular oedema by acting via the S1P3 receptor agonism.[46] All cases in the ozanimod program were associated with confounding conditions associated with macular oedema but the potential for an incremental risk in patients with predisposing comorbid conditions cannot be excluded.

Summary

Ozanimod and fingolimod have different selectivity for the S1P receptors and differ in in the extent of ALC reduction to achieve similar efficacy results.

Ozanimod has a more favourable safety profile than fingolimod with regard to the frequency and character of cardiac first dose effects, infections including serious opportunistic infections, macular oedema, skin malignancies and increase in hepatic enzymes.

However, to which extent this can be attributed to differences in SP1 receptor modulator selectivity and potency as well as differences in PKPD profile remains to be investigated further.

For further details on the safety profile of ozanimod and fingolimod, please refer to section 5.3 (p. 34).

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7 Appendices

7.1.1 Literature search

Table 46 Literature search inclusion and exclusion criteria for question 1

Inclusion criteria	**Population:** Patients with recurrent multiple sclerosis and moderate disease activity **Intervention(s):** Ozanimod Dimethyl fumarate **Comparator(s):** Interferon beta-1a Placebo **Outcomes:** • Persistent disease exacerbation confirmed after 3 months • Adverse events o Serious adverse events o Adverse drug reactions • Annualised attack rate • Cognitive function impairment o Symbol Digit Modality Test • Quality of life o MSQOL54 • For 12 to 24 month data **Settings (if applicable):** N/A **Study design:** Randomized control studies **Language restrictions:** English, Norwegian, Swedish, or Danish **Other search limits or restrictions applied:**
Exclusion criteria	**Population:** Patients without recurrent multiple sclerosis and moderate disease activity **Intervention(s):** Not Ozanimod or Dimethyl fumarate **Comparator(s):** Not interferon beta-1a or placebo **Outcomes:** Others not specified by the Danish Medicines Council in the protocol **Settings (if applicable):** N/A **Study design:**

	Not randomized control trial, Single arm studies, Animal, Review, Comment, letter, Case report, Non-adult populations, Real world data **Language restrictions:** Not English, Norwegian, Danish or Swedish **Other search limits or restrictions applied:** Publications with only subgroup populations to be excluded

Table 47 Literature search inclusion and exclusion criteria for question 2

Inclusion criteria	**Population:** Patients with recurrent multiple sclerosis and high disease activity **Intervention(s):** Ozanimod Fingolimod Hydrochloride **Comparator(s):** Interferon beta-1a Placebo **Outcomes:** • Persistent disease exacerbation confirmed after 3 months • Adverse events o Serious adverse events o Adverse drug reactions • Annualised attack rate • Cognitive function impairment o Symbol Digit Modality Test • Quality of life o MSQOL54 • For 12 to 24 month data **Settings (if applicable):** N/A **Study design:** Randomized control studies **Language restrictions:** English, Norwegian, Swedish, or Danish **Other search limits or restrictions applied:**
Exclusion criteria	**Population:** Patients without recurrent multiple sclerosis and high disease activity **Intervention(s):** Not Ozanimod or Fingolimod Hydrochloride **Comparator(s):** Not interferon beta-1a or placebo **Outcomes:** Others not specified by the Danish Medicines Council in the protocol

	Settings (if applicable): N/A **Study design:** Not randomized control trial, Single arm studies, Animal, Review, Comment, letter, Case report, Non-adult populations, Real world data **Language restrictions:** Not English, Norwegian, Danish or Swedish **Other search limits or restrictions applied:** Publications with only subgroup populations to be excluded

The following publications/studies were excluded during the systematic literature review.

Table 48 Full text publications excluded during the Systematic Literature Review

	Publication	Study title	Reason for exclusion	Comment
1	Arnold DL, Gold R, Kappos L, Bar-Or A, Giovannoni G, Selmaj K, Yang M, Zhang R, Stephan M, Sheikh SI, Dawson KT. Magnetization transfer ratio in the delayed-release dimethyl fumarate DEFINE study. J Neurol. 2014 Dec;261(12):2429-37. doi: 10.1007/s00415-014-7504-7. Epub 2014 Oct 1. PMID: 25270680; PMCID: PMC4242981.	DEFINE	Outcomes	Not requested by DMC
2	Arnold DL, Gold R, Kappos L, Bar-Or A, Giovannoni G, Selmaj K, Yang M, Zhang R, Stephan M, Sheikh SI, Dawson KT. Effects of delayed-release dimethyl fumarate on MRI measures in the Phase 3 DEFINE study. J Neurol. 2014 Sep;261(9):1794-802. doi: 10.1007/s00415-014-7412-x. Epub 2014 Jul 3. PMID: 24989666; PMCID: PMC4155185.	DEFINE	Outcomes	Not requested by DMC
3	Bar-Or A, Gold R, Kappos L, Arnold DL, Giovannoni G, Selmaj K, O'Gorman J, Stephan M, Dawson KT. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the DEFINE study. J Neurol. 2013 Sep;260(9):2297-305. doi: 10.1007/s00415-013-6954-7. PMID: 23797999.	DEFINE	Outcomes	Not relevant
4	Cohen JA, Arnold DL, Comi G, Bar-Or A, Gujrathi S, Hartung JP, Cravets M, Olson A, Frohna PA, Selmaj KW; RADIANCE Study Group. Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2016 Apr;15(4):373-81. doi: 10.1016/S1474-4422(16)00018-1. Epub 2016 Feb 12. PMID: 26879276.	RADIANCE	Outcomes	Not of interest
5	Cohen JA, Barkhof F, Comi G, Izquierdo G, Khatri B, Montalban X, Pelletier J, Eckert B, Häring DA, Francis G. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol. 2013 Aug;260(8):2023-32. doi: 10.1007/s00415-013-6932-0. Epub 2013 Apr 30. PMID: 23632946; PMCID: PMC3737385.	TRANSFORMS	Outcomes	Not of interest
6	Cohen JA, Comi G, Arnold DL, Bar-Or A, Selmaj KW, Steinman L, Havrdová EK, Cree BA, Montalbán X, Hartung HP, Huang V, Frohna P, Skolnick BE, Kappos L; RADIANCE Trial Investigators. Efficacy and safety of ozanimod in multiple sclerosis: Dose-blinded extension of a randomized phase II study. Mult Scler. 2019 Aug;25(9):1255-1262. doi: 10.1177/1352458518789884. Epub 2018 Jul 25. PMID: 30043658; PMCID: PMC6681431.	RADIANCE	Study design	Not RCT
7	Cohen JA, Khatri B, Barkhof F, Comi G, Hartung HP, Montalban X, Pelletier J, Stites T, Ritter S, von Rosenstiel P, Tomic D, Kappos L; TRANSFORMS (TRial Assessing injectable interferoN vS. FTY720 Oral in RRMS) Study Group. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. J Neurol Neurosurg Psychiatry. 2016 May;87(5):468-75. doi: 10.1136/jnnp-2015-310597. Epub 2015 Jun 25. PMID: 26111826; PMCID: PMC4853559.	TRANSFORMS	Study design	Not RCT

8	Comi G, Patti F, Rocca MA, Mattioli FC, Amato MP, Gallo P, Centonze D, Pozzilli C, Saccà F, Bergh FT, Bartezaghi M, Turrini R, Filippi M; Golden Study Group. Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomised, multicentre study (the GOLDEN study). J Neurol. 2017 Dec;264(12):2436-2449. doi: 10.1007/s00415-017-8642-5. Epub 2017 Oct 23. PMID: 29063244; PMCID: PMC5688215.	GOLDEN	Comparator	
9	Cree BAC, Arnold DL, Cascione M, Fox EJ, Williams IM, Meng X, Schofield L, Tenenbaum N. Phase IV study of retention on fingolimod *versus* injectable multiple sclerosis therapies: a randomized clinical trial. Ther Adv Neurol Disord. 2018 May 20;11:1756286418774338. doi: 10.1177/1756286418774338. PMID: 29844796; PMCID: PMC5964857.	PREFERMS	Study design	Not RCT
10	Derfuss T, Bergvall NK, Sfikas N, Tomic DL. Efficacy of fingolimod in patients with highly active relapsing-remitting multiple sclerosis. Curr Med Res Opin. 2015;31(9):1687-91. doi: 10.1185/03007995.2015.1067191. Epub 2015 Aug 20. PMID: 26121423.	FREEDOMS and FREEDOMS II	Outcomes	Not of interest
11	Derfuss T, Ontaneda D, Nicholas J, Meng X, Hawker K. Relapse rates in patients with multiple sclerosis treated with fingolimod: Subgroup analyses of pooled data from three phase 3 studies. Mult Scler Relat Disord. 2016 Jul;8:124-30. doi: 10.1016/j.msard.2016.05.015. Epub 2016 May 24. PMID: 27456887; PMCID: PMC4985567.	FREEDOMS, FREEDOMS II, and TRANSFORMS	Outcomes	Subgroup analysis
12	Devonshire V, Havrdova E, Radue EW, O'Connor P, Zhang-Auberson L, Agoropoulou C, Häring DA, Francis G, Kappos L; FREEDOMS study group. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 2012 May;11(5):420-8. doi: 10.1016/S1474-4422(12)70056-X. Epub 2012 Apr 10. Erratum in: Lancet Neurol. 2012 Aug;11(8):658. PMID: 22494956.	FREEDOMS	Outcomes	Subgroup analysis
13	Fox E, Edwards K, Burch G, Wynn DR, LaGanke C, Crayton H, Hunter SF, Huffman C, Kim E, Pestreich L, McCague K, Barbato L; EPOC study investigators. Outcomes of switching directly to oral fingolimod from injectable therapies: Results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis. Mult Scler Relat Disord. 2014 Sep;3(5):607-19. doi: 10.1016/j.msard.2014.06.005. Epub 2014 Jul 4. PMID: 26265273.	EPOC	Study design	Not RCT
14	Gold R, Arnold DL, Bar-Or A, Fox RJ, Kappos L, Chen C, Parks B, Miller C. Safety and efficacy of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: 9 years' follow-up of DEFINE, CONFIRM, and ENDORSE. Ther Adv Neurol Disord. 2020 May 12;13:1756286420915005. doi: 10.1177/1756286420915005. PMID: 32426039; PMCID: PMC7222239.	DEFINE, CONFIRM, AND ENDORSE	Study design	Not RCT
15	Gold R, Arnold DL, Bar-Or A, Hutchinson M, Kappos L, Havrdova E, MacManus DG, Yousry TA, Pozzilli C, Selmaj K, Sweetser MT, Zhang R, Yang M, Potts J, Novas M, Miller DH, Kurukulasuriya NC, Fox RJ, Phillips TJ. Long-term effects of delayed-release dimethyl fumarate in multiple sclerosis: Interim analysis of ENDORSE, a randomized extension study. Mult Scler. 2017 Feb;23(2):253-265. doi: 10.1177/1352458516649037. Epub 2016 Jul 11. PMID: 27207449; PMCID: PMC5418934.	ENDORSE	Study design	Not RCT

16	Gold R, Giovannoni G, Phillips JT, Fox RJ, Zhang A, Marantz JL. Sustained Effect of Delayed-Release Dimethyl Fumarate in Newly Diagnosed Patients with Relapsing-Remitting Multiple Sclerosis: 6-Year Interim Results From an Extension of the DEFINE and CONFIRM Studies. Neurol Ther. 2016 Jun;5(1):45-57. doi: 10.1007/s40120-016-0042-8. Epub 2016 Mar 1. PMID: 26932146; PMCID: PMC4919132.	DEFINE AND CONFIRM	Study design	Not RCT
17	Gold R, Giovannoni G, Phillips JT, Fox RJ, Zhang A, Meltzer L, Kurukulasuriya NC. Efficacy and safety of delayed-release dimethyl fumarate in patients newly diagnosed with relapsing-remitting multiple sclerosis (RRMS). Mult Scler. 2015 Jan;21(1):57-66. doi: 10.1177/1352458514537013. Epub 2014 Jul 2. PMID: 24990854; PMCID: PMC4361464.	DEFINE and CONFIRM	Outcomes	Subgroup analysis
18	Havrdova E, Giovannoni G, Gold R, Fox RJ, Kappos L, Phillips JT, Okwuokenye M, Marantz JL. Effect of delayed-release dimethyl fumarate on no evidence of disease activity in relapsing-remitting multiple sclerosis: integrated analysis of the phase III DEFINE and CONFIRM studies. Eur J Neurol. 2017 May;24(5):726-733. doi: 10.1111/ene.13272. Epub 2017 Mar 22. PMID: 28328179; PMCID: PMC5413827.	DEFINE AND CONFIRM	outcome: not of interest to DMC	Not requested by DMC
19	Hunter SF, Thomas FP, Cascione M, Williams IM, Meng X, Schofield L, Weiss JL, Tenenbaum N, Cree BAC; PREFERMS investigators. Switching to fingolimod in PREFERMS: Effect of treatment history and naïvety on clinical, MRI and treatment satisfaction outcomes☆. Mult Scler Relat Disord. 2020 Jul 3;45:102346. doi: 10.1016/j.msard.2020.102346. Epub ahead of print. PMID: 32717684.	PREFERMS	Study design	Not RCT
20	Hutchinson M, Fox RJ, Miller DH, Phillips JT, Kita M, Havrdova E, O'Gorman J, Zhang R, Novas M, Viglietta V, Dawson KT. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study. J Neurol. 2013 Sep;260(9):2286-96. doi: 10.1007/s00415-013-6968-1. Epub 2013 Jun 8. PMID: 23749293.	CONFIRM	Outcomes	Subgroup analysis
21	Kappos L, Cohen J, Collins W, de Vera A, Zhang-Auberson L, Ritter S, von Rosenstiel P, Francis G. Fingolimod in relapsing multiple sclerosis: An integrated analysis of safety findings. Mult Scler Relat Disord. 2014 Jul;3(4):494-504. doi: 10.1016/j.msard.2014.03.002. Epub 2014 Mar 25. PMID: 25877062.	FREEDOMS	Outcomes	Not of interest
22	Kappos L, Giovannoni G, Gold R, Phillips JT, Arnold DL, Hotermans C, Zhang A, Viglietta V, Fox RJ; DEFINE and CONFIRM study investigators. Time course of clinical and neuroradiological effects of delayed-release dimethyl fumarate in multiple sclerosis. Eur J Neurol. 2015 Apr;22(4):664-71. doi: 10.1111/ene.12624. Epub 2015 Jan 2. PMID: 25557371; PMCID: PMC4674988.	DEFINE AND CONFIRM	Outcomes	Not of interest
23	Kappos L, Gold R, Miller DH, Macmanus DG, Havrdova E, Limmroth V, Polman CH, Schmierer K, Yousry TA, Yang M, Eraksoy M, Meluzinova E, Rektor I, Dawson KT, Sandrock AW, O'Neill GN; BG-12 Phase IIb Study Investigators. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008 Oct 25;372(9648):1463-72. doi: 10.1016/S0140-6736(08)61619-0. Erratum in: Lancet. 2009 Apr 18;373(9672):1340. PMID: 18970976.	NCT00168701	Outcomes	Short term follow-up
24	Kappos L, O'Connor P, Radue EW, Polman C, Hohlfeld R, Selmaj K, Ritter S, Schlosshauer R, von Rosenstiel P, Zhang-Auberson L, Francis G. Long-term effects of fingolimod in multiple sclerosis: the randomized	FREEDOMS	Study design	Not RCT

	FREEDOMS extension trial. Neurology. 2015 Apr 14;84(15):1582-91. doi: 10.1212/WNL.0000000000001462. Epub 2015 Mar 20. PMID: 25795646; PMCID: PMC4408283.			
25	Kappos L, Radue EW, Chin P, Ritter S, Tomic D, Lublin F. Onset of clinical and MRI efficacy occurs early after fingolimod treatment initiation in relapsing multiple sclerosis. J Neurol. 2016 Feb;263(2):354-360. doi: 10.1007/s00415-015-7978-y. Epub 2015 Dec 8. PMID: 26645392; PMCID: PMC4751181.	FREEDOMS AND FREEDOMS II	Outcomes	Not requested by DMC
26	Khatri B, Barkhof F, Comi G, Hartung HP, Kappos L, Montalban X, Pelletier J, Stites T, Wu S, Holdbrook F, Zhang-Auberson L, Francis G, Cohen JA; TRANSFORMS Study Group. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. Lancet Neurol. 2011 Jun;10(6):520-9. doi: 10.1016/S1474-4422(11)70099-0. Epub 2011 May 13. PMID: 21571593.	TRANSFORMS	Study design	Not RCT
27	Khatri BO, Pelletier J, Kappos L, Hartung HP, Comi G, Barkhof F, von Rosenstiel P, Meng X, Grinspan A, Hashmonay R, Cohen JA; TRANSFORMS Study Group. Effect of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod vs. interferon β-1a intramuscular: Subgroup analyses of the Trial Assessing Injectable Interferon vs. Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS). Mult Scler Relat Disord. 2014 May;3(3):355-63. doi: 10.1016/j.msard.2013.11.006. Epub 2013 Dec 12. PMID: 25876473.	TRANSFORMS	Population	Not of interest
28	Kita M, Fox RJ, Gold R, Giovannoni G, Phillips JT, Sarda SP, Kong J, Viglietta V, Sheikh SI, Okwuokenye M, Kappos L. Effects of delayed-release dimethyl fumarate (DMF) on health-related quality of life in patients with relapsing-remitting multiple sclerosis: an integrated analysis of the phase 3 DEFINE and CONFIRM studies. Clin Ther. 2014 Dec 1;36(12):1958-1971. doi: 10.1016/j.clinthera.2014.08.013. Epub 2014 Oct 12. Erratum in: Clin Ther. 2018 Mar 7;: PMID: 25315404.	DEFINE AND CONFIRM	Outcomes	Not requested by DMC
29	Kita M, Fox RJ, Phillips JT, Hutchinson M, Havrdova E, Sarda SP, Agarwal S, Kong J, Zhang A, Viglietta V, Sheikh SI, Seidman E, Dawson KT. Effects of BG-12 (dimethyl fumarate) on health-related quality of life in patients with relapsing-remitting multiple sclerosis: findings from the CONFIRM study. Mult Scler. 2014 Feb;20(2):253-7. doi: 10.1177/1352458513507818. Epub 2013 Oct 22. PMID: 24150778.	CONFIRM	Outcomes	Not requested by DMC
30	Kondo T, Kawachi I, Onizuka Y, Hiramatsu K, Hase M, Yun J, Matta A, Torii S. Efficacy of dimethyl fumarate in Japanese multiple sclerosis patients: interim analysis of randomized, double-blind APEX study and its open-label extension. Mult Scler J Exp Transl Clin. 2019 Jul 31;5(3):2055217319864974. doi: 10.1177/2055217319864974. PMID: 31391949; PMCID: PMC6669851.	APEX	Study design	Not RCT
31	Kremenchutzky M, O'Connor P, Hohlfeld R, Zhang-Auberson L, von Rosenstiel P, Meng X, Grinspan A, Hashmonay R, Kappos L. Impact of prior treatment status and reasons for discontinuation on the efficacy and safety of fingolimod: Subgroup analyses of the Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study. Mult Scler Relat Disord. 2014 May;3(3):341-9. doi: 10.1016/j.msard.2013.10.006. Epub 2013 Nov 5. PMID: 25876471.	FREEDOMS	Population	Not of interest

32	Mori M, Ohashi T, Onizuka Y, Hiramatsu K, Hase M, Yun J, Matta A, Torii S. Efficacy and safety of dimethyl fumarate in treatment-naïve Japanese patients with multiple sclerosis: Interim analysis of the randomized placebo-controlled study. Mult Scler J Exp Transl Clin. 2019 Jun 10;5(2):2055217319852727. doi: 10.1177/2055217319852727. PMID: 31218077; PMCID: PMC6558550.	APEX	Outcomes	Short term follow-up
33	Ochi H, Niino M, Onizuka Y, Hiramatsu K, Hase M, Yun J, Matta A, Torii S. 72-Week Safety and Tolerability of Dimethyl Fumarate in Japanese Patients with Relapsing-remitting Multiple Sclerosis: Analysis of the Randomised, Double Blind, Placebo-Controlled, Phase III APEX Study and its Open-Label Extension. Adv Ther. 2018 Oct;35(10):1598-1611. doi: 10.1007/s12325-018-0788-8. Epub 2018 Sep 11. PMID: 30206820; PMCID: PMC6182629.	APEX	Outcomes	Short term follow-up
34	Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, Tang D, Zhang-Auberson L, Kira J. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler. 2012 Sep;18(9):1269-77. doi: 10.1177/1352458511435984. Epub 2012 Feb 21. PMID: 22354739.	SAIDA 2012 NCT00537082	Outcomes	Short term follow-up
35	Saida T, Yamamura T, Kondo T, Yun J, Yang M, Li J, Mahadavan L, Zhu B, Sheikh SI. A randomized placebo-controlled trial of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis from East Asia and other countries. BMC Neurol. 2019 Jan 7;19(1):5. doi: 10.1186/s12883-018-1220-3. PMID: 30616596; PMCID: PMC6322309.	APEX PART A	Outcomes	Short term follow-up
36	Viglietta V, Miller D, Bar-Or A, Phillips JT, Arnold DL, Selmaj K, Kita M, Hutchinson M, Yang M, Zhang R, Dawson KT, Sheikh SI, Fox RJ, Gold R. Efficacy of delayed-release dimethyl fumarate in relapsing-remitting multiple sclerosis: integrated analysis of the phase 3 studies. Ann Clin Transl Neurol. 2015 Feb;2(2):103-18. doi: 10.1002/acn3.148. Epub 2014 Dec 4. PMID: 25750916; PMCID: PMC4338952.	DEFINE and CONFIRM	Outcomes	Not of interest

7.1.2 Annualised relapse rate definitions across the relevant studies

Table 49 Annualised relapse rate definitions across relevant studies

Study name	Relapse definition
BRAVO [9]	A confirmed relapse was defined as the appearance of one or more new **neurological abnormalities**, or **reappearance of one or more previously observed neurological abnormalities**, in the absence of fever, **persisting for >= 48 h,** preceded by > 30 days of a stable or improving condition, and accompanied by at least one of the following: **an increase of at least 0.5 point in EDSS score, an increase of one grade in the score of two of the seven functional systems (FS) on the EDSS**, or an increase
CONFIRM [5]	Relapse: **new or recurrent neurologic symptoms** not associated with fever or infection, lasting **at least** 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses **by at least 30 days**) that were confirmed by the independent neurologic evaluation committee.
DEFINE [4]	Relapses were **new or recurrent neurologic symptoms**, not associated with fever or infection, **that lasted for at least 24 hours** and that were accompanied by new objective neurologic findings according to the examining neurologist's evaluation
FREEDOMS [6]	To constitute a confirmed relapse the symptoms must have been accompanied by **an increase of at least half a point in the EDSS score, of one point in each of two EDSS functional-system score, or of two points in one EDSS functional-system score** (excluding scores for the bowel-bladder or cerebral functional systems) accompanied by symptoms
FREEDOMS II [7]	A relapse was confirmed when it was accompanied by an increase of at least half a step (**0·5) on the EDSS, an increase of 1 point on two different functional systems of the EDSS,** or **2 points on one of the functional systems**
TRANSFORMS [8]	Relapse was defined as new, worsening, or recurrent neurologic symptoms that occurred at least 30 days after the onset of a preceding relapse, that lasted at least 24 hours without fever or infection, and that were accompanied **by an increase of at least half a point on the EDSS or an increase of at least one point in two** functional systems scores or of at least two points in one functional system score

7.1.3 Network meta-analysis – Input values and process

Table 50: CDP3 24 months and 12 months

Study name	Treatments	Total N	Number of events
SUNBEAM	Ozanimod	447	13
SUNBEAM	Interferon	448	19
BRAVO study	Placebo	450	60
BRAVO study	Interferon	447	47
FREEDOMS II study	Placebo	355	103
FREEDOMS II study	Fingolimod	358	91
FREEDOMS study	Placebo	418	101
FREEDOMS study	Fingolimod	425	75
DEFINE Study	Placebo	408	110
DEFINE Study	Dimethyl fumarate	409	65
CONFIRM study	Placebo	363	62
CONFIRM study	Dimethyl fumarate	359	47
TRANSFORMS study	Fingolimod	429	25
TRANSFORMS study	Interferon	431	34
RADIANCE	Ozanimod	433	54
RADIANCE	Interferon	441	50

Table 51: Annualised relapse rate 24 months and 12 months

Study name	Treatments	Person years	Total number of events
SUNBEAM	Ozanimod	276.5952	50
SUNBEAM	Interferon	210.0875	74
BRAVO study	Placebo	808.82	275
BRAVO study	Interferon	826.92	215
FREEDOMS II study	Placebo	615	246
FREEDOMS II study	Fingolimod	623.81	131
FREEDOMS study	Placebo	897.5	359
FREEDOMS study	Fingolimod	955.6	172
DEFINE Study	Placebo	282.24	102
DEFINE Study	Dimethyl fumarate	533.12	91
CONFIRM study	Placebo	561.43	212
CONFIRM study	Dimethyl fumarate	552.99	124
TRANSFORMS study	Fingolimod	303.5338	49
TRANSFORMS study	Interferon	198.0825	65
RADIANCE	Ozanimod	533.12	91
RADIANCE	Interferon	531.1842	149

Table 52: Adverse events 24 months and 12 months

Study name	Treatments	Total N	Number of events
RADIANCE	Ozanimod	434	324
RADIANCE	Interferon beta-1a	440	365

BRAVO	Interferon beta-1a	442	362
BRAVO	Placebo	449	314
FREEDOMS	Fingolimod	425	401
FREEDOMS	Placebo	418	387
FREEDOMS II	Fingolimod	358	350
FREEDOMS II	Placebo	355	343
CONFIRM	Dimethyl-fumarate	359	338
CONFIRM	Placebo	363	333
DEFINE	Dimethyl-fumarate	409	395
DEFINE	Placebo	408	387
SUNBEAM	Interferon beta-1a	445	336
SUNBEAM	Ozanimod	448	268
TRANSFORM	Fingolimod	429	369
TRANSFORM	Interferon beta-1a	431	395

Table 53: Seriuos adverse events 24 months and 12 months

Study name	Treatments	Total N	Number of events
RADIANCE	Ozanimod	434	28
RADIANCE	Interferon beta-1a	440	28
BRAVO	Interferon beta-1a	442	34
BRAVO	Placebo	449	54
FREEDOMS	Fingolimod	425	43
FREEDOMS	Placebo	418	56
FREEDOMS II	Fingolimod	358	53
FREEDOMS II	Placebo	355	45
CONFIRM	Dimethyl-fumarate	359	61
CONFIRM	Placebo	363	79
DEFINE	Dimethyl-fumarate	409	74
DEFINE	Placebo	408	86
SUNBEAM	Interferon beta-1a	445	11
SUNBEAM	Ozanimod	448	13
TRANSFORM	Fingolimod	429	30
TRANSFORM	Interferon beta-1a	431	25

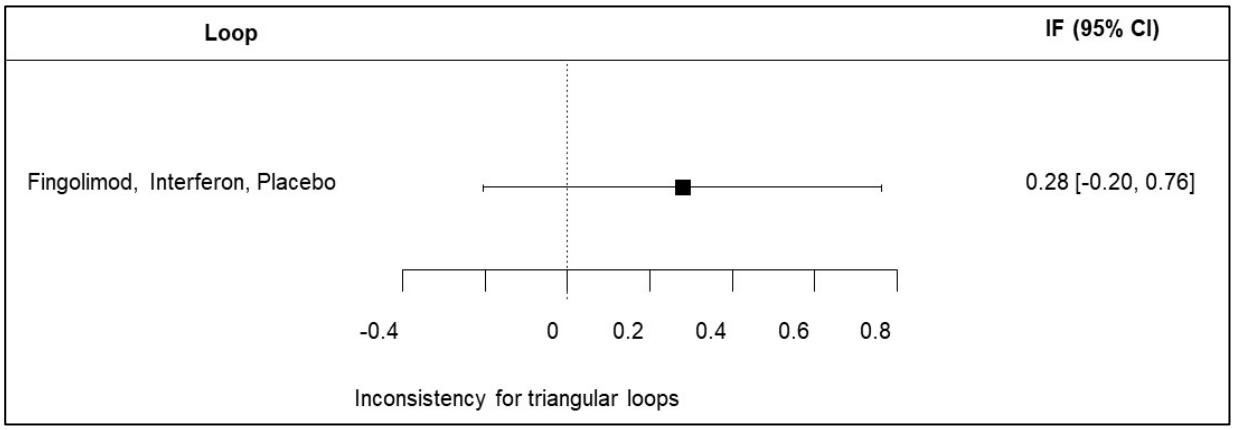
7.1.4 Assessment of inconsistency of the network meta analysis

Table 54 Inconsistency evaluation for annulised relapse rate

Evidence	Comparison	Risk ratio (LCI-UCI)
Direct	interferon vs. placebo	0.765 (0.608, 0.962)
Indirect (NMA)	interferon vs. placebo	0.797 (0.677, 0.935)
Direct	fingolimod vs. interferon	0.485 (0.330, 0.713)
Indirect (NMA)	fingolimod vs. interferon	0.588 (0.485, 0.713)
Direct	fingolimod vs. placebo	0.451 (0.428, 0.464)
Indirect (NMA)	fingolimod vs. placebo	0.468 (0.411, 0.534)

NMA, Network Meta Analysis; LCI, lower confidence interval; UCI,u pper confidence intervals

Figure 4 Inconsistency plot for ARR



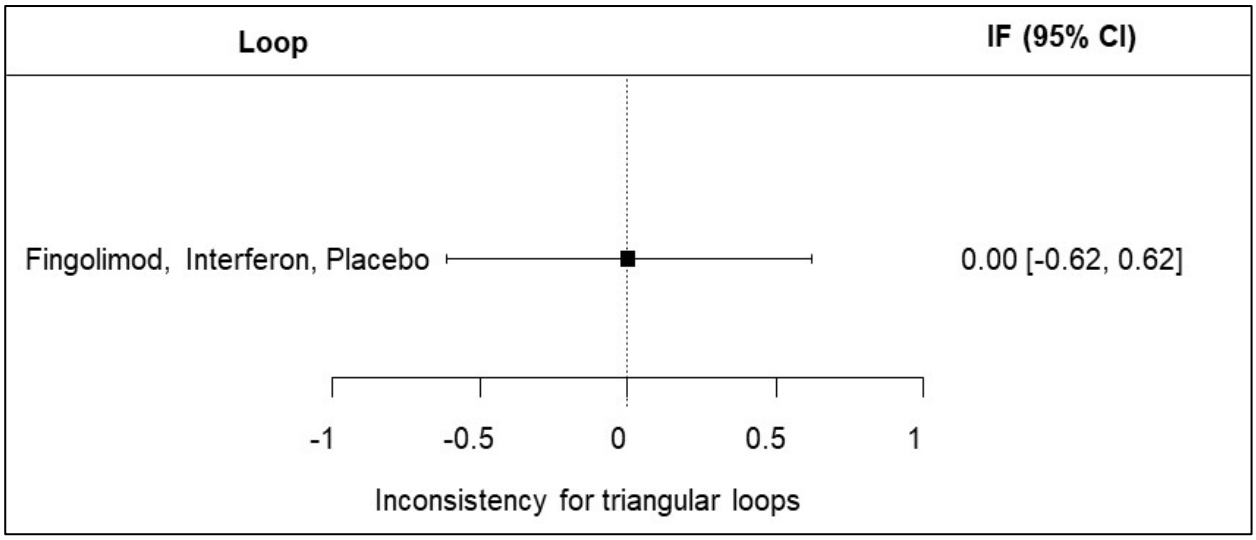
IF, inconsistency factor; CI, credible interval

Table 55 Inconsistency evaluation for CDP3

Evidence	Comparison	HR (LCI-UCI)
Direct	interferon vs. placebo	0.740 (0.510, 1.09)
Indirect (NMA)	interferon vs. placebo	0.859 (0.627, 1.18)
Direct	fingolimod vs. interferon	1.03 (0.670, 1.60)
Indirect (NMA)	fingolimod vs. interferon	1.22 (0.895, 1.67)
Direct	fingolimod vs. placebo	0.763 (0.615, 0.947)
Indirect (NMA)	fingolimod vs. placebo	0.7561 (0.621, 0.919)

NMA, Network Meta Analysis; HR, hazard ration; LCI, lower confidence interval; UCI,u pper confidence intervals

Figure 5 Inconsistency plot for CDP3



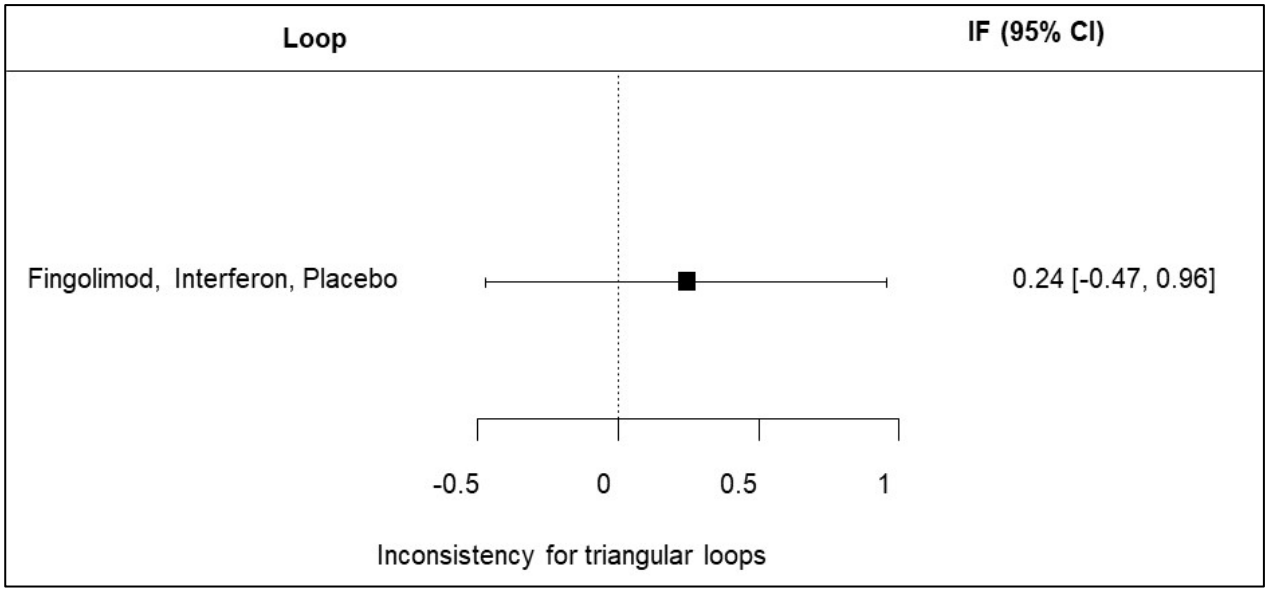
IF, inconsistency factor; CI, credible interval

Table 56 Inconsistency evaluation for AEs

Evidence	Comparison	RR (LCI-UCI)
Direct	interferon vs. placebo	1.17 (1.09, 1.26)
Indirect (NMA)	interferon vs. placebo	1.04 (1.03, 1.06)
Direct	fingolimod vs. interferon	0.870 (0.800, 0.940)
Indirect (NMA)	fingolimod vs. interferon	0.975 (0.953, 0.993)
Direct	fingolimod vs. placebo	1.02 (0.993, 1.04)
Indirect (NMA)	fingolimod vs. placebo	1.02 (0.990, 1.04)

NMA, Network Meta Analysis; RR, relative risk; LCI, lower confidence interval; UCI, upper confidence interval

Figure 6 Inconsistency plot for AEs



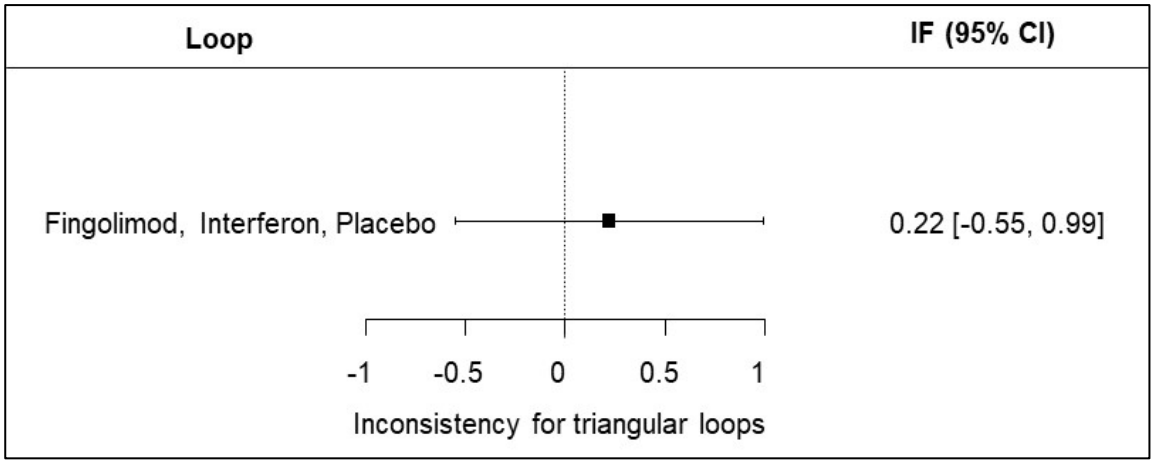
IF, inconsistency factor; CI, credible interval

Table 57 Inconsistency evaluation for SAEs

Evidence	Comparison	RR (LCI-UCI)
Direct	Interferon vs. placebo	0.640 (0.425, 0.962)
Indirect (NMA)	Interferon vs. placebo	0.691 (0.498, 0.953)
Direct	Fingolimod vs. interferon	1.470 (0.900, 2.38)
Indirect (NMA)	Fingolimod vs. interferon	1.32 (0.940, 1.86)
Direct	Fingolimod vs. placebo	0.939 (0.723, 1.22)
Indirect (NMA)	Fingolimod vs. placebo	0.913 (0.719, 1.16)

NMA, Network Meta Analysis; RR, relative risk; LCI, lower confidence interval; UCI, upper confidence interval

Figure 7 Inconsistency plot for SAEs



IF, inconsistency factor; CI, credible interval

7.1.5 WinBUGs codes

Network meta-analysis for Binomial likelihood, cloglog link (Fixed effects model)

```
# Fixed effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)              # vague priors for all trial baselines
   for (k in 1:na[i]) {              # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k])            # Binomial likelihood
      cloglog(p[i,k]) <- log(time[i]) + mu[i] + d[t[i,k]] - d[t[i,1]]
    # model for linear predictor
      rhat[i,k] <- p[i,k] * n[i,k]    # expected value of the numerator

      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  #Deviance contribution
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])              #Total Residual Deviance
d[1]<-0            # treatment effect is zero for reference treatment
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
for (c in 1:(nt-1))
                {
                for (k in (c+1):nt)
                                {
                                HR[k,c] <- exp(d[k] - d[c] )
                                HR[c,k] <- 1/HR[k,c]
                                                        }
                }

# Treatment A effect size, based on average of the studies including it.
for (i in 1:ns)
                {
```

```
                mu1[i] <- mu[i] * equals(t[i,1],1)
                count1[i] <- equals(t[i,1],1)
                }
for (i in 1:nt)
                {
                cloglog(T[i])<- log(timeA)+ (sum(mu1[])/sum(count1[])) +d[i]
                #rk[i]<- nt + 1 - rank(d[],i) # assumes events are "good"
                rk[i]<- rank(d[],i)  # assumes events are "bad"
                for (j in 1:nt)
                                {
                                # Is treatment i the jth best, assuming lower outcomes are good.
                   best[i,j]<-equals(rk[i], j)
                                #best[i,j]<-equals(rk[i], nt + 1 - j) # if higher outcomes are good.
                                }
                }

for(i in 1:nt) {
                                for(j in 1:nt) {
                                                cumeffectiveness[i,j]<- sum(best[i,1:j])
                                }
                }

#SUCRAS#

                for(i in 1:nt) {
                                SUCRA[i]<- sum(cumeffectiveness[i,1:(nt-1)]) /(nt-1)
                }


#relative risk of each treatment vs. 1
for (k in 2:nt){
#NNT[k]<-1/(T[k]-T[1]) #Assume that the probability is small for treatment 1
NNT[k] <-1/(T[1]-T[k]) #Assume that the probability is greater for treatment 1
RD[k]<- 1/NNT[k]
}
```

```
# *** PROGRAM ENDS
 }
```

Network meta-analysis for Binomial likelihood, cloglog link (Random effects model)

```
# Random effects model for multi-arm studies
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm studies is zero for control arm
   delta[i,1] <- 0            # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
   for (k in 1:na[i]) {             # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
      cloglog(p[i,k]) <- log(time[i]) + mu[i] + delta[i,k]
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm studies
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
  }
totresdev <- sum(resdev[])           #Total Residual Deviance
```

```
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,2)     # vague prior for between-trial SD
tau2<-sd*sd # between trial variance
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA, over a time period timeA
A ~ dnorm(-4.2,1.11)



for (c in 1:(nt-1))
                {
                for (k in (c+1):nt)
                                {
                                HR[k,c] <- exp(d[k] - d[c] )
                                HR[c,k] <- 1/HR[k,c]
                                                                }
                }

# Treatment A effect size, based on average of the studies including it.
for (i in 1:ns)
                {
                mu1[i] <- mu[i] * equals(t[i,1],1)
                count1[i] <- equals(t[i,1],1)
                }
for (i in 1:nt)
                {
                cloglog(T[i])<- log(timeA)+ sum(mu1[])/sum(count1[]) +d[i]
                #rk[i]<- nt + 1 - rank(d[],i) # assumes events are "good"
                rk[i]<- rank(d[],i)  # assumes events are "bad"
                for (j in 1:nt)
                                {
                                # Is treatment i the jth best, assuming lower outcomes are good.
```

```
                best[i,j]<-equals(rk[i], j)
                        #best[i,j]<-equals(rk[i], nt + 1 - j) # if higher outcomes are good.
                        }
        }

for(i in 1:nt) {
                        for(j in 1:nt) {
                                cumeffectiveness[i,j]<- sum(best[i,1:j])
                        }
        }

#SUCRAS#

        for(i in 1:nt) {
                        SUCRA[i]<- sum(cumeffectiveness[i,1:(nt-1)]) /(nt-1)
        }


#relative risk of each treatment vs. 1
for (k in 2:nt){
#NNT[k]<-1/(T[k]-T[1]) #Assume that the probability is small for treatment 1
NNT[k] <-1/(T[1]-T[k]) #Assume that the probability is greater for treatment 1
RD[k]<- 1/NNT[k]
}

# *** PROGRAM ENDS
 }
```

Network meta-analysis for Poisson likelihood, log link (Fixed effects model)

```
# Fixed effects model for multi-arm studies
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
   for (k in 1:na[i]) {             # LOOP THROUGH ARMS
      r[i,k] ~ dpois(theta[i,k])   # Poisson likelihood
```

```
        theta[i,k] <- lambda[i,k]*E[i,k] # event rate * exposure
        log(lambda[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))           }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }


                # Rate ratios
for (c in 1:(nt-1))
                {
                for (k in (c+1):nt)
                                {
                                RR[k,c] <- exp(d[k] - d[c] )
                                RR[c,k] <- 1/RR[k,c]
                                }
                }
for (i in 1:ns) {
                                mu1[i] <- mu[i] * equals(t[i,1],1)
                                count1[i] <- equals(t[i,1],1)
                                }


# Risk estimates for each treatment and treatment ranking
for (i in 1:nt)
                {
                rk[i]<-  rank(d[],i) # assumes events are "bad"
                for (j in 1:nt)
                                {
                                # Is treatment i the jth best, assuming lower outcomes are good.
```

```
                best[i,j]<-equals(rk[i], j)
                        #best[i,j]<-equals(rk[i], nt + 1 - j) # if higher outcomes are good.
                        }
        }


for(i in 1:nt) {
                        for(j in 1:nt) {
                                cumeffectiveness[i,j]<- sum(best[i,1:j])
                        }
        }

#SUCRAS#

        for(i in 1:nt) {
                        SUCRA[i]<- sum(cumeffectiveness[i,1:(nt-1)]) /(nt-1)
        }


for (k in 1:nt) { log(T[k]) <- sum(mu1[])/sum(count1[]) + d[k]  }

for (k in 2:nt){

#NNT[k]<-1/(T[k]-T[1]) #Assume that the rate is small for treatment 1

NNT[k] <-1/(T[1]-T[k]) #Assume that the rate is greater for treatment 1

}

}                       # *** PROGRAM ENDS
```

Network meta-analysis for Poisson likelihood, log link (Random effects model)

```
# Random effects model for multi-arm studies
model{                  # *** PROGRAM STARTS
for(i in 1:ns){         # LOOP THROUGH STUDIES
```

```
    w[i,1] <- 0    # adjustment for multi-arm studies is zero for control arm
    delta[i,1] <- 0                # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
    for (k in 1:na[i]) {             # LOOP THROUGH ARMS
       r[i,k] ~ dpois(theta[i,k])   # Poisson likelihood
       theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
       log(lambda[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
       dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))           }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
       delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
       md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
       taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
       w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm studies
       sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
  }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)
}


                    # Rate ratios
for (c in 1:(nt-1))
                    {
                    for (k in (c+1):nt)
```

```
                                {
                                RR[k,c] <- exp(d[k] - d[c] )
                                RR[c,k] <- 1/RR[k,c]
                                }
                        }
sd ~ dunif(0,2)     # vague prior for between-trial SD

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
tau2<- 1/tau

# Provide estimates of treatment effects T[k] on the natural (rate) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
#A ~ dnorm(meanA,precA)-use the posterior if not using below code (meanA=-3, precA=1.77)

for (i in 1:ns) {
                                mu1[i] <- mu[i] * equals(t[i,1],1)
                                count1[i] <- equals(t[i,1],1)
                                }


# Risk estimates for each treatment and treatment ranking
for (i in 1:nt)
                        {
                        rk[i]<-  rank(d[],i)   # assumes events are "bad"
                        for (j in 1:nt)
                                {
                                # Is treatment i the jth best, assuming lower outcomes are good.
                           best[i,j]<-equals(rk[i], j)
                                #best[i,j]<-equals(rk[i], nt + 1 - j) # if higher outcomes are good.
                                }
                        }


for(i in 1:nt) {
```

```
                    for(j in 1:nt) {
                        cumeffectiveness[i,j]<- sum(best[i,1:j])
                    }
            }

#SUCRAS#

            for(i in 1:nt) {
                    SUCRA[i]<- sum(cumeffectiveness[i,1:(nt-1)]) /(nt-1)
            }


for (k in 1:nt) { log(T[k]) <- sum(mu1[])/sum(count1[]) + d[k]  }

for (k in 2:nt){

#NNT[k]<-1/(T[k]-T[1]) #Assume that the rate is small for treatment 1
RD[k]<- T[k]-T[1]
NNT[k] <-1/(T[1]-T[k]) #Assume that the rate is greater for treatment 1

}

}

# *** PROGRAM ENDS
```

Network meta-analysis for binary outcomes (Fixed effects model)

```
## Binomial likelihood logit link
## Fixed effects model

model
{

# Loop over studies
for(s in 1:NS)
                {
                # Adjustments for comparator arms
                delta[s,trt[s,1]] <- 0

                # Loop over all arms within a study for likelihood and regression
                for (a in 1:na[s])
                                {
                                # Binomial likelihood
                                r[s,trt[s,a]]~dbin(p[s,trt[s,a]],n[s,trt[s,a]])

                                # Regression (model)
                                logit(p[s,trt[s,a]])<-mu[s]+ delta[s,trt[s,a]]

                                #Deviance contribution
  rhat[s,trt[s,a]] <- p[s,trt[s,a]] * n[s,trt[s,a]]
  dev[s,a] <- 2 * (r[s,trt[s,a]] * (log(r[s,trt[s,a]])-log(rhat[s,trt[s,a]]))
                                                                                                +
(n[s,trt[s,a]]-r[s,trt[s,a]]) * (log(n[s,trt[s,a]]-r[s,trt[s,a]])
                                                                                                -
log(n[s,trt[s,a]]-rhat[s,trt[s,a]])))
                                }

                                # Deviance contribution of study s
                                sumdev[s]<- sum(dev[s,1:na[s]])

                # Loop over active arms for trial-specific LORs
                for (a in 2:na[s])
                                {
                                # Fixed effects: trial-specific LORs
                                delta[s,trt[s,a]] <- md[s,trt[s,a]]

                                # Means of studies-specific LORS
                  md[s,trt[s,a]] <- d[trt[s,a]] - d[trt[s,1]]

                                }

                }

# Vague priors for the study effects (log odds of treatment 1)
for(s in 1:NS)
                {
                mu[s]~dnorm(0,0.0001)
                }
```

```
# Priors for the treatment effects (log odds ratios vs treatment 1)
d[1] <- 0
d[2]~dnorm(0,0.001)
for (i in 3:NT)
                {
                prd.m[i] <- pr.m[i]+d[2]-d[1]
                d[i]~dnorm(prd.m[i],pr.prec[i])
                }


# Odds ratios
for (c in 1:(NT-1))
                {
                for (k in (c+1):NT)
                                {
                                or[k,c] <- exp(d[k] - d[c] )
                                or[c,k] <- 1/or[k,c]
                                }
                }

# Treatment A effect size, based on average of the studies including it.
for (s in 1:NS)
                {
                mu1[s] <- mu[s] * equals(trt[s,1],1)
                count1[s] <- equals(trt[s,1],1)
                }

# Risk estimates for each treatment and treatment ranking
for (i in 1:NT)
                {
                logit(T[i])<- sum(mu1[])/sum(count1[]) +d[i]
                #rk[i]<- NT + 1 - rank(d[],i) # assumes events are "good"
                rk[i] <- rank(d[],i)                                    # assumes events are "bad"

                for (j in 1:NT)
                                {
                                # Is treatment i the jth best, assuming lower outcomes are good.
                 best[i,j]<-equals(rk[i], j)
                                }
                }
for(i in 1:NT) {
                                for(j in 1:NT) {
                                                cumeffectiveness[i,j]<- sum(best[i,1:j])
                                }
                }

#SUCRAS#

                for(i in 1:NT) {
                                SUCRA[i]<- sum(cumeffectiveness[i,1:(NT-1)]) /(NT-1)
                }
```

```
# Total deviance
resdev <- sum(sumdev[])


# Relative Risk
for (c in 1:(NT-1)) {
                                for (k in (c+1):NT) {
                                                RD[c,k]<-T[c]-T[k]
                                                RD[k,c] <- T[k] - T[c]
                                                RR[c,k] <- T[c]/T[k]
                                                RR[k,c] <- 1/RR[c,k]
                                }

                }


}
```

Network meta-analysis for binary outcomes (Random effects model)

```
## Binomial likelihood logit link
## Random effects model

model
{

# Loop over studies
for(s in 1:NS)
                {
                # Adjustments for comparator arms
                w[s,1] <- 0
                delta[s,trt[s,1]] <- 0

                # Loop over all arms within a study for likelihood and regression
                for (a in 1:na[s])
                                {
                                # Binomial likelihood
                                r[s,trt[s,a]]~dbin(p[s,trt[s,a]],n[s,trt[s,a]])

                                # Regression
                                logit(p[s,trt[s,a]])<-mu[s]+ delta[s,trt[s,a]]

                                #Deviance contribution
  rhat[s,trt[s,a]] <- p[s,trt[s,a]] * n[s,trt[s,a]]
  dev[s,a] <- 2 * (r[s,trt[s,a]] * (log(r[s,trt[s,a]])-log(rhat[s,trt[s,a]])))
                                                                                                +
(n[s,trt[s,a]]-r[s,trt[s,a]]) * (log(n[s,trt[s,a]]-r[s,trt[s,a]])
                                                                                                -
log(n[s,trt[s,a]]-rhat[s,trt[s,a]])))
                                }

                                # Deviance contribution of study s
```

```
                        sumdev[s]<- sum(dev[s,1:na[s]])

                # Loop over active arms for trial-specific LORs
                for (a in 2:na[s])
                        {
                        # Random effects: trial-specific LORs
                        delta[s,trt[s,a]] ~ dnorm(md[s,trt[s,a]],taud[s,trt[s,a]])

                        # Means of studies-specific LORS
                        md[s,trt[s,a]] <- d[trt[s,a]] - d[trt[s,1]] + sw[s,a]

                        # Precision of LOR distributions
                        taud[s,trt[s,a]] <- tau*2*(a-1)/a

                        # Adjustment for multi-arm RCTs
                        w[s,a] <- (delta[s,trt[s,a]] - d[trt[s,a]] + d[trt[s,1]])
 sw[s,a] <-sum(w[s,1:a-1])/(a-1)
                        }

                }

# Vague priors for the study effects (log odds of treatment 1)
for(s in 1:NS)
                {
                mu[s]~dnorm(0,0.0001)
                }

# Priors for the treatment effects (log odds ratios vs treatment 1)
d[1] <- 0
d[2]~dnorm(0,0.001)
for (i in 3:NT)
                {
                prd.m[i] <- pr.m[i]+d[2]-d[1]
                d[i]~dnorm(prd.m[i],pr.prec[i])
                }

# Vague prior for random effects standard deviation
sd~dunif(0,2)
tau<-1/pow(sd,2)
tau2<- 1/tau

# Odds ratios
for (c in 1:(NT-1))
                {
                for (k in (c+1):NT)
                        {
                        or[k,c] <- exp(d[k] - d[c] )
                        or[c,k] <- 1/or[k,c]
                        }
                }

# Treatment A effect size, based on average of the studies including it.
```

```
for (s in 1:NS)
                {
                mu1[s] <- mu[s] * equals(trt[s,1],1)
                count1[s] <- equals(trt[s,1],1)
                }

# Risk estimates for each treatment and treatment ranking
for (i in 1:NT)
                {
                logit(T[i])<- sum(mu1[])/sum(count1[]) +d[i]
                #rk[i]<- NT + 1 - rank(d[],i)
                rk[i] <- rank(d[],i)                                    # assumes events are "bad"
                for (j in 1:NT)
                                {
                                # Is treatment i the jth best, assuming lower outcomes are good.
                 best[i,j]<-equals(rk[i], j)
                                #best[i,j]<-equals(rk[i], NT + 1 - j) # if higher outcomes are good.
                                }
                }
for(i in 1:NT) {
                                for(j in 1:NT) {
                                                cumeffectiveness[i,j]<- sum(best[i,1:j])
                                }
                }

#SUCRAS#

                for(i in 1:NT) {
                                SUCRA[i]<- sum(cumeffectiveness[i,1:(NT-1)]) /(NT-1)
                }

# Total deviance
resdev <- sum(sumdev[])

#relative risk of each treatment vs. 1
for (k in 2:NT){

NNT[k]<-1/(T[k]-T[1]) #Assume that the probability is small for treatment 1

#NNT[k] <-1/(T[1]-T[k]) #Assume that the probability is greater for treatment 1

}

# Relative Risk
for (c in 1:(NT-1)) {
                                for (k in (c+1):NT) {
                                                RD[c,k]<-T[c]-T[k]
                                                RD[k,c] <- T[k] - T[c]
                                                RR[c,k] <- T[c]/T[k]
                                                RR[k,c] <- 1/RR[c,k]
                                }
```

```
                }
}
```

7.1.6 Main characteristics of included studies

Study characteristics – ozanimod studies

Table 58 The RADIANCE phase III study - Main study characteristics

Trial name	RADIANCE
NCT number	NCT02047734 The study is a two-part trial (Part A and B), phase II/III, with Part A (NCT01628393) consisting of a placebo-controlled phase (II) with an optional extension period and Part B (NCT02047734) as an active-controlled phase III study. Part B is presented within this table. [2]
Objective	The purpose of this study is to determine whether ozanimod is effective in the treatment of relapsing multiple sclerosis (RMS). [2]
Publications – title, author, journal, year	Cohen JA, Comi G, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, Hartung HP, Montalban X, Kubala Havrdová E, Cree BAC, Sheffield JK, Minton N, Raghupathi K, Huang V, Kappos L; RADIANCE Trial Investigators. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. Lancet Neurol. 2019 Nov;18(11):1021-1033. doi: 10.1016/S1474-4422(19)30238-8. Epub 2019 Sep 3. PubMed PMID: 31492652.[2]
Study type and design	24-month, multicentre, randomized, double-blind, double-dummy, active-controlled, three-arm (1:1:1), parallel group, phase 3 trial. [2] Randomization was performed 1:1:1 via an interactive voice response system, stratified by baseline EDSS (≤3.5 vs >3.5, and country). [2] Participants, investigators, EDSS assessors, study personnel, MRI reviewers, and the sponsor were masked to treatment and total and differential white blood cell counts. [2] The RADIANCE phase 3 commenced after a planned interim analysis, including thorough safety review by the data monitoring committee, of RADIANCE phase 2. [2]
Follow-up time	Follow-up time was 24 months. [2]
Population (inclusion and exclusion criteria)	Inclusion criteria 1. MS, as diagnosed by the revised 2010 McDonald criteria 2. Exhibited a relapsing clinical course consistent with RMS and history of brain MRI lesions consistent with MS 3. Ages 18–55 years, inclusive 4. EDSS score between 0 and 5·0 at baseline 5. Met one of the following disease activity criteria: • At least 1 documented relapse within the last 12 months prior to screening or • At least 1 documented relapse occurred within the last 24 months prior to screening and evidence of at least 1 GdE lesion on brain MRI within the last 12 months prior to randomisation 6. No history of relapse from 30 days prior to screening until randomisation; during this period, subjects must have been clinically stable, without systemic corticosteroid treatment or adrenocorticotrophic hormone (ACTH) 7. Able to provide written informed consent and to be compliant with the schedule of protocol assessments

	8. Subjects of reproduction potential (males and females) must have practiced an acceptable method of birth control (acceptable methods of birth control in this study included: surgical sterilisation, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, vasectomy, or double-barrier method [condom or diaphragm with spermicide OR condom and diaphragm]) during study participation and for 30 days after their last dose of treatment of study drug or true sexual abstinence (periodic abstinence [calendar, symptothermal, post-ovulation methods] and withdrawal were not acceptable methods of contraception) 9. Subjects must have had documentation of positive Varicella zoster virus (VZV) immunoglobulin G antibody status, or complete VZV vaccination at least 30 days prior to study entry. *Exclusion criteria* 1. Primary progressive MS at screening 2. Disease duration of more than 15 years in patients with an EDSS ≤2·0 3. Contraindications to MRI or gadolinium contrast, such as known allergy to gadolinium contrast dyes, renal insufficiency, claustrophobia, body size incompatible with the scanner, pacemaker, cochlear implants, intracranial vascular clips 4. Incompatibility with beta interferon use (e.g., intolerable side effects), including: • Prior cessation of interferon beta-1a therapy due to poor tolerability • Prior cessation of interferon beta-1a therapy due to liver function abnormalities or other toxicities • Prior cessation of other interferon-beta therapy due to poor tolerability or toxicity that was likely to recur with interferon beta-1a therapy *Exclusions Related to General Health*: 5. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin measured during screening 6. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, renal, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the subject at risk by participating in the study in the opinion of the treating investigator 7. Specific cardiac conditions were excluded, including history or presence of: • Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalisation, class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnoea • Prolonged corrected QT interval using Fridericia's formula (QTcF) interval (QTcF >450 msec males, >470 msec females), or at additional risk for QT prolongation (eg, hypokalaemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT-prolonging drugs) • Subjects with other pre-existing stable cardiac conditions who were not cleared for the study by an appropriate cardiac evaluation by a cardiologist • Other clinically significant conduction abnormalities or any other significant cardiac condition that could jeopardise a subject's health or put them at significant safety risk during the course of the study in the opinion of treating investigator

	8. Resting heart rate less than 55 bpm at screening 9. Diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with haemoglobin A1c >7%, or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy 10. History of uveitis 11. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease [but excluding fungal infection of nail beds, minor upper respiratory tract infection and minor skin conditions]), or any major episode of infection that required hospitalisation or treatment with IV antibiotics within 30 days of screening or oral antibiotics within 14 days prior to screening 12. History or known presence of recurrent or chronic infection (e.g., hepatitis A, B, or C, human immunodeficiency virus, syphilis, TB); recurring urinary tract infections could be allowed (testing for viral serology and syphilis was performed during screening) 13. History of cancer, including solid tumors and haematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) 14. Suicide attempts in the past or current signs of major depression 15. History of alcohol or drug abuse within 1 year prior to randomisation 16. History of or currently active primary or secondary immunodeficiency *Exclusions Related to Medications*: 17. Prior use of any investigational agent within 6 months prior to enrollment 18. Receipt of a live vaccine within 4 weeks prior to randomisation 19. Non-lymphocyte-depleting disease-modifying MS agents (eg, glatiramer acetate, interferons) must have been discontinued from signing of informed consent 20. Previous treatment with lymphocyte-depleting therapies (eg, alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation) 21. Treatment with other immunosuppressant agents such as azathioprine, cyclosporine, methotrexate, or mycophenolate within 6 months prior to randomisation 22. Systemic corticosteroid therapy or ACTH use within 30 days prior to screening 23. Prior treatment with lymphocyte trafficking blockers (eg, natalizumab, fingolimod, other $S1P_{R1}$ agonists) 24. Treatment with intravenous immune globulin, plasmapheresis, within 3 months prior to randomization 25. Treatment with other disease modifying therapies (eg, dimethyl fumarate, teriflunomide, daclizumab, laquinimod) within 3 months prior to randomisation 26. Intolerance of or contraindication to oral or IV corticosteroids 27. Use of therapies that were not allowed based on cytochrome P450 3A4 (CYP3A4) metabolism within 4 weeks prior to randomisation 28. Treatment with medications with a known impact on the cardiac conduction system were excluded (eg, beta blockers, calcium channel blockers, class Ia or class III anti-arrhythmic drugs, and QT prolonging drugs with a known risk of torsades de pointes [eg, citalopram, chlorpromazine, haloperidol, methadone, and erythromycin])

	Exclusions Related to Laboratory Results: 29. Positive rapid plasma reagin 30. Serum creatinine >1·4 mg/dL for women or >1·6 mg/dL for men 31. Liver function impairment or persisting elevations of aspartate aminotransferase or alanine aminotransferase >1·5 times the upper limit of normal (ULN), or direct bilirubin >1·5 times the ULN 32. Platelet count <100,000/µL 33. Haemoglobin <8·5 g/dL 34. Neutrophils <1500/µL 35. Absolute white blood cell (WBC) count <3500/µL; absolute lymphocyte count <800/µL 36. Clinically significant findings on brain MRI scan consistent with conditions other than MS 37. ECG showing any clinically significant abnormality (eg, acute ischaemia, significant heart conduction abnormality [eg, left bundle branch block]) 38. FEV_1 or FVC <70% of predicted values at screening 39. Presence of >20 GdE lesions on baseline brain MRI scan [2]
Intervention	Ozanimod HCl 1.0 mg (equivalent to 0.92 mg ozanimod) oral capsule once daily (n=433) Ozanimod HCl 0.5 mg (~0.46 mg ozanimod) oral capsule once daily (n=439) Patients were given once weekly sham injections of the comparator to maintain blinding. [2]
Baseline characteristics	*Table 59 The RADIANCE phase III study - Baseline characteristics*

Cohen et al. 2019 [2]	**Interferon beta-1a (n=441))**	**Ozanimod 0.5 mg (n=439)**	**Ozanimod 1.0 mg (n=433)**
Age, years	35·1 (9·1)	35·4 (8·8)	36·0 (8·9)
Sex			
Female	304 (68·9%)	287 (65·4%)	291 (67·2%)
Male	137 (31·1%)	152 (34·6%)	142 (32·8%)
Race			
White	432 (98·0%)	431 (98·2%)	428 (98·8%)
Black	7 (1·6%)	6 (1·4%)	5 (1·2%)
Asian	1 (0·2%)	0	0
Other	1 (0·2%)	2 (0·5%)	0
Bodyweight, kg	70·1 (16·4)	69·5 (14·7)	70·9 (17·0)
Region			
Eastern Europe	379 (85·9%)	378 (86·1%)	374 (86·4%)
Western Europe	40 (9·1%)	40 (9·1%)	36 (8·3%)
North America	16 (3·6%)	16 (3·6%)	16 (3·7%)
Southern Africa	6 (1·4%)	5 (1·1%)	7 (1·6%)
Time since multiple sclerosis symptom	6·4 (6·07)	6·2 (5·55)	6·9 (6·20)
onset, years			
Time since multiple sclerosis diagnosis, years	3·6 (4·61)	3·5 (4·21)	4·0 (5·17)
Type of multiple sclerosis			
Relapsing-remitting multiple sclerosis	432 (98·0%)	432 (98·4%)	425 (98·2%)
Progressive-relapsing multiple sclerosis	8 (1·8%)	7 (1·6%)	8 (1·8%)
Secondary progressive multiple sclerosis	1 (0·2%)	0	0

	Expanded disability status scale score	2·5 (1·16)	2·5 (1·17)	2·6 (1·15)
	Number of relapses in previous 12 months	1·3 (0·58)	1·4 (0·64)	1·3 (0·56)
	Number of relapses in previous 24 months	1·8 (0·86)	1·8 (0·90)	1·7 (0·82)
	Previous disease-modifying therapy*	126 (28·6%)	131 (29·8%)	123 (28·4%)
	Number of gadolinium-enhancing lesions	1·8 (3·54)	1·8 (3·62)	1·6 (3·78)
	Gadolinium-enhancing lesion volume, cm^3	0·25 (0·62)	0·23 (0·53)	0·21 (0·53)
	Number of T2 lesions	48·7 (32·62)	48·7 (36·27)	47·9 (32·37)
	T2 lesion volume, cm^3	11·50 (13·29)	11·18 (13·64)	11·64 (13·40)
	Normalised brain volume, cm^3†	1449·58 (77·16)	1452·85 (71·98)	1441·95 (79·23)
	From Cohen et al. [2]			
	Data from the ITT-population. Data are n (%) or mean (SD). *Previous disease-modifying therapies include interferon beta-1a, pegylated interferon beta-1a, interferon beta-1b, glatiramer acetate, daclizumab, dimethyl fumarate, and teriflunomide. †Data available for 432 participants in the ozanimod 1.0 mg group, 437 in the ozanimod 0.5 mg group, and 439 in the interferon beta-1a group.			
Primary and secondary endpoints	The primary endpoint was annualised relapse rate (ARR) over 24 months based on confirmed, protocol-defined relapses. Relapses were defined as new or worsening neurological symptoms persisting for more than 24 h, not attributable to confounding factors, and preceded by stable or improving neurological status for at least 30 days. Relapses were confirmed when accompanied by objective neurological worsening (EDSS increase ≥0.5 on overall score, 2 points on one functional system scale score, or 1 point on two or more functional system scale scores). Key secondary endpoints were: • number of new or enlarging T2 brain MRI lesions over 24 months • number of gadolinium-enhancing brain MRI lesions at month 24 • time to onset of disability progression (EDSS worsening of ≥1-point increase, confirmed after 3 and 6 months). Disability progression was assessed as a prespecified pooled analysis with data from the phase 3 SUNBEAM trial (NCT02294058; EudraCT 2014–002320–27; treatment duration, ≥12 months), which was conducted concurrently with RADIANCE phase 3 and reported separately. See the study description in the table below. Other secondary endpoints were: • proportions of participants free of GdH and new or enlarging T2 lesions at month 24 • changes in multiple sclerosis functional composite (MSFC) score and the physical and mental health composite scores of the multiple sclerosis quality of life-54 (MSQOL-54) measurement from baseline to month 24 • percentage change in whole brain atrophy from baseline to 24 months Changes in cortical grey matter and thalamic volume were prespecified exploratory endpoints. Safety analyses included the incidence and type of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to discontinuation of study treatment. [2]			
Method of analysis	A sample size of about 400 participants per treatment group was estimated using a Poisson regression model and the method of Nicholas and colleagues.12 This sample size was predicted to provide about 90% power at a two-sided significance level of 0.025 to detect a 37% lower 24-month ARR (ARR 0.19) for each ozanimod dose group, assuming an ARR of 0.3 in the interferon beta-1a group extra-Poisson variation ($\sigma 2=1.3$), and a 17% dropout rate.			

	The primary endpoint was analysed using a prespecified Poisson regression model adjusted for region (eastern Europe *vs* rest of world), baseline age, and baseline number of GdH lesions and included the natural log transformation of time on study as an offset term. Statistical testing was performed between each ozanimod dose and interferon beta-1a at a two-sided significance level of 0.025 to account for multiple comparisons. Additional sensitivity analyses were performed to assess assumptions regarding the Poisson model (described in the publication, appendix p 12). To control for type 1 error, a hierarchical testing procedure was used to assess key secondary endpoints (described in the publication, appendix p 10). If both ozanimod doses reached statistical significance on the primary endpoint, then ozanimod 1.0 mg would be compared with interferon beta-1a for number of new or enlarging T2 lesions over 24 months at a two-sided α of 0.05. If that comparison was statistically significant, then this endpoint would be tested for ozanimod 0.5 mg versus interferon beta-1a at a two-sided α of 0.05. The same procedure was then followed for number of GdH lesions at month 24, followed by time to onset of confirmed disability progression (pooled with data from the SUNBEAM study), until a comparison did not reach statistical significance, after which all subsequent comparisons would be considered exploratory. If only one of the ozanimod doses was statistically significant on the primary endpoint, then the hierarchical testing procedure would be executed on the surviving dose at a two-sided α of 0.025. The number of new or enlarging T2 lesions over 24 months and number of GdH lesions at month 24 were analysed using a negative binomial regression model adjusted for region, baseline age, and baseline number of GdH lesions and included the natural log transformation of the number of available MRI scans as an offset term. Analysis of time to onset of 3-month and 6-month confirmed disability progression was pooled with SUNBEAM because neither RADIANCE phase 3 nor SUNBEAM was powered to detect a treatment difference with a two-sided α of 0.05. For both the pooled analysis and the analysis of RADIANCE phase 3 only, time to onset of disability progression was analysed using a Cox proportional hazards model adjusted for study, region, baseline age, and baseline EDSS score. A Kaplan-Meier analysis of the difference in time to onset of disability progression curves was done. For brain volume loss, change from baseline was calculated using descriptive statistics. Comparisons of percentage change from baseline in brain volume loss between interferon beta-1a and ozanimod 1.0 mg or 0.5 mg used an analysis of covariance (ANCOVA) model adjusted for region, baseline EDSS category, and baseline brain volume, with missing data imputed via the last observation-carried-forward method. Using the study population as the reference population, Z scores were calculated for each MSFC component (timed 25-foot walk test, nine-hole peg test, and paced auditory serial addition test [PASAT]) and averaged to derive an overall composite score. Ozanimod was compared with interferon beta-1a for change from baseline in MSFC scores and MSQOL-54 physical and mental health composite scores using ANCOVA, with models adjusted for region, EDSS score, and baseline value of interest. Safety outcomes were reported as incidence of TEAEs in each treatment group, with inclusion limited to one occurrence of a preferred term per participant. Statistical hypothesis testing was not performed on any safety results. The primary analysis was done in the intention-to-treat population of all randomly assigned participants who received study drug, grouped by assigned treatment. The safety population included all randomly assigned participants who received study drug, grouped by highest dose of ozanimod received. [2]
Subgroup analyses	Prespecified analyses were performed for ARR and the MRI lesion count endpoints for the following subgroups: baseline EDSS (≤3・5 *vs* >3・5); baseline gadolinium enhancing lesions (present *vs* absent); treatment-naïve versus previous disease-modifying therapy; baseline age (≤40 years *vs* >40 years); sex (female *vs* male); race (white *vs*

	non-white); bodyweight (less than median *vs* median or greater); relapses in previous 12 months (less than two *vs* two or more; ARR endpoint only); and region (eastern Europe *vs* rest of world). [2] Analyses were not performed for any subgroup comprising less than 5% of the overall population. [2]

Table 60 The SUNBEAM phase III study - Main study characteristics

Trial name	SUNBEAM
NCT number	NCT02294058
Objective	The SUNBEAM study aimed to assess the safety and efficacy of ozanimod versus intramuscular interferon beta-1a in participants with relapsing multiple sclerosis. [3]
Publications – title, author, journal, year	Comi G, Kappos L, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, Hartung HP, Montalban X, Kubala Havrdová E, Cree BAC, Sheffield JK, Minton N, Raghupathi K, Ding N, Cohen JA; SUNBEAM Study Investigators. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol. 2019 Nov;18(11):1009-1020. doi: 10.1016/S1474-4422(19)30239-X. Epub 2019 Sep 3. PubMed PMID: 31492651. [this publication reports the results of the SUNBEAM study separately][3]
Study type and design	12-month, multicentre, randomized, double-blind, double-dummy, active-controlled, three-arm (1:1:1), parallel group, phase 3 trial. Randomization was performed 1:1:1 via an interactive voice response system, stratified by baseline EDSS (≤3.5 vs >3.5, and country). Participants, investigators, EDSS assessors, study personnel, MRI reviewers, and the sponsor were masked to treatment and total and differential white blood cell counts. [3]
Follow-up time	The primary endpoint was assessed after 12 months of treatment. [3] Participants continued treatment until the last participant was treated for 12 months. Participants who completed the study were eligible for a long-term, open-label extension study (RPC01-3001; NCT02576717). [3]
Population (inclusion and exclusion criteria) [3]	<u>*SUNBEAM inclusion criteria*</u> 1. MS, as diagnosed by the 2010 McDonald criteria 2. Exhibited a relapsing clinical course consistent with RMS and history of brain MRI lesions consistent with MS 3. Aged 18 to 55 years, inclusive 4. EDSS score between 0 and 5·0 at baseline 5. Met 1 of the following disease activity criteria: At least 1 documented relapse within the last 12 months prior to screening or At least 1 documented relapse occurred within the last 24 months prior to screening and evidence of at least 1 GdE lesion on brain MRI within the last 12 months prior to randomisation 6. No history of relapse from 30 days prior to screening until randomisation; during this period, subjects must have been clinically stable, without systemic corticosteroid treatment or adrenocorticotrophic hormone (ACTH)

	7. Able to provide written informed consent and to be compliant with the schedule of protocol assessments 8. Subjects of reproduction potential (males and females) must have agreed to practice an acceptable method of birth control (acceptable methods of birth control in this study include: surgical sterilisation, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, vasectomy, or double-barrier method [condom or diaphragm with spermicide]) during study participation and for 30 days after their last dose of treatment of study drug or true sexual abstinence (periodic abstinence [calendar, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception) 9. Subjects must have had documentation of positive varicella zoster virus (VZV) immunoglobulin antibody status or complete VZV vaccination at least 30 days prior to randomisation *SUNBEAM exclusion criteria* 1. Primary progressive MS at screening 2. Disease duration of more than 15 years in subjects with an EDSS ≤2·0 3. Contraindications to MRI or gadolinium contrast, such as known allergy to gadolinium contrast dyes, renal insufficiency, claustrophobia, body size incompatible with the scanner, pacemaker, cochlear implants, intracranial vascular clips 4. Incompatibility with beta interferon use (eg, intolerable side effects), including: Prior cessation of interferon beta-1a therapy due to poor tolerability Prior cessation of interferon beta-1a therapy due to liver function abnormalities or other toxicities Prior cessation of other interferon beta-1a therapy due to poor tolerability or toxicity that is likely to recur with interferon beta-1a therapy *Exclusions Related to General Health:* 5. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin measured during screening 6. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, renal, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the subject at risk by participating in the study in the opinion of the treating investigator 7. Specific cardiac conditions are excluded, including history or presence of: Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalisation, class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnoea Prolonged QTcF interval (QTcF >450 msec males, >470 msec females), or at additional risk for QT prolongation (eg, hypokalaemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT-prolonging drugs) Subjects with other pre-existing stable cardiac conditions who were not cleared for the study by an appropriate cardiac evaluation by a cardiologist Other clinically significant conduction abnormalities or any other significant cardiac condition that could jeopardise a subject's health or put them at significant safety risk during the course of the study in the opinion of the treating investigator 8. Resting heart rate <55 bpm at screening

	9. Diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with haemoglobin A1c >9%, or diabetic subjects with significant comorbid conditions such as retinopathy or nephropathy 10. History of uveitis 11. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease [but excluding fungal infection of nail beds, minor upper respiratory tract infection and minor skin conditions]) or any major episode of infection that required hospitalisation or treatment with IV antibiotics within 30 days of screening or oral antibiotics within 14 days prior to screening 12. History or known presence of recurrent or chronic infection (eg, hepatitis A, B, or C, HIV, syphilis, TB); recurring urinary tract infections could be allowed Testing for viral serology and syphilis were to be performed during screening 13. History of cancer, including solid tumours and haematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) 14. Suicide attempts in the past or current signs of major depression 15. History of alcohol or drug abuse within 1 year prior to randomisation 16. History of or currently active primary or secondary immunodeficiency <u>Exclusions Related to Medications:</u> 17. Prior use of any investigational agent within 6 months prior to enrolment 18. Receipt of a live vaccine within 4 weeks prior to randomisation 19. Non-lymphocyte-depleting disease-modifying MS agents (eg, glatiramer acetate, interferons) must be discontinued from signing of informed consent until randomisation 20. Previous treatment with lymphocyte-depleting therapies (eg, alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation) 21. Treatment with other immunosuppressant agents such as azathioprine, cyclosporine, methotrexate, or mycophenolate within 6 months prior to randomisation 22. Systemic corticosteroid therapy or ACTH use within 30 days prior to screening 23. Prior treatment with lymphocyte trafficking blockers (eg, natalizumab, fingolimod, other sphingosine 1-phosphate receptor 1 agonists) 24. Treatment with intravenous immune globulin, plasmapheresis, within 3 months prior to randomisation 25. Treatment with other disease modifying therapies (eg, dimethyl fumarate, teriflunomide, daclizumab, laquinimod) within 3 months prior to randomisation 26. Intolerance of or contraindication to oral or IV corticosteroids 27. Use of therapies that were not allowed based on cytochrome P450 3A4 (CYP3A4) metabolism within 4 weeks prior to randomisation 28. Treatment with medications with a known impact on the cardiac conduction system were excluded (e.g., beta blockers, calcium channel blockers, class Ia or class III antiarrhythmic drugs, and QT prolonging drugs with a known risk of torsades de pointes, e.g., citalopram, chlorpromazine, haloperidol, methadone, and erythromycin) *Exclusions Related to Laboratory Results:* 29. Positive rapid plasma reagin

<table>
<tr><td></td><td>30. Serum creatinine >1·4 mg/dL for women or >1·6 mg/dL for men
31. Liver function impairment or persisting elevations of aspartate aminotransferase (SGOT/AST) or alanine aminotransferase (SGPT/ALT) >1·5 times the upper limit of normal (ULN), or direct bilirubin >1·5 times the ULN
32. Platelet count <100,000/µL
33. Haemoglobin <8·5 g/dL
34. Neutrophils <1500/µL
35. Absolute white blood cell count <3500/µL; absolute lymphocyte count <800/µL
36. Clinically significant findings on brain MRI scan consistent with conditions other than MS
37. ECG showing any clinically significant abnormality (eg, acute ischemia, significant heart conduction
abnormality (eg, left bundle branch block)
38. FEV1 or FVC <70% of predicted values at screening
39. Presence of >20 GdE lesions on baseline brain MRI scan</td></tr>
<tr><td>Intervention</td><td>Ozanimod HCl 1.0 mg (equivalent to 0.92 mg ozanimod) oral capsule once daily (n=433)
Ozanimod HCl 0.5 mg (~0.46 mg ozanimod) oral capsule once daily (n=439)
Patients were given once weekly sham injections of the comparator to maintain blinding. [3]</td></tr>
<tr><td>Baseline characteristics</td><td>Table 61 The SUNBEAM phase III study - Baseline characteristics
<table>
<tr><th></th><th>Interferon beta-1a (n=448)</th><th>Ozanimod 0.5 mg (N=451)</th><th>Ozanimod 1.0 mg (n=447)</th></tr>
<tr><td>Age, years</td><td>35·9 (9·1)</td><td>36·0 (9·4)</td><td>34·8 (9·2)</td></tr>
<tr><td>Sex</td><td></td><td></td><td></td></tr>
<tr><td>Female</td><td>300 (67·0%)</td><td>311 (69·0%)</td><td>283 (63·3%)</td></tr>
<tr><td>Male</td><td>148 (33·0%)</td><td>140 (31·0%)</td><td>164 (36·7%)</td></tr>
<tr><td>Race</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>447 (99·8%)</td><td>447 (99·1%)</td><td>446 (99·8%)</td></tr>
<tr><td>Black</td><td>0</td><td>2 (0·4%)</td><td>0</td></tr>
<tr><td>Asian</td><td>0</td><td>1 (0·2%)</td><td>1 (0·2%)</td></tr>
<tr><td>Other</td><td>1 (0·2%)</td><td>1 (0·2%)</td><td>0</td></tr>
<tr><td>Bodyweight, kg</td><td>70·0 (16·2)</td><td>69·3 (15·6)</td><td>69·7 (15·5)</td></tr>
<tr><td>Region</td><td></td><td></td><td></td></tr>
<tr><td>Eastern Europe*</td><td>419 (93·5%)</td><td>419 (92·9%)</td><td>415 (92·8%)</td></tr>
<tr><td>Western Europe</td><td>16 (3·6%)</td><td>17 (3·8%)</td><td>17 (3·8%)</td></tr>
<tr><td>North America</td><td>11 (2·5%)</td><td>13 (2·9%)</td><td>12 (2·7%)</td></tr>
<tr><td>Oceania†</td><td>2 (0·4%)</td><td>2 (0·4%)</td><td>3 (0·7%)</td></tr>
<tr><td>Time since multiple sclerosis symptom onset, years</td><td>6·9 (5·9)</td><td>7·2 (6·3)</td><td>6·9 (6·4)</td></tr>
<tr><td>Time since multiple sclerosis diagnosis, years</td><td>3·7 (4·4)</td><td>3·7 (4·5)</td><td>3·6 (4·2)</td></tr>
<tr><td>Type of multiple sclerosis</td><td></td><td></td><td></td></tr>
<tr><td>Relapsing-remitting multiple sclerosis</td><td>441 (98·4%)</td><td>443 (98·2%)</td><td>438 (98·0%)</td></tr>
<tr><td>Progressive-relapsing multiple sclerosis</td><td>5 (1·1%)</td><td>5 (1·1%)</td><td>9 (2·0%)</td></tr>
<tr><td>Secondary progressive multiple sclerosis</td><td>2 (0·4%)</td><td>3 (0·7%)</td><td>0</td></tr>
<tr><td>Expanded disability status scale score</td><td>2·6 (1·1)</td><td>2·7 (1·1)</td><td>2·6 (1·2)</td></tr>
</table></td></tr>
</table>

	Number of relapses in previous 12 months	1·3 (0·6)	1·3 (0·6)	1·3 (0·6)
	Number of relapses in previous 24 months	1·7 (0·8)	1·7 (0·8)	1·8 (0·9)
	Previous disease-modifying therapy‡	151 (33·7)	132 (29·3)	128 (28·6)
	Number of gadolinium-enhancing lesions	1·7 (3·2)	1·6 (3·0)	1·8 (3·4)
	Gadolinium-enhancing lesion volume, cm^3	0·18 (0·46)	0·16 (0·41)	0·20 (0·54)
	Number of T2 lesions	53·7 (37·8)	53·6 (35·6)	54·5 (39·5)
	T2 lesion volume, cm^3	13·6 (15·2)	13·1 (15·3)	12·5 (15·3)
	Normalised brain volume, cm^3	1443·4 (78·7)	1447·4 (79·5)	1456·0 (77·9)
	Comi et al. [3]			
	Data are mean (SD) or n (%). *Eastern Europe includes Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Latvia, Lithuania, Moldova, Poland, Romania, Russia, Serbia, and Ukraine. †The Oceania region included only New Zealand. ‡Disease-modifying therapy includes interferon beta-1a, pegylated interferon beta-1a, interferon beta-1b, glatiramer acetate, daclizumab, dimethyl fumarate, teriflunomide, and mitoxantrone.			
Primary and secondary endpoints	The primary efficacy endpoint was annualised relapse rate (ARR) during the treatment period based on confirmed, protocol-defined relapses (i.e., new or worsening neuro logical symptoms attributable to multiple sclerosis persisting for >24 h, not attributable to confounding clinical factors, and immediately preceded by a mostly stable or improving neurological state for ≥30 days). Relapse was confirmed when accompanied by objective neurological worsening (i.e., EDSS score increase ≥0.5 on overall score, 2 points on one functional system scale score, or 1 point on two or more functional system scale scores). Key secondary efficacy endpoints were: • number of new or enlarging T2 brain lesions over 12 months; • number of GdH brain lesions at month 12; and • time to onset of disability progression (defined as a sustained worsening in EDSS ≥1-point increase) confirmed after 3 months and 6 months. Disability progression was assessed as a prespecified pooled analysis with the RADIANCE phase 3 trial (treatment duration 24 months); the methods and results are reported with the RADIANCE phase 3 trial. [2] Percentage change from baseline to month 12 in whole brain volume was a secondary endpoint; changes in cortical grey matter and thalamic volume were prespecified exploratory endpoints. Other secondary endpoints were the proportions of participants free of GdH or new or enlarging T2 lesions at month 12; changes from baseline to month 12 in multiple sclerosis functional composite (MSFC) score; and the physical and mental health composite scores of the 54-item multiple sclerosis quality of life (MSQOL-54) scale. The symbol digit modalities test (SDMT) was included as a component of the MSFC for assessment of cognitive processing speed. Standard safety parameters were recorded. [3]			
Method of analysis	Assuming an ARR in the interferon beta-1a group of 0.3, using a Poisson regression model with an extra-Poisson variation of σ^2=1.3, a two-sided α of 0.025, and 12 months of follow-up per participant, the method of Nicholas and colleagues resulted in a sample size of 353 participants per treatment group to provide 80% power to detect a 43% lower ARR among ozanimod-treated participants (ARR 0.17). Assuming a 12% dropout rate, about 400 participants per treatment group were to be randomly assigned to each group.			

	ARR was compared for each ozanimod dose versus interferon beta-1a using a prespecified Poisson regression model adjusted for geographic region (eastern Europe *vs* rest of world), baseline age, and baseline number of GdH lesions; the natural log transformation of time on study was included as an offset term. To account for multiple comparisons, each ozanimod group was compared with interferon beta-1a at a two-sided α of 0.025. Additional sensitivity analyses were done to assess assumptions regarding the Poisson model as described in the publication appendix pp 10–11. A hierarchical testing procedure was used to assess key secondary endpoints (publication appendix p 8). If both ozanimod doses reached statistical significance on the primary endpoint (ARR), then ozanimod 1.0 mg would be compared with interferon beta-1a for the number of new or enlarging T2 lesions over 12 months at a two-sided α of 0.05. If that comparison was statistically significant, then this endpoint would be tested for ozanimod 0.5 mg versus interferon beta-1a at a two-sided α of 0.05. The same procedure was then to be followed for number of GdH lesions at month 12, followed by time to onset of confirmed disability progression (pooled with the RADIANCE phase 3 trial), until a comparison did not reach statistical significance, after which all subsequent comparisons would be considered exploratory. If only one ozanimod dose was statistically significant on the primary endpoint, then the hierarchical testing procedure would be executed on the surviving dose at a two-sided of 0.025. The number of new or enlarging T2 lesions over 12 months and number of GdH lesions at month 12 were analysed using a negative binomial regression model adjusted for geographic region (eastern Europe *vs* rest of world), baseline age, and baseline number of GdH lesions; the natural log transformation of the number of available MRI scans was included as an offset term. Change from baseline in brain volume measures was calculated using descriptive statistics. Comparisons of percentage change from baseline in brain volume between interferon beta-1a and ozanimod 1.0 mg or 0.5 mg were made using an analysis of covariance (ANCOVA) model adjusted for region (eastern Europe *vs* rest of world), baseline EDSS category, and baseline brain volume, with missing data imputed using the last-observation-carried forward method. MSFC score was a composite of average Z scores calculated for each MSFC component, using the study population as the reference population. Differences in MSFC score and the physical and mental health composite scores of the MSQOL-54 between each ozanimod group and the interferon beta-1a group were compared using ANCOVA, with models adjusted for region (eastern Europe *vs* rest of world), EDSS score, and baseline value of interest. Safety outcomes were reported as incidence in each treatment group, with inclusion limited to one occurrence of a preferred term per participant. Statistical hypothesis testing was not done on safety results. Efficacy analyses were done in the intention-to-treat population, defined as all participants who received at least one dose of their assigned study drug. The safety population consisted of all participants who received at least one dose of study drug, categorised by the highest ozanimod dose received. No interim analyses were planned. An independent data monitoring committee monitored enrolment, treatment compliance, adherence to the follow-up schedule, and safety data, but not efficacy data; they monitored accumulating data on a quarterly basis and had the ability to modify or stop the trial because of safety concerns. [3]

Subgroup analyses	Prespecified subgroup analyses were done for ARR, new or enlarging T2 lesions, and GdH lesions for the following subgroups: baseline EDSS score (≤3.5 vs >3.5), baseline GdH lesions (present vs absent), treatment-naive versus previous disease-modifying treatment, baseline age (≤40 years vs >40 years), sex (female vs male), race (white vs non-white), bodyweight (less than median vs median or greater), relapses in the preceding 12 months (less than two vs two or more; ARR endpoint only), and region (eastern Europe vs rest of world). Analyses were not done for subgroups comprising less than 5% of the overall sample size. [3]

7.1.7 Study characteristics - dimethyl fumarate studies

Table 62 The CONFIRM phase III study - Main study characteristics

Trial name	CONFIRM
NCT number	NCT00451451
Objective	To assess the safety and efficacy of dimethyl fumarate for the treatment of patients with RRMS.
Publications – title, author, journal, year	Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012 Sep 20;367(12):1087-1097.[5] [main publication]
Study type and design	Randomized, Multicenter, Placebo-Controlled and Active Reference phase III study. Patients were randomized 1:1:1:1. Patients receiving glatiramer acetate s.c. were aware of their treatment assignment. All study management and site personnel, investigators, and patients were unaware of assignment to the dimethyl fumarate and placebo groups; examining neurologists, technicians at the magnetic resonance imaging (MRI) reading center, and members of the independent neurologic evaluation committee were unaware of all study-group assignments Each site used separate examining and treating neurologists, thereby maintaining rater blinding for all study groups, including the group that received glatiramer acetate.
Follow-up time	The primary endpoint was assessed over a period of two years. The mean time in the study of 86.1, 84.4, 84.1, and 88.5 weeks in the placebo, twice daily dimethyl fumarate, thrice-daily dimethyl fumarate, and glatiramer acetate groups, respectively.
Population (inclusion and exclusion criteria)	Key Inclusion Criteria: • Must have confirmed diagnosis of RRMS according to McDonald criteria #1-4 • Must have a baseline EDSS between 0.0 and 5.0, inclusive. • Must have relapsing-remitting disease course. Key Exclusion Criteria: • Other chronic disease of immune system, malignancies, urologic, pulmonary, gastrointestinal disease • Pregnant or nursing women
Intervention	Dimethyl fumarate 240 mg oral capsules twice daily (N=359) Dimethyl fumarate 240 mg oral capsules three times daily (N=345) Glatiramer acetate 20 mg s.c. once daily (N=350) Placebo (N=363)
Baseline characteristics	*Table 63 The CONFIRM study -Baseline demographics*

	Placebo	Twice-Daily DMF	Thrice-Daily DMF	Glatiramer Acetate
Characteristic	**(N = 363)**	**(N = 359)**	**(N = 345)†**	**(N = 350)†**
Age — yr	36.9±9.2	37.8±9.4	37.8±9.4	36.7±9.1
Female sex — no. (%)	251 (69)	245 (68)	250 (72)	247 (71)
Weight — kg	72.6±16.9	71.9±17.9	72.5±17.8	71.4±19.1

	Race — no. (%)‡ | | | | | White | 305 (84) | 304 (85) | 292 (85) | 290 (83) Asian | 28 (8) | 28 (8) | 26 (8) | 25 (7) Black | 9 (2) | 2 (<1) | 5 (1) | 11(3) Other or unknown | 21 (6) | 25 (7) | 22 (6) | 24 (7) Time since diagnosis — yr | 4.8±5.0 | 4.9±5.1 | 4.6±5.2 | 4.4±4.7 Any prior approved DMT — no. (%)§ | 111 (31) | 101 (28) | 100 (29) | 103 (29) Relapses in previous 12 mo — no. | 1.4±0.8 | 1.3±0.6 | 1.4±0.7 | 1.4±0.6 EDSS score at baseline — no. (%)¶ | | | | | 0 | 13 (4) | 15 (4) | 15 (4) | 18 (5) 1.0 or 1.5 | 78 (21) | 85 (24) | 84 (24) | 77 (22) 2.0 or 2.5 | 111 (31) | 94 (26) | 94 (27) | 96 (27) 3.0 or 3.5 | 98 (27) | 105 (29) | 99 (29) | 99 (28) 4.0 or 4.5 | 50 (14) | 47 (13) | 42 (12) | 46 (13) 5.0 | 13 (4) | 12 (3) | 11 (3) | 14 (4) Mean score on EDSS¶ | 2.6±1.2 | 2.6±1.2 | 2.5±1.2 | 2.6±1.2 All baseline characteristics were well balanced among the study groups (nominal P>0.05). Plus–minus values are means ±SD. DMT denotes disease-modifying therapy, EDSS Expanded Disability Status Scale, and ITT intention to treat. † One patient randomly assigned to the thrice-daily DMF group took glatiramer acetate throughout the study. This patient was counted in the thrice-daily DMF group of the ITT population and in the glatiramer acetate group of the safety population. ‡ Race was self-reported. § Prior exposure to interferon beta-1a (in 21% of the ITT population), interferon beta-1b (11%), natalizumab (1%), and glatiramer acetate (<1%) was balanced across groups; one patient was randomly assigned to glatiramer acetate who had previously been exposed to the drug. Patients may have received more than one prior multiple sclerosis medication.Patients may also have received other, nonapproved therapies for multiple sclerosis (the proportion of patients receiving any multiple sclerosis medication before the study was 40 to 41% across study groups). ¶ Scores on the EDSS range from 0 to 10, with higher scores indicating a greater degree of disability. One patient in the twice-daily DMF group had a baseline score higher than 5.0.
Primary and secondary end-points	The primary efficacy end point was the annualised relapse rate at 2 years, based on protocol defined relapses (new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days) that were confirmed by the independent neurologic evaluation committee. Secondary efficacy end points included: • the number of new or enlarging hyperintense lesions on T2-weighted images • the number of new hypointense lesions on T1-weighted images, • the proportion of patients with a relapse, and • the time to disability progression, each at 2 years. Disability progression was defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later.
Method of analysis	Primary and secondary end points were analyzed in the intention-to-treat (ITT) population (all randomly assigned patients who received study treatment) and in the MRI cohort (patients in the ITT population for whom any postbaseline MRI data were available), with the use of two-sided statistical tests at a significance level of 0.05. The annualised relapse rate (total number of relapses divided by patient-years in the study, excluding data obtained after patients switched to alternative multiple sclerosis medications) was analyzed with the use of a negative binomial regression model adjusted for baseline EDSS score, age, region (regions were defined on the basis of not

	only geography but also the type of health care system and access to health care in each country), and number of relapses in the 12 months before study entry. Negative binomial regression was used for analysis of the total number of new or enlarging hyperintense lesions on T2-weighted images and the total number of new hypointense lesions on T1-weighted images at 2 years. A Cox proportional hazards model was used for analysis of the proportion of patients with clinical relapse and the time to disability progression. Models were adjusted for region, EDSS score, age, relapse rate, and volume of lesions, as appropriate. Safety was analyzed with the use of descriptive statistics for the safety population (all patients who received at least one dose of the study medication), excluding data obtained after patients switched to alternative multiple sclerosis medications.
Subgroup analyses	For each analysis, provide the following information: - characteristics of included population - method of analysis - prespecified or post hoc - assessment of validity, including statistical power of the analysis.

Table 64 The DEFINE (dimethyl fumarate) phase III study - Main study characteristics

Trial name	DEFINE
NCT number	NCT00420212
Objective	To assess the safety and efficacy of dimethyl fumarate for the treatment of patients with RRMS.
Publications – title, author, journal, year	Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012 Sep 20;367(12):1098-1107. [4][primary publication]
Study type and design	A phase III randomized (1:1:1:), multicenter, double-blind, placebo-controlled, dose-comparison study. Randomization was performed centrally and stratified according to site. To maintain concealment of the study-group assignments, each study center used separate examining and treating neurologists (all of whom remained unaware of the assignments throughout the trial). All patients were eligible to switch to an alternative therapy for multiple sclerosis if they had completed 48 weeks of the study treatment and had had one or more confirmed relapses after 24 weeks; patients could switch at any time if they had confirmed progression of disability.
Follow-up time	The primary endpoint was assessed over a period of two years.
Population (inclusion and exclusion criteria)	Key Inclusion Criteria: • Must have a confirmed diagnosis of RRMS according to McDonald criteria #1-4. • Must have a baseline EDSS between 0.0 and 5.0, inclusive. • Must have relapsing-remitting disease course. Key Exclusion Criteria:

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- Other chronic disease of the immune system, malignancies, acute urologic, pulmonary, gastrointestinal disease.
- Pregnant or nursing women

</td></tr>
<tr><td>Intervention</td><td>Dimethyl fumarate 240 mg oral capsules twice daily (N=410)
Dimethyl fumarate 240 mg oral capsules three times daily (N=416)
Placebo (N=408)</td></tr>
<tr><td>Baseline characteristics</td><td>

Table 65 The DEFINE study -Baseline demographics

Characteristic	Placebo (N = 408)	Twice-Daily DMF (N = 410)	Thrice-Daily DMF-12 (N = 416)
Age — yr	38.5±9.1	38.1±9.1	38.8±8.8
Female sex — no. (%)	306 (75)	296 (72)	306 (74)
Weight — kg	71.1±17.0	70.7±18.5	71.3±16.9
Race — no. (%)†			
White	318 (78)	321 (78)	330 (79)
Asian	42 (10)	38 (9)	36 (9)
Black	8 (2)	8 (2)	10 (2)
Other or unknown	40 (10)	43 (10)	40 (10)
Previous use of approved medication for multiple sclerosis	172 (42)	162 (40)	168 (40)
— no. (%)‡			
Time since diagnosis — yr	5.8±5.8	5.6±5.4	5.1±5.3
Relapses in previous 12 mo — no.	1.3±0.7	1.3±0.7	1.3±0.6
EDSS score at baseline — no. (%)§			
0	21 (5)	29 (7)	24 (6)
1.0 or 1.5	105 (26)	109 (27)	104 (25)
2.0 or 2.5	112 (27)	116 (28)	146 (35)
3.0 or 3.5	97 (24)	82 (20)	85 (20)
4.0 or 4.5	56 (14)	56 (14)	42 (10)
5.0	16 (4)	16 (4)	14 (3)
Mean score on EDSS	2.48±1.24	2.40±1.29	2.36±1.19
MRI findings¶			
Gadolinium-enhancing T1-weighted lesions — no.	1.6±3.4	1.2±3.3	1.2±4.1
Hyperintense T2-weighted lesions			
Mean no.	49.2±38.6	47.6±34.7	55.8±44.3
<9 — no. of patients	12	9	14
≥9 — no. of patients	168	167	170

* Plus–minus values are means ±SD. The intention-to-treat population included all patients who underwent randomization and received at least one dose of the study drug. All the baseline characteristics were well balanced among the study groups (nominal P>0.05).
† Race was self-reported.
‡ Approved medications for multiple sclerosis include interferon beta-1a (used in 27% of all randomly assigned patients), glatiramer acetate (15%), interferon beta-1b (14%), and natalizumab (3%). Patients may have received more than one prior medication for multiple sclerosis. Patients may also have received other, nonapproved therapies for multiple sclerosis. (The percentage of patients receiving any medication for multiple sclerosis before study entry was 54 to 56% across treatment groups.)
§ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating a greater degree of disability. The baseline score was higher than 5.0 in one patient in each group, and the score was unknown for one patient in the twice-daily DMF group.
¶ Magnetic resonance imaging (MRI) was performed in 180 patients in the placebo group, 176 in the twice-daily DMF group, and 184 in the thrice-daily DMF group.

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<tr><td>Primary and secondary endpoints</td><td>The primary end point was the proportion of patients who had a relapse by 2 years. (Protocol defined relapses were new or recurrent neurologic symptoms, not associated with fever or infection, that lasted for at least 24 hours and that were accompanied by new objective neurologic findings according to the examining neurologist's evaluation).</td></tr>
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	Secondary end points at 2 years included • the number of GdH lesions and of new or enlarging hyperintense lesions on T2-weighted images, • the annualised relapse rate (the total number of relapses divided by the number of patient-years in the study, excluding data obtained after patients switched to alternative multiple sclerosis medications), and • the time to progression of disability. (Disability progression was defined as at least a 1.0-point increase on the EDSS in patients with a baseline score of 1.0 or higher or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks).
Method of analysis	All efficacy analyses were performed on data from the intention-to-treat population, which included all patients who underwent randomization and who received at least one dose of the study drug. All statistical tests were two-sided, with an overall type I error rate of 0.05. Sensitivity analyses were performed on the primary end point. The primary end point was analyzed with the use of a Cox proportional-hazards model, adjusted for baseline EDSS score, age, region, and number of relapses in the year before study entry. The estimated proportion of patients with a relapse was derived with the use of the Kaplan–Meier product-limit method, which was based on the time-to-first-relapse survival distribution. For secondary end points, the analyses were conducted in the following ranked order: an analysis of the number of new or newly enlarging hyperintense lesions on T2-weighted images, with the use of a negative binomial model; an analysis of the number of GdH lesions, with the use of an ordinal logistic-regression model; an analysis of the annualised relapse rate, with the use of a negative binomial regression model; and an analysis of the time to progression of disability that was sustained for 12 weeks, with the use of a Cox proportional hazards model. The analytic models included adjustments for region and baseline characteristics, including EDSS score, age, relapse rate, and number or volume of baseline lesions, as appropriate. A sequential (closed) testing procedure was used to control the overall type I error rate due to multiple comparisons. Formal testing of the comparison of twice-daily dimethyl fumarate with placebo was undertaken only if the comparison of thrice daily dimethyl fumarate with placebo was significant (P≤0.05). Analysis of secondary end points, according to the ranked order, followed an additional sequential testing procedure such that if statistical significance was not achieved for an end point, all lower-ranking end points were also considered to be nonsignificant. Among patients who switched to an alternative therapy for multiple sclerosis, all the data before the switch were used for the analysis of the clinical end points. For the analyses of MRI end points in these patients, the data before the switch were used and then data after the rescue therapy was initiated were imputed with the use of a constant rate assumption. Safety analyses were summarized with the use of descriptive statistics for all patients who received at least one dose of the study drug. Among patients who switched to alternative medications, data collected after the switch were excluded from the safety analyses.
Subgroup analyses	A subgroup of patients (n=540) underwent MRI-scans. See the method for analysis above.

7.1.8 Study characteristics – fingolimod studies

Table 66 The FREEDOMS (fingolimod) phase III study - Main study characteristics

<table>
<tr><td>Trial name</td><td>FREEDOMS</td></tr>
<tr><td>NCT number</td><td>NCT00289978</td></tr>
<tr><td>Objective</td><td>Investigated the effects of daily fingolimod treatment for 24 months on the relapse rate, disability progression, and MRI measures of inflammation, burden of disease, and tissue destruction in patients with relapsing–remitting multiple sclerosis.</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387-401[6]</td></tr>
<tr><td>Study type and design</td><td>This is a phase III, double-blind, placebo-controlled trial.
Patients were randomly assigned, in a 1:1:1 ratio, to receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg or matching placebo, once daily for 24 months. Randomization was performed centrally, with the use of a validated system and stratification according to site, with a block size of six within each site. [6]</td></tr>
<tr><td>Follow-up time</td><td>24 months[6]</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion Criteria:
• Male and female patients between ages 18-55 with a diagnosis of multiple sclerosis
• Patients with a relapsing-remitting disease course
• Patients with EDSS score of 0-5.5

Exclusion Criteria:
• Patients with other chronic disease of the immune system, malignancies, acute pulmonary disease, cardiac failure, etc.
• Pregnant or nursing women

Other protocol-defined inclusion/exclusion criteria applied to this study.[47]</td></tr>
<tr><td>Intervention</td><td>Fingolimod 1.25 mg (n=429)
Fingolimod 0.5 mg (n=425)
Placebo (n=418)
[6]</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Fingolimod 1.25 mg</th><th>Fingolimod 0.5 mg</th><th>Placebo</th></tr>
<tr><th>Characteristic</th><th>(N = 429)</th><th>(N = 425)</th><th>(N = 418)</th></tr>
<tr><td>Age — yr</td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>37.4±8.9</td><td>36.6±8.8</td><td>37.2±8.6</td></tr>
<tr><td>Median (range)</td><td>38.0 (17–55)</td><td>36.0 (18–55)</td><td>37.0 (18–55)</td></tr>
<tr><td>Female sex — no. (%)</td><td>295 (68.8)</td><td>296 (69.6)</td><td>298 (71.3)</td></tr>
<tr><td colspan="4">Disease and treatment history</td></tr>
<tr><td>Time from first MS symptom to randomization — yr</td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>8.4±6.9</td><td>8.0±6.6</td><td>8.1±6.4</td></tr>
<tr><td>Median (range)</td><td>6.9 (0–37)</td><td>6.6 (0–35)</td><td>7.0 (0–32)</td></tr>
<tr><td>Relapses — no.</td><td></td><td></td><td></td></tr>
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	Within previous yr			
	Mean	1.5±0.8	1.5±0.8	1.4±0.7
	Median (range)	1.0 (0–6)	1.0 (0–5)	1.0 (0–6)
	Within previous 2 yr			
	Mean	2.1±1.3	2.1±1.1	2.2±1.2
	Median (range)	2.0 (1–10)	2.0 (1–11)	2.0 (1–10)
	EDSS score†			
	Mean	2.4±1.4	2.3±1.3	2.5±1.3
	Median (range)	2.0 (0–5.5)	2.0 (0–5.5)	2.0 (0–5.5)
	No history of disease-modifying treatment — no. (%)	259 (60.4)	244 (57.4)	249 (59.6)
	Features on MRI‡			
	Absence of gadolinium-enhancing lesions — no. (%)	257 (60.6)	263 (62.0)	262 (63.0)
	No. of gadolinium-enhancing lesions on T1-weighted images			
	Mean	1.8±4.7	1.6±5.6	1.3±2.9
	Median (range)	0 (0–50)	0 (0–84)	0 (0–26)
	Volume of lesions on T2-weighted images — mm3			
	Mean	6829±8491	6128±7623	6162±7085
	Median (range)	3557 (0–47,734)	3303 (0–47,148)	3416 (0–37,148)
	Volume of hypointense lesions on T1-weighted images — mm3			
	Mean	2114±3220	1898±2854	1962±3131
	Median (range)	860 (0–25,886)	814 (0–22,378)	811 (0–20,956)
	Normalized brain volume — ml			
	Mean	1511±86	1521±83	1512±85
	Median (range)	1515 (1217–1764)	1529 (1144–1734)	1515 (1230–1723)
	Source: [6]			

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline for any characteristic. MS denotes multiple sclerosis.
† The Expanded Disability Status Scale (EDSS) ranges from 0 to 10, with higher scores indicating greater disability.
‡ MRI data were available for 424 patients in each of the fingolimod groups and for 416 patients in the placebo group. The means and medians were calculated on the basis of all images, not just those showing lesions.

Primary and secondary endpoints	**Primary endpoint** Annualised relapse rate: - defined as the number of confirmed relapses per year. Relapses were verified by the examining neurologist within 7 days after the onset of symptoms. The symptoms must have been accompanied by an increase of at least half a point in the EDSS score, of one point in each of two EDSS functional system scores, or of two points in one EDSS functional-system score (excluding scores for the bowel–bladder or cerebral functional systems). **Secondary endpoints** Time to confirmed disability progression - defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and

	with all EDSS scores measured during that time meeting the criteria for disability progression. Time to a first relapse Time to disability progression (confirmed after 6 months) Changes in the EDSS score MSFC z score between baseline and 24 months Number of GdH lesions Proportion of patients free from GdH lesions, Number of new or enlarged lesions on T_2-weighted MRI scans Proportion of patients free from new or enlarged lesions on T_2-weighted scans Volumes of hyperintense lesions on T_2-weighted scans and hypointense lesions on T_1-weighted scans Change in brain volume between baseline and 24 months Safety and tolerability measures. [6]
Method of analysis	Both the intention-to-treat population and the safety population included all patients who had undergone randomization. The study tested two null hypotheses: that there were no differences in the annualised relapse rate between the group receiving fingolimod at a dose of 1.25 mg and the group receiving placebo or between the group receiving fingolimod at a dose of 0.5 mg and the group receiving placebo. The aggregate annualised relapse rate was estimated by means of a negative binomial regression model with adjustment for study group, country, number of relapses within 2 years before baseline, and EDSS score at baseline. The time to relapse or progression was estimated with the use of the Kaplan–Meier method. The times to disability progression (confirmed after 3 or 6 months) were compared in the main analysis by means of the log-rank test and in the supportive analysis by means of a Cox proportional-hazards model with adjustment for study group, country, baseline EDSS score, and age. To control for a type I statistical error, a prospectively planned, hierarchical testing procedure was used to compare fingolimod with placebo regarding the primary and key secondary end points, in the following order: the annualised relapse rate, first in association with 1.25 mg of fingolimod and next in association with 0.5 mg of fingolimod, and then the time to disability progression (confirmed after 3 months), first with 1.25 mg of fingolimod and next with 0.5 mg of fingolimod. Each test was performed with a significance level of 0.05. However, the next test was performed only when the preceding test was statistically significant. Missing data were not imputed. Safety analyses were summarized by means of descriptive statistics; inferential significance testing was not performed. [6]
Subgroup analyses	Post-hoc subgroup analysis to further explore the possible contribution of patients with baseline EDSS of 0 to the overall results in both FREEDOMS and FREEDOMS II, to assess whether the risk of disability progression was reduced in the fingolimod 0·5 mg group compared with placebo for the subgroup of patients with a baseline EDSS greater than 1. [7]

Table 67 The FREEDOMS II (fingolimod) phase III study - Main study characteristics

Trial name	FREEDOMS II
NCT number	NCT00355134

<table>
<tr><td>Objective</td><td>Assessed the safety, tolerability and efficacy of two doses of oral fingolimod compared to placebo on efficacy parameters in patients with relapsing-remitting multiple sclerosis (RRMS).[48]</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Neurology. 2014;13(6):545-556.[7]</td></tr>
<tr><td>Study type and design</td><td>Randomized, multicenter, parallel-group study consisted of 2 phases: a 24-month double-blind, randomized, multicenter, placebo-controlled, parallel-group study and an Extension phase which consisted of a dose-blinded period and an open-label period.
In the Core phase, patients were randomized to receive a fixed dose of fingolimod (0.5 mg/day), fingolimod (1.25 mg/day) or placebo for up to 24 months.
For the Extension phase, patients who were treated with fingolimod during the Core phase continued treatment at the assigned dose level, while those previously treated with placebo during the Core phase were re-randomized in a 1:1 ratio to receive one of the two doses of fingolimod (1.25 mg or 0.5 mg). All patients in the extension received blinded investigational drug: fingolimod 1.25 mg and 0.5 mg in capsules for oral administration once daily until the decision to discontinue the fingolimod 1.25 mg dose became effective and subsequently all patients were switched to open-label fingolimod 0.5 mg.
With the implementation of Amendment 11, the 1.25 mg dose was discontinued and all patients were switched to fingolimod 0.5 mg dose. With the implementation of Amendment 12, all patients treated with Placebo in the fingolimod Core phase were switched to treatment with 0.5 mg fingolimod per day. The Extension phase continued until all patients either discontinued or transferred to Study CFTY720D2399. [48]
The core phase study is of interest to the Ozanimod application and the following will center on such.</td></tr>
<tr><td>Follow-up time</td><td>24 months</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion Criteria:
Male and female patients between ages 18-55 with a diagnosis of multiple sclerosis
Patients with a relapsing-remitting disease course
Patients with expanded disability status scale (EDSS) score of 0-5.5
Exclusion Criteria:
Patients with other chronic disease of the immune system, malignancies, acute pulmonary disease, cardiac failure, etc.
Pregnant or nursing women
[48]
Other protocol-defined inclusion/exclusion criteria may apply.</td></tr>
<tr><td>Intervention</td><td>Fingolimod 1.25 mg (n=370)
Fingolimod 0.5 mg (n=358)
Placebo (n=355) [7]</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Fingolimod 1.25 mg</th><th>Fingolimod 0.5 mg</th><th>Placebo</th></tr>
<tr><th>Characteristic</th><th>(N = 370)</th><th>(N = 358)</th><th>(N = 355)</th></tr>
<tr><td>Age — yr</td><td></td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>40·9 (8·9)</td><td>40.6 (8.4)</td><td>40·1 (8·4)</td></tr>
<tr><td>Median (range)</td><td>42·0 (18 to 57)</td><td>41·0 (18 to 55)</td><td>40·0 (19 to 55)</td></tr>
<tr><td>Female sex — no. (%)</td><td>281 (76)</td><td>275 (77)</td><td>288 (81)</td></tr>
<tr><td>Body-mass index (kg/m^2)</td><td></td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>27·41 (5·956)</td><td>27·74 (5·952)</td><td>27·67 (6·458)</td></tr>
</table>
</td></tr>
</table>

Median (range)	26·57 (16·7 to 45·9)	26·96 (13·9 to 50·8)	26·66 (16·9 to 56·6)
Disease and treatment history			
Years from first symptom to randomization			
Mean (SD)	10·8 (8·2)	10·4 (8·0)	10·6 (7·9)
Median (range)	8·9 (0 to 50)	8·6 (0 to 49)	9·2 (0 to 40)
Relapses — no.			
Within previous yr			
Mean (SD)	1·5 (1·0)	1·4 (0·9)	1·5 (0·9)
Median (range)	1·0 (0 to 12)	1·0 (0 to 6)	1·0 (0 to 7)
Within previous 2 yr			
Mean (SD)	2·3 (2·0)	2·2 (1·4)	2·2 (1·5)
Median (range)	2·0 (1 to 30)	2·0 (1 to 8)	2·0 (1 to 14)
EDSS score			
Mean (SD)	0·0 (0·7)	0·04 (0·7)	–0·02 (0·8)
Median (range)	0·11 (–4·5 to 1·1)	0·18 (–2·7 to 2·1)	0·13 (–4·5 to 1·8)
No history of disease-modifying treatment — no. (%)	287 (78%)	264 (74%)	259 (73%)
Any interferon β	245 (66%)	218 (61%)	209 (59%)
Interferon beta-1a (intramuscularly)	153 (41%)	129 (36%)	125 (35%)
Interferon beta-1a (subcutaneously)	91 (25%)	91 (25%)	94 (27%)
Interferon β-1b (subcutaneously)	90 (24%)	73 (20%)	76 (21%)
Glatiramer acetate	169 (46%)	129 (36%)	146 (41%)
Natalizumab	23 (6%)	17 (5%)	23 (7%)
MRI disease features*			
Number of patients without gadolinium-enhancing lesions on T1-weighted images (%)	254/367 (69%)	218/357 (61%)	225/354 (64%)
No. of gadolinium-enhancing lesions on T1-weighted images			
Mean (SD)	1·3 (3·6)	1·3 (3·4)	1·2 (3·2)
Median (range)	0 (0 to 26)	0 (0 to 33)	0 (0 to 46)
Total volume of gadolinium-enhancing lesions on T1 weighted images (mm3)			
Mean (SD)	103 (299)	144 (448)	107 (307)
Median (range)	0 (0 to 3162)	0 (0 to 5570)	0 (0 to 4060)
Total volume of lesions on T2-weighted images — mm3			
Mean	4936 (7286)	5484 (8000)	5553 (7841)
Median (range)	2123 (0 to 55 257)	2356 (0 to 54 369)	2702 (0 to 69 203)
Volume of hypointense lesions on T1-weighted images — mm^3			
Mean (SD)	1144 (2312)	1417 (3011)	1434 (2732)
Median (range)	273 (0 to 19 431)	343 (0 to 23 937)	377 (0 to 17 362)

<table>
<tr><td></td><td>
<table>
<tr><td>Normalized brain volume — cm³</td><td></td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>1518 (79)</td><td>1522 (82)</td><td>1526 (85)</td></tr>
<tr><td>Median (range)</td><td>1520 (1321 to 1741)</td><td>1530 (1285 to 1721)</td><td>1532 (1253 to 1756)</td></tr>
<tr><td>Source: [7]</td><td></td><td></td><td></td></tr>
</table>
MSFC=Multiple Sclerosis Functional Composite. EDSS=Expanded Disability Status Scale. *MRI data are for patients with assessable scans at baseline.
</td></tr>
<tr><td>Primary and secondary end-points</td><td>
Primary objective
Annualised relapse rates for up to 24 months (analysed by intention to treat).
- A relapse was confirmed when it was accompanied by an increase of at least half a step (0.5) on the EDSS, an increase of 1 point on two different functional systems of the EDSS, or 2 points on one of the functional systems (excluding bowel, bladder, or cerebral functional systems).

Secondary endpoints
Percent brain-volume change from baseline and time to disability progression (1 point EDSS change [0.5 point if baseline EDSS was >5.0]) confirmed at 3 months for up to 24 months.
Safety and tolerability
Time to first relapse and proportion of relapse free patients
Time to disability progression confirmed at 6 months, as measured by EDSS
Change from baseline to the end of study on the MSFC score;
Effect on MRI measurements of inflammatory disease activity
- Number and volume of GdH T1 lesions
- Number of new or newly enlarged T2 lesions, proportion of patients free of gadolinium-enhanced T1 lesions,
- Proportion of patients free of new or newly enlarged T2 lesions
- Proportion of patients free of new inflammatory activity [no gadolinium-enhanced T1 lesions and no new or newly enlarged T2 lesions])
- MRI measurements of burden of disease (percentage change from baseline in volume of gadolinium-enhanced T1 lesions, percentage change from baseline in volume of new or newly enlarged T2 lesions, and brain volume [at visits other than month 24]).
Quality of life
- Euro quality of life scale (EQ-5D)
- Patient Reported Indices in Multiple Sclerosis (PRIMUS) instrument assessments;
Fatigue
- Modified Fatigue Impact Scale (MFIS)
[7]
</td></tr>
<tr><td>Method of analysis</td><td>The primary endpoint was analysed by intention-to-treat analysis. Annualised relapse rates were compared using a negative binomial regression model adjusted for treatment, region, number of relapses within 2 years before randomisation, and baseline EDSS score. Proportion of patients free of relapses was analysed using logistic regression adjusted for the same four variables as for the primary analysis. Brain volume, T2 lesion volume, and T1 lesion number and volume was compared using rank ANCOVA adjusted for treatment, region, and baseline measurements. The number of new or newly enlarging T2 lesions was analysed using negative binomial and rank ANCOVA and analysed the proportion of patients free of lesions using a logistic regression model, both also adjusted for treatment, region, and baseline measurements.</td></tr>
</table>

	Time to first relapse or disability progression was estimated using the Kaplan–Meier method, and compared the treatment groups by means of a log-rank test. A supportive analysis included the Cox proportional-hazards model with adjustment for treatment, region, baseline EDSS score, and age. The proportion of patients free of disability progression was analysed with Kaplan–Meier estimates and treatment differences were compared with log-rank test. At the request of the European Medicines Agency, additional post-hoc subgroup analysis was done to further explore the possible contribution of patients with baseline EDSS of 0 to the overall results in both FREEDOMS and FREEDOMS II, to assess whether the risk of disability progression was reduced in the fingolimod 0.5 mg group compared with placebo for the subgroup of patients with a baseline EDSS greater than. Summary statistics for safety variables were used; summaries were presented by treatment group using the safety population. [7]
Subgroup analyses	Post-hoc subgroup analysis to further explore the possible contribution of patients with baseline EDSS of 0 to the overall results in both FREEDOMS and FREEDOMS II, to assess whether the risk of disability progression was reduced in the fingolimod 0·5 mg group compared with placebo for the subgroup of patients with a baseline EDSS greater than 1. [7]

Table 68 The TRANSFORMS (fingolimod) phase III study - Main study characteristics

Trial name	TRANSFORMS
NCT number	NCT00340834
Objective	Assessed the safety, tolerability, and efficacy of 2 doses of oral fingolimod versus interferon beta-1a to reduce the frequency of relapses in patients with relapsing-remitting multiple sclerosis. [49]
Publications – title, author, journal, year	Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402-415.[8]
Study type and design	Phase 3, multicenter, randomized, double-blind, double-dummy, parallel group study. Patients were randomly assigned to 12 months of treatment with oral fingolimod, at a daily dose of either 1.25 or 0.5 mg, or intramuscular interferon beta-1a, at a weekly dose of 30 µg. Randomization was performed centrally in blocks of six within each site and was stratified according to site. The study included and optional extension phase. [8]
Follow-up time	12 months[8]
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Male and female patients between ages 18-55 with a diagnosis of multiple sclerosis (MS) • Patients with a relapsing-remitting disease course • Patients with Expanded Disability Status Scale (EDSS) score of 0-5.5 Exclusion Criteria: • Patients with other chronic disease of the immune system, malignancies, acute pulmonary disease, cardiac failure, etc • Pregnant or nursing women • Patients who cannot tolerate treatment with an interferon Other protocol-defined inclusion/exclusion criteria applied to the study. [8, 49]

Intervention	Fingolimod 1.25 mg (n=426) Fingolimod 0.5 mg (n=431) Placebo (n=435) [8]

Baseline characteristics

Characteristic	Fingolimod 1.25 mg (N = 426)	Fingolimod 0.5 mg (N = 431)	Placebo (N = 435)
Age — yr			
Mean (SD)	35.8±8.4	36.7±8.8	36.0±8.3
Median (range)	36 (18–54)	37 (18–55)	36 (18–55)
Female sex — no. (%)	293 (68.8)	282 (65.4)	295 (67.8)
White race — no. (%)†	404 (94.8)	404 (93.7)	408 (93.8)
Clinical characteristics			
Interval from onset of symptoms to randomization — yr			
Mean	7.3±6.0	7.5±6.2	7.4±6.3
Median (range)	6 (0–33)	6 (0–34)	6 (0–40)
Relapses — no.			
Within previous yr			
Mean	1.5±0.9	1.5±1.2	1.5±0.8
Median (range)	1 (0–7)	1 (0–20)	1 (0–6)
Within previous 2 yr			
Mean	2.2±1.2	2.3±2.2	2.3±1.2
Median (range)	2 (1–8)	2 (1–40)	2 (1–12)
EDSS score‡			
Mean	2.21±1.31	2.24±1.33	2.19±1.26
Median (range)	2.0 (0–5.5)	2.0 (0–5.5)	2.0 (0–5.5)
Treatment history§			
Any therapy — no. (%)	249 (58.5)	238 (55.2)	245 (56.3)
Any interferon β	209 (49.1)	219 (50.8)	207 (47.6)
Glatiramer acetate	67 (15.7)	57 (13.2)	67 (15.4)
Natalizumab	3 (0.7)	4 (0.9)	1 (0.2)
MRI disease features*			
Patients with no gadolinium-enhancing lesions on T1-weighted images — no./total no. (%)	270/412 (65.5)	288/427 (67.4)	268/425 (63.1)
No. of gadolinium-enhancing lesions on T1-weighted images			
Mean	1.49±4.77	0.98±2.81	1.06±2.80
Median (range)	0 (0–66)	0 (0–29)	0 (0–36)
Total volume of lesions on T2-weighted images — mm^3			
Mean	5085±5962	5170±6642	4924±5711
Median (range)	3096 (0–38,870)	2382 (0–46,280)	2901 (0–38,712)
Normalized brain volume — cm3			
Mean	1526.2±76.4	1524.1±83.9	
Median (range)	1528 (1300–1794)	1526 (1185–1862)	1533 (1231–1762)
Source: [8]			

	* Plus–minus values are means ±SD. None of the between-group comparisons were significant. † Race was self-reported. ‡ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating a greater degree of disability. § Patients may have received more than one treatment before study entry. ¶ All MRI findings were based on all images that could be evaluated.
Primary and secondary end-points	**Primary Endpoint** Annualised Aggregate Relapse Rate (ARR) in the Core Phase of the Study [Time Frame: Baseline to Month 12] - Defined as the number of confirmed relapses in a year. A relapse is defined as the appearance of a new or worsening of a previously stable or improving pre existing neurological abnormality, separated by at least 30 days from onset of a preceding relapse. The abnormality must be present for at least 24 hours and occur in the absence of fever or infection. The annualised ARR for each treatment group was calculated using negative binomial regression adjusted by treatment, country, number of relapses in the previous 2 years, and the baseline Expanded Disability Status Scale score. **Secondary Endpoints** Number of New or Newly Enlarged T2 Lesions in Comparison With Baseline in the Core Phase of the Study [Time Frame: Baseline to Month 12] Percentage of Participants Free of 3-month Disability Progression Assessed With the Expanded Disability Status Scale (EDSS) at the End of the Core Phase of the Study [Time Frame: Baseline to Month 12] Estimated Annualised Aggregate Relapse Rate (ARR) in the Core and Extension Phases of the Study [Time Frame: Month 0 to end of study (up to approximately 4.5 years)] Number of New or Newly Enlarged T2 Lesions in the Extension Phase of the Study [Time Frame: Month 12 to end of study (up to approximately 3.5 years)] Percentage of Participants Free of 3-month and 6-month Disability Progression Assessed With the Expanded Disability Status Scale (EDSS) at the End of the Extension Phase of the Study [Time Frame: Baseline to end of study (up to approximately 4.5 years)] [49]
Method of analysis	To control for type I errors, multiplicity adjustment was applied to testing for comparisons between fingolimod and interferon beta-1a in a hierarchical order, according to the dose of fingolimod, for the study end points. Each test was performed at a significance level of 0.05. However, the lower-rank testing was performed only when every higher-rank test indicated statistical significance. The modified intention-to-treat cohort, which consisted of all patients who underwent randomization and received at least one dose of a study drug, was the primary focus for efficacy and safety analyses. The study was designed to test the null hypothesis that there would be no significant differences in the annualised relapse rate between either of the fingolimod groups and the interferon group with the use of a negative binomial regression model with adjustment for study group, country, number of relapses in the previous 2 years, and baseline EDSS score. These prespecified covariates were based on exploratory analyses of the phase 2 study data. Heterogeneity in efficacy according to whether patients had undergone previous therapy was tested as a post hoc analysis with the use of the same negative binomial regression model, with

	the addition of the interaction term for therapy during the study and before baseline. [8]
Subgroup analyses	N/A[8]

7.1.9 Study characteristics – NMA bridging studies

Table 69 The BRAVO (laquinimod) phase III study - Main study characteristics

Trial name	BRAVO
NCT number	NCT00605215
Objective	To assess laquinimod effect in patients with relapsing-remitting MS (RRMS), and descriptively compare laquinimod with interferon beta (IFNb)-1a (Avonex® reference arm)
Publications – title, author, journal, year	Vollmer, T. L., Sorensen, P. S., Selmaj, K., Zipp, F., Havrdova, E., Cohen, J. A., Sasson, N., Gilgun-Sherki, Y., & Arnold, D. L. (2014). A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. Journal of Neurology, 261(4), 773–783
Study type and design	A Multinational, Multicenter, Randomized, Parallel-group Study Performed in Subjects With RRMS to Assess the Efficacy, Safety and Tolerability of Laquinimod Over Placebo in a Double-blind Design and a Reference Arm of Interferon beta-1a (Avonex®) in a Rater-blinded Design. Patients were evaluated at 12 scheduled visits: months -1 (screening), 0 (baseline), 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24. Safety assessments (laboratory measures, vital signs) were performed at all visits, and electrocardiograms (ECGs) were performed at months -1, 0, 1, 2, 3, 6, 12, 18, and 24/early termination. Neurological evaluations by EDSS were performed at months -1, 0, and every 3 months thereafter, and multiple sclerosis functional composite (MSFC) score was measured at month 0 and every 6 months thereafter to month 24. MRI scans were performed at baseline and months 12 and 24/early termination.
Follow-up time	• Accumulation of physical disability [Time Frame: 24 months] • The cumulative number of enhancing lesions on T1-weighted images [Time Frame: 24 months] • General health status [Time Frame: 24 months] • Using Short Form (SF-36) survey subject-reported questionnaire obtained at month 0 and every 6 months thereafter. • The cumulative number of new hypointense lesions on enhanced T1 scans [Time Frame: 24 months]
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Subjects must have a confirmed and documented MS diagnosis as defined by the Revised McDonald criteria [Ann Neurol 2005: 58:840-846], with a relapsing-remitting disease course. • Subjects must be ambulatory with converted Kurtzke EDSS score of 0-5.5. • Subjects must be in a stable neurological condition between screening (month -1) and baseline visits (month 0). • Subjects must have had experienced one of the following:

	• At least one documented relapse in the 12 months prior to screening • At least two documented relapses in the 24 months prior to screening • One documented relapse between 12 and 24 months prior to screening with at least one documented T1-Gd enhancing lesion in an MRI performed within 12 months prior to screening. • Subjects must be between 18 and 55 years of age, inclusive. • Subjects must have disease duration of at least 6 months (from first symptom) prior to screening. • Women of child-bearing potential must practice 2 acceptable methods of birth control [acceptable methods of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy or double-barrier method (condom or diaphragm with spermicide)]. • Subjects must be willing and able to comply with the protocol requirements for the duration of the study. o Exclusion Criteria: • An onset of relapse or any treatment with corticosteroids (intravenous [iv], intramuscular [im] and/or per os [po]) or ACTH between month -1 (screening) and 0 (baseline). • Use of experimental or investigational drugs, and/or participation in drug clinical studies within the 6 months prior to screening. • Use of immunosuppressive (including Mitoxantrone (Novantrone®) or cytotoxic agents within 6 months prior to the screening visit. • Previous use of either of the following: natalizumab (Tysabri®), cladribine or laquinimod. • Previous treatment with glatiramer acetate (Copaxone®) or IVIG within 3 months prior to screening visit. • Previous treatment with Interferon beta-1a (Avonex® or Rebif®) or Interferon beta-1b (Betaseron®). • Systemic corticosteroid treatment of ≥30 consecutive days duration within 2 months prior to screening visit. • Previous total body irradiation or total lymphoid irradiation. • Previous stem-cell treatment, autologous bone marrow transplantation or allogenic bone marrow transplantation. • A known history of tuberculosis. • Acute infection 2 weeks prior to baseline visit. • Major trauma or surgery 2 weeks prior to baseline visit. • A history of vascular thrombosis (excluding catheter-site superficial venous thrombophlebitis). • A carrier state of factor V Leiden mutation (either homo- or heterozygous) by history or as disclosed at screening. • Positive screening test for Hepatitis B surface antigen, Hepatitis C antibody, or HIV antibody as disclosed at screening visit. • Use of potent inhibitors of CYP3A4 within 2 weeks prior to baseline visit (see detailed list of drugs in protocol) (1 month for fluoxetine).

	• Use of amiodarone within 2 years prior to screening visit. • Pregnancy or breastfeeding. • Subjects with a clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation, as determined by medical history, physical examinations, ECG, laboratory tests or chest X-ray. Such conditions may include: o A cardiovascular or pulmonary disorder that cannot be well-controlled by standard treatment permitted by the study protocol. o A gastrointestinal disorder that may affect the absorption of study medication. o Renal, metabolic, endocrinological or hematological diseases. o Any form of chronic liver disease, including known non-alcoholic steatohepatitis. o A ≥2xULN serum elevation of either of the following at screening: ALT, AST or direct bilirubin. o A QTc interval (obtained from either two ECG recordings at screening or from the mean value calculated from three measurements at baseline visit) which is ≥450msec. o A family history of Long-QT syndrome. o A history of drug and/or alcohol abuse. o Major psychiatric disorder. o A history of a convulsive disorder. o Known hypersensitivity to either of the following: mannitol, meglumine or sodium stearyl fumarate. o Known hypersensitivity that would preclude administration of laquinimod. • The subject's inability to give informed consent, or to complete the study, or if the subject is considered by the investigator to be, for any reason, an unsuitable candidate for this study. • A known history of sensitivity to Gadolinium. • Inability to successfully undergo MRI scanning. • A known history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation of Avonex®. Exclusion Criteria: • Subjects who suffer from any form of progressive MS • Any condition which the investigator feels may interfere with participation in the study • Subjects with a clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation • Subjects who received any investigational medication, immunosuppressives or cytotoxic agents within 6 months prior to screening • Previous treatment with immunomodulators within two months prior to screening

<table>
<tr><td></td><td>

- Pregnancy or breastfeeding

</td></tr>
<tr><td>Intervention</td><td>

- Drug: laquinimod

  0.6 mg oral once daily for 24 months
- Drug: placebo

  oral placebo once daily for 24 months
- Drug: Interferon beta-1a (Avonex®)

  Interferon beta-1a (Avonex®) 30 mcg IM once weekly for 24 months

</td></tr>
<tr><td>Baseline characteristics</td><td>

Table 70 The BRAVO study - Baseline demographics

Characteristic	Laquinimod (n = 434)	Placebo (n = 450)	IFNb-1a IM (n = 447)
Women, n (%)	282 (65.0 %)	321 (71.3 %)	307 (68.7 %)
Age (years)			
Median (P25, P75)	36.7 (29.6, 44.0)	37.5 (30.3, 45.4)	38.5 (30.3, 45.9)
Time from first MS symptom year			
Median (P25, P75)	4.9 (2.2, 9.3)	4.7 (2.0, 9.7)	5.3 (2.4, 10.3)
Time from MS diagnosis years			
Median (P25, P75)	1.2 (0.3, 3.8)	1.2 (0.3, 4.0)	1.4 (0.3, 4.7)
Patients with > 1 relapse in 1 year before entry, n (%)	425 (97.9)	435 (96.7)	430 (96.2)
Relapses in the previous year			
Median (P25, P75)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Relapses in previous 2 years			
Median (P25, P75)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)
EDSS score			
Median (P25, P75)	2.5 (1.5, 3.5)	2.5 (1.5, 3.5)	2.5 (1.5, 3.5)
Prior disease-modifying treatment for MSa, n (%)	30 (6.9)	27 (6.0)	42 (9.4)
% of patients with GdE lesions	39.6	33.4	38.1
Volume of T2 lesions (cm^3)			
Median (P25, P75)	6.3 (2.3, 13.5)	4.7 (1.7, 10.3)	5.7 (1.9, 11.7)
Normalized brain volume (cm^3)			
Mean (SD)	1,582 (96)	1,586 (93)	1,586 (84)

EDSS Expanded Disability Status Scale, MRI magnetic resonance imaging, GdE gadolinium-enhancing P25, 25th percentile; P75, 75th percentile

a At any time before study entry. DMAMS included mitoxantrone, immunoglobulin (Ig), IgG, glatiramer acetate, IFNb drugs, meglumine acridonacetate, and azathioprine

</td></tr>
<tr><td>Primary and secondary endpoints</td><td>

The primary endpoint was annualised relapse rate (ARR); secondary endpoints included percent brain volume change (PBVC) and 3-month confirmed disability worsening.

Primary Outcome Measures:

- Assess efficacy, as measured by number of confirmed relapses

</td></tr>
</table>

	Secondary Outcome Measures: • Accumulation of physical disability Measured by the time to confirmed progression of Expanded Disability Status Scale (EDSS). A confirmed progression of EDSS is defined as a 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5, confirmed 3 months later • The cumulative number of enhancing lesions on T1-weighted images • General health status Using Short Form (SF-36) survey subject-reported questionnaire obtained at month 0 and every 6 months thereafter • The cumulative number of new hypointense lesions on enhanced T1 scans
Method of analysis	The primary endpoint (ARR) was assessed for all randomized patients using all study assessments made before early termination or until study end, using the negative binomial regression model with treatment group as the contrast. In addition to treatment group, baseline EDSS score, log of the number of relapses in the previous 2 years (+1), and country/geographical region (CGR) were covariates in the model. If baseline disease characteristics were appreciably different between placebo and active treatment groups, a prespecified sensitivity analysis was performed to evaluate the robustness of treatment effects using a repeat of the negative binomial model with the imbalanced baseline characteristics as covariates. Time to EDSS progression confirmed at 3 months was analyzed based on a Cox Proportional Hazards model (SAS® PROC PHREG). The model included baseline EDSS score, log of the number of relapses in the previous 2 years (+1) and CGR as covariates. The time to confirmed progression of EDSS was also presented by Kaplan–Meier (KM) curves stratified by treatment group. Disability as measured by MSFC z-score at month 24 was analyzed using an ANCOVA model (SAS———————————— PROC GLM) with baseline MSFC z-score, baseline EDSS score, log of the number of relapses in the previous 2 years (+1) and CGR as covariates.
Subgroup analyses	N/A

7.1.10 Results per study

Table 71 The RADIANCE phase III study – Results

Trial name:	**RADIANCE [2]**										
NCT number:	NCT02047734										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Annualised relapse rate	Ozanimod 1 mg	433	0.17 (0.14 – 0.21)	0.11	0.0538 – 0.1662	0.0001	Rate ratio: 0.62	0.51-0.77	<0.0001	Analysed using a prespecified Poisson regression model adjusted for region (eastern Europe vs rest of world), baseline age, and baseline number of GdH lesions and included the natural log transformation of time on study as an offset term. To control for type 1 error, a hierarchical testing procedure was used to assess key secondary endpoints	[2]
	Interferon beta-1a	441	0.28 (0.23 – 0.32)								
CDP3	Ozanimod 1 mg	433	12.5%	0.012	-0.0317 – 0.0557	0.5907	HR: 1.05	0.71 – 1.54	0.8334	Analysis of time to onset of 3-month and 6-month confirmed disability progression was pooled with SUNBEAM because neither RADIANCE phase 3 nor SUNBEAM was powered to detect a treatment difference with a two-sided α of 0.05. For both the pooled analysis and the analysis of RADIANCE phase 3 only, time to onset of disability progression was analysed using a Cox proportional hazards model adjusted for study, region, baseline age, and baseline EDSS score. A Kaplan-Meier analysis	[2]
	Interferon beta-1a	441	11.3%								
CDP3 (pooled RADIANCE and SUNBEAM)	Ozanimod 1 mg	880	7.6%	0.002	-0.0228 – 0.0268	0.8746	HR: 0.95	0.68 – 1.33	0.7651		[2]
	Interferon beta-1a	889	7.8%								

										of the difference in time to on-set of disability progression curves was done.	
MSQOL-54 physical composite	Ozanimod 1 mg	433	0.209 (12.321)	1.345	(–0·252 to 2·943)†	0·0988				Analysed using ANCOVA, with models adjusted for region, EDSS score, and baseline value of interest	[2]
	Interferon beta-1a	441	-1.831 (12.319)								
MSQOL-54 mental composite	Ozanimod 1 mg	433	-1.517 (15.544)	0.380	(–1.553 to 2.313)†	0.6997					[2]
	Interferon beta-1a	441	-1.831 (16.422)								
AE	Ozanimod 1 mg	434	74.3%	0.079	0.0251-0.1329	0.0041	RR: 0.91	0.845-0.970	0.0047	Statistical hypothesis testing was not performed on any safety results.	[2]
	Interferon beta-1a	440	74.7%								
SAE	Ozanimod 1 mg	434	7.1%	0.001	-0.0316 – 0.0336	0.952	RR: 1.01	0.611-1.683	0.9576		[2]
	Interferon beta-1a	440	6.5								

Abbreviations: ANCOVA, analysis of covariance; AE, adverse event; CDP3, confirmed disease progression at 3 months; CI, confidence interval; EDSS, Expanded Disability Status Scale; MSQOL54, 54 item multiple scoliosis quality of life; SAE, serious adverse events

Table 72 The SUNBEAM phase III study – Results

Trial name:	SUNBEAM [3]									
NCT number:	NCT02294058									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Annualised relapse rate	Ozanimod 1 mg	447	0·18 (0·14 to 0·24)	0.17	0.1122 – 0.2278	<0.0001	Rate Ratio: 0.52	0.41-0.66	<0.0001	Poisson regression model adjusted for geographic region (eastern Europe vs rest of world), baseline age, and baseline number of GdH lesions; the natural log transformation of time on study was included as an offset term. A hierarchical testing procedure was used to assess key secondary endpoints	[3]
	Interferon beta-1a	448	0·35 (0·28 to 0·44)								
SDMT	Ozanimod 1 mg	447								Please note: DMC requested data for patients who avoided a 10% worsening, which was not available in the clinical study. Therefore, values have not been reported	[3]
	Interferon beta-1a	448									
MSQOL-54 physical composite	Ozanimod 1 mg	443	1·925 (11·870)	1·642	(0·104 to 3·180)	0·0364				Compared using ANCOVA, with models adjusted for region (eastern Europe *vs* rest of world), EDSS score, and baseline value of interest	[3]
	Interferon beta-1a	445	0·046 (12·578)								
MSQOL-54 mental composite	Ozanimod 1 mg	447	0·260 (15·800)	0·356	(–1·523 to 2·234)	0·7104					[3]
	Interferon beta-1a	448	–0·123 (15·240)								
AE	Ozanimod 1 mg	448	57.2%	0.155	0.0937-0.2163	<0.0001	RR: 0.79	0.722-0.869	<0.0001	Statistical hypothesis testing was not performed on any safety results.	[3]
	Interferon beta-1a	445	59.8%								
SAE	Ozanimod 1 mg	448	3.5%	0.004	-0.0173 – 0.0253	0.7124)	RR: 1.17	0.530-2.586	0.6957		[3]

	Interferon beta-1a	445	2.9%				

Abbreviations: ANCOVA, analysis of covariance; AE, adverse event; CDP3, confirmed disease progression at 3 months; CI, confidence interval; EDSS, Expanded Disability Status Scale; MSFC, multiple sclerosis functional composite; MSQOL54, 54 item multiple scoliosis quality of life; SAE, serious adverse events SDMT, Symbol Digit Modalities Test.

Table 73 The DEFINE phase III study – Results

Trial name:	*DEFINE [4]*										
NCT number:	*NCT00420212*										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Annualised relapse rate	DMF 2x/daily	410	0.17 (0.14–0.21)	0.19	0.1295 – 0.2505	<0.0001)	Rate Ratio: 0.47	0.37 – 0.61	<0.001	Analyzed with the use of a Cox proportional-hazards model, adjusted for baseline EDSS score, age, region, and number of relapses in the year before study entry. The estimated proportion of patients with a relapse was derived with the use of the Kaplan–Meier product-limit method, which was based on the time-to-first-relapse survival distribution	*[4]*
	Placebo	408	0.36 (0.30–0.44)								
CDP3	DMF 2x/daily Placebo	409 408	16% 27%	0.11	0.0547 – 0.1673	<0.0001	HR: 0.62	(0.44–0.87)	0.005	Analysis of the time to progression of disability that was sustained for 12 weeks, with the use of a Cox proportional hazards model.	*[4]*
AE	DMF 2x/daily Placebo	410 408	96% 95%	0.014	-0.0141-0.0421	0.3289	RR: 1.02	0.986-1.046	0.2999	Statistical hypothesis testing was not performed on any safety results.	*[4]*
SAE	DMF 2x/daily Placebo	410 408	10% 15%	0.031	-0.234-0.0854	0.2636	RR: 0.86	0.648-1.132	0.2755		

Abbreviations: AE, adverse event; CDP3, confirmed disease progression at 3 months; CI, confidence interval; DMF, dimethyl fumarate; EDSS, Expanded Disability Status Scale; SAE, serious adverse events

Table 74 The CONFIRM phase III study – Results

Trial name:	*CONFIRM [5]*										
NCT number:	*NCT00451451*										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Annualised relapse rate	DMF 2x/daily	359	0.22 (0.18–0.28)	0.18	0.1125 – 0.2475	<0.0001	Rate Ratio: 0.55	0.437-0.695	<0.0001	Analyzed with the use of a negative binomial regression model adjusted for baseline EDSS score, age, region (regions were defined on the basis of not only geography but also the type of health care system and access to health care in each country), and number of relapses in the 12 months before study entry.	*[4]*
	Placebo	363	0.40 (0.33–0.49)								
CDP3	DMF 2x/daily	359	13%	0.04	-0.0123 – 0.0923	0.1335	HR: 0.79	0.52–1.19	P=0.25	A Cox proportional hazards model was used for analysis of the proportion of patients with clinical relapse and the time to disability progression.	*[4]*
	Placebo	363	17%								
AE	DMF 2x/daily	359	94%	0.025	-0.0124-0.0624	0.1897	RR: 1.03	0.986-1.069	0.2055	Statistical hypothesis testing was not performed on any safety results.	*[4]*
	Placebo	363	92%								
SAE	DMF 2x/daily	359	17%	0.048	-0.0097-0.1057	0.103	RR: 0.78	0.578-1.055	0.1065		*[4]*
	Placebo	363	22%								

Table 75 The FREEDOMS phase III study – Results

Trial name:	FREEDOMS [6]									
NCT number:	NCT00289978									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Annualised relapse rate	Fingolimod 0.5 mg	425	0.18 (0.15 to 0.22)	0.22	0.1588-0.2812	<0.0001	Rate Ratio: 0.45	0.359-0.573	<0.0001	Estimated by means of a negative binomial regression model with adjustment for study group, country, number of relapses within 2 years before baseline, and EDSS score at baseline. The time to relapse or progression was estimated with the use of the Kaplan–Meier method.	[6]
	Placebo	418	0.40 (0.34 to 0.47)								
CDP3	Fingolimod 0.5 mg	425	82.3±1. 9% (78.6 to 86.1)	0.0639	0.0091- 0.1189	0.0222	HR:0.70	(0.52 to 0.96)	0.02	Compared in the main analysis by means of the log-rank test and in the supportive analysis by means of a Cox proportional-hazards model with adjustment for study group, country, baseline EDSS score, and age.	[6]
	Placebo	418	75.9±2.2% (71.7 to 80.2)								
AE	Fingolimod 0.5 mg	425	94.4%	0.0169	-0.0164-0.0504	0.3183	RR: 1.02	0.983-1.056	0.2992	. Statistical hypothesis testing was not performed on any safety results.	[6]
	Placebo	418	92.6%								
SAE	Fingolimod 0.5 mg	425	10.1%	0.033	-0.0105- 0.0765	0.1366	RR: 0.76	0.520-1.098	0.1410		[6]
	Placebo	418	12.4%								

Abbreviations: AE, adverse event; CDP3, confirmed disease progression at 3 months; CI, confidence interval; EDSS, Expanded Disability Status Scale; SAE, serious adverse events

Table 76 The FREEDOMS II phase III study – Results

Trial name:	FREEDOMS II [7]									
NCT number:	NCT00355134									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Annualised relapse rate	Fingolimod 0.5 mg	358	0·21 (0·17 to 0·25)	0.19	0.1224- 0.2576	<0.0001	Rate Ratio: 0.52	0.413-0.665	<0.0001	Compared by a negative binomial regression model adjusted for treatment, region, number of relapses within 2 years before randomisation, and baseline EDSS score.	[7]
	Placebo	355	0·40 (0·34 to 0·48)								
CDP3	Fingolimod 0.5 mg	358	74·7% (69·9 to 79·5)	0.037	-0.0283-0.1023	0.2666	HR: 0.83	(0·61 to 1·12)	<0·0001	Analysed with Kaplan–Meier estimates and treatment differences were compared with log-rank test.	[7]
	Placebo	355	71·0% (65·9 to 76·1)								
AE	Fingolimod 0.5 mg	358	98%	0.012	-0.0122-0.0362	0.3313	RR: 1.01	0.987-1.037	0.3550	Statistical hypothesis testing was not performed on any safety results.	[7]
	Placebo	355	97%								
SAE	Fingolimod 0.5 mg	358	15%	0.021	-0.0296-0.0716	0.4156	RR: 1.17	0.807-1.689	0.4099		[7]
	Placebo	355	13%								

Abbreviations: AE, adverse event; CDP3, confirmed disease progression at 3 months; CI, confidence interval; EDSS, Expanded Disability Status Scale; SAE, serious adverse events.

Table 77 The TRANSFORMS phase III study - Results

Trial name:	TRANSFORMS [8]									
NCT number:	NCT00340834									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Annualised relapse rate	Fingolimod 0.5 mg	429	0.16 (0.12 to 0.21)	0.17	0.1125- 0.2275	<0.0001	Rate Ratio: 0.49	0.378-0.630	<0.0001	Analysed with a negative binomial regression model with adjustment for study group, country, number of relapses in the previous 2 years, and baseline EDSS score.	[8]
	Interferon beta-1a	431	0.33 (0.26 to 0.42)								
CDP3	Fingolimod 0.5 mg	429	94.1 (91.8 to 96.3)	0.0199	-0.0139- 0.0539	0.2473	RR: 1.02	0.986-1.060	0.2321	Time to confirmed disability progression was estimated using the Kaplan–Meier method and logistic regression model adjusting for baseline EDSS score and age. Cox's proportional hazards model was used to model time-to-event and was adjusted for treatment, country, baseline EDSS score, and age.	[8]
	Interferon beta-1a	431	92.1 (89.4 to 94.7)								
AE	Fingolimod 0.5 mg	429	86%	0.056	0.0139-0.0981	0.0092	RR: 0.94	0.895-0.984	0.0090	Statistical hypothesis testing was not performed on any safety results.	[8]
	Interferon beta-1a	431	91.6%								
SAE	Fingolimod 0.5 mg	429	7%	0.012	-0.02007- 0.0447	0.4722	RR: 1.21	0.721-2.015	0.4756)		[8]
	Interferon beta-1a	331	5.8%								

Abbreviations: AE, adverse event; CDP3, confirmed disease progression at 3 months; CI, confidence interval; EDSS, Expanded Disability Status Scale; SAE, serious adverse events

Table 78 The BRAVO phase III study – Results

Trial name:	BRAVO [9]										
NCT number:	NCT02047734										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Annualised relapse rate	Placebo	405	0.34 (SD: 0.03)	0.08	0.02 – 0.14	0.009)	Rate Ratio: 0.74	(0.60–0.92)	0.007	All randomized patients using all study assessments made before early termination or until study end, using the negative binomial regression model with treatment group as the contrast.	[9] and data on file
	Interferon beta-1a	447	0.26 (SD: 0.02)								
CDP3	Placebo	450	60	0.028	-0.0144 – 0.0704	0.1954	HR: 0.74	0.51–1.09	0.13	Time to EDSS CDP3 was analyzed based on a Cox Proportional Hazards model. The time to confirmed progression of EDSS was also presented by Kaplan–Meier curves stratified by treatment group.	
	Interferon beta-1a	447	35								
AE	Placebo	449	70	0.05	-0.0092 – 0.1092	0.0978	RR: 0.93	0.858-1.011	0.0886	. Statistical hypothesis testing was not performed on any safety results.	
	Interferon beta-1a	442	82								
SAE	Placebo	449	34	0.043	0.0038 – 0.0822	0.0314	RR: 0.64	0.425-0.962	0.0320)		
	Interferon beta-1a	442	54								

Abbreviations: AE, adverse event; CDP3, confirmed disease progression at 3 months; CI, confidence interval; EDSS, Expanded Disability Status Scale; SAE, serious adverse events.

7.1.11 Results per PICO (clinical question #1)

Table 79 Results referring to clinical question #1

Results per outcome	Absolute difference in effect			Relative difference in effect	
	Assumed event rate	Difference	Credibility Interval	Relative risk	Credibility Interval
Annualised relapse rate	0.20	-0.03	-0,10-0,11	Rate ratio: 0.85	0.5-1.58
CDP3 (Assumed event rate is the proportion of patients without 3-month EDSS progression)	86%	5%	-8%-19%	Hazard Ratio: 1.32	0.48-3.25
Adverse events	93%	-2%	-8%-4%	Risk ratio: 0.98	0.92-1.04
Serious adverse events	11%	-1,48%	-11%-22%	Risk ratio: 0.92	0.37-2.23

Abbreviations: CDP3, confirmed disease progression at 3 months.

7.1.12 Results per PICO (clinical question #2)

Table 80 Results referring to clinical question #2

Results per outcome	Absolute difference in effect			Relative difference in effect	
	Assumed event rate	Difference	Credibility Interval	Relative risk	Credibility Interval
Annualised relapse rate	0.18	0,00	-0,07-0,13	Rate ratio 0.98	0.61-1.69
CDP3 (Assumed event rate is the proportion of patients without 3-month EDSS progression)	84%	2%	-8%-19%	Hazard Ratio 1.11	0.48-2.44
Adverse events	95%	-1%	-6%-3%	Risk ratio 0.99	0.93-1.03
Serious adverse events	11%	-2%	-7%-8%	Risk ratio 0.81	0.37-1.73

Abbreviations: CDP3, confirmed disease progression at 3 months.

7.1.13 Calculations comparative analyses

The calculations for the absolute difference in effect and for the relative difference in effect are presented in the print screens below.

Calculations ARR_12& 24				
Study name	**Treatments**	**Person ye**	**Total number of events**	**Event rate**
SUNBEAM	Ozanimod	276.5952	50	0.18
SUNBEAM	Interferon	210.0875	74	0.35
BRAVO trial	Placebo	808.82	275	0.34
BRAVO trial	Interferon	826.92	215	0.26
FREEDOMS II trial	Placebo	615	246	0.40
FREEDOMS II trial	Fingolimod	623.81	131	0.21
FREEDOMS trial	Placebo	897.5	359	0.40
FREEDOMS trial	Fingolimod	955.6	172	0.18
DEFINE Trial	Placebo	282.24	102	0.36
DEFINE Trial	DMF	533.12	91	0.17
CONFIRM trial	Placebo	561.43	212	0.38
CONFIRM trial	DMF	552.99	124	0.22
TRANSFORMS trial	Fingolimod	303.5338	49	0.16
TRANSFORMS trial	Interferon	198.0825	65	0.33
RADIANCE	Ozanimod	533.12	91	0.17
RADIANCE	Interferon	531.1842	149	0.28

Average event rate (Assumed event rate)	
Fingolimod	0.18
DMF	0.20
Ozanimod	0.18

ARR (12 & 24 Months): Random effect model					
Ozanimod vs.	**Median Rate Ratio**	**LCrI**	**UCrI**	**Mean RR**	**SD**
Fingolimod	0.9837	0.6064	1.69	1.029	0.3723
DMF	0.854	0.4962	1.578	0.9062	0.4921
Calculated event rate for intervention	**Point estimate**	**LCrI**	**UCrL**		
Fingolimod	0.18	0.11	0.31		
DMF	0.17	0.10	0.31		
Ozanimod vs.	**Absolute difference**	**LCrI**	**UCrL**		
Fingolimod	0.00	-0.07	0.13		
DMF	-0.03	-0.10	0.11		

Calculations CDP3M_12&24

Study name	Treatments	Total N	Number o	Event rate
SUNBEAM	Ozanimod	447	13	3%
SUNBEAM	Interferon	448	19	4%
BRAVO trial	Placebo	450	60	13%
BRAVO trial	Interferon	447	47	11%
FREEDOMS II trial	Placebo	355	103	29%
FREEDOMS II trial	Fingolimod	358	91	25%
FREEDOMS trial	Placebo	418	101	24%
FREEDOMS trial	Fingolimod	425	75	18%
DEFINE Trial	Placebo	408	110	27%
DEFINE Trial	DMF	409	65	16%
CONFIRM trial	Placebo	363	62	17%
CONFIRM trial	DMF	359	47	13%
TRANSFORMS trial	Fingolimod	429	25	6%
TRANSFORMS trial	Interferon	431	34	8%
RADIANCE	Ozanimod	433	54	12%
RADIANCE	Interferon	441	50	11%

Average event rate (Assumed event rate)

Fingolimod	84%
DMF	86%
Ozanimod	92%

Mogard, Olof:
Calculated as 1-average event rate

Ozanimod vs.	Median HR	LCrI	UCrI	Mean HR	SD
Fingolimod	1.11	0.4754	2.439	1.215	1.242
DMF	1.322	0.4784	3.248	1.511	4.851

Ozanimod vs.	Absolute differ	LCrI	UCrI
Fingolimod	2%	-8%	19%
DMF	5%	-8%	28%

e^ln$(ACR)*HR-ACR$ (5)

Calculations AEs 12 & 24

Study name	Treatments	Total N	Number of events	Event rate
Radiance	Ozanimod	434	324	75%
Radiance	Interferon b	440	365	83%
Bravo	Interferon b	442	362	82%
Bravo	Placebo	449	314	70%
FREEDOMS	Fingolimod	425	401	94%
FREEDOMS	Placebo	418	387	93%
FREEDOMS II	Fingolimod	358	350	98%
FREEDOMS II	Placebo	355	343	97%
CONFIRM	Dimethyl-fu	359	338	94%
CONFIRM	Placebo	363	333	92%
DEFINE	Dimethyl-fu	409	395	97%
DEFINE	Placebo	408	387	95%
SUNBEAM	Interferon b	445	336	76%
SUNBEAM	Ozanimod	448	268	60%
TRANSFORM	Fingolimod	429	369	86%
TRANSFORM	Interferon b	431	395	92%

Average event rate (Assumed event rate)	
Fingolimod	93%
DMF	95%
Interferon	83%
Placebo	89%
Ozanimod	67%

AEs (12 & 24 Months): Random effect model					
Ozanimod vs.	**Median RR**	**LCrI**	**UCrI**	**Mean RR**	**SD**
Fingolimod	0.9907	0.9307	1.034	0.9886	0.03098
DMF	0.9834	0.9168	1.038	0.9818	0.03595
Calculated event rate for inte	**oint estimat**	**LCrI**	**UCrL**		
Fingolimod	0.92	0.86	0.96		
DMF	0.94	0.87	0.99		
Ozanimod vs.	**Absolute dif**	**LCrI**	**UCrL**		
Fingolimod	-1%	-6%	3%		
DMF	-2%	-8%	4%		

Calculations SAEs 12 & 24 months

Study name	Treatments	Total N	Number of events	Event rate
Radiance	Ozanimod	434	28	6%
Radiance	Interferon b	440	28	6%
Bravo	Interferon b	442	34	8%
Bravo	Placebo	449	54	12%
FREEDOMS	Fingolimod	425	43	10%
FREEDOMS	Placebo	418	56	13%
FREEDOMS II	Fingolimod	358	53	15%
FREEDOMS II	Placebo	355	45	13%
CONFIRM	Dimethyl-fu	359	61	17%
CONFIRM	Placebo	363	79	22%
DEFINE	Dimethyl-fu	409	74	18%
DEFINE	Placebo	408	86	21%
SUNBEAM	Interferon b	445	11	2%
SUNBEAM	Ozanimod	448	13	3%
TRANSFORM	Fingolimod	429	30	7%
TRANSFORM	Interferon b	431	25	6%

Average event rate (Assumed event rate)	
Fingolimod	11%
DMF	18%
Ozanimod	5%

SAE (12 & 24 Months): Random effect model					
Ozanimod vs.	**Median RR**	**LCrI**	**UCrI**	**Mean RR**	**SD**
Fingolimod	0.8124	0.3688	1.73	0.8781	0.4412
DMF	0.9157	0.3749	2.228	1.021	0.646
Calculated event rate for inte	**oint estimat**	**LCrI**	**UCrL**		
Fingolimod	0.09	0.04	0.18		
DMF	0.16	0.07	0.39		
Ozanimod vs.	**Absolute dif**	**LCrI**	**UCrL**		
Fingolimod	-2.00%	-7%	8%		
DMF	-1.48%	-11%	22%		

Economic analysis of Zeposia (ozanimod) for treatment of multiple sclerosis

Application to the Medicine Council

4.1

2020-12-09

Contents

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ARR	Absolute risk reduction
AST	aspartate aminotransferase
AV	Atrioventricular block
CBC	Complete blood count
CBP3	Confirmed disability progression at 3 months
CrI	Credibility interval
DKK	Danish kroner
DRG	Disease related groups
ECG	Electrocardiograph
DMF	Dimethyl fumarate
GdH	Gadolinium-enhancing
HR	Hazard ratio
MC	Medicines Council
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NMA	Network meta-analysis
PPP	Pharmacy Purchase Price
RR	Rate ratio
RRMS	Relapsing-remittent multiple sclerosis
SAE	Serious adverse event
SmPC	Summary of product characteristics
TAE	Treatment emergent adverse event
VZV	Varicella Zoster virus

1 Background

BMS/Celgene Aps is applying to the Medicines Council for commissioning the use of ozanimod (Zeposia) for treatment of relapsing-remitting multiple sclerosis (RRMS) in adults.

The Medicines Council protocol for assessment of added clinical value of Zeposia in this indication [1] states the following scientific questions:

- *Hvilken værdi har ozanimod sammenlignet med dimethylfumarat for patienter med attakvis multipel sklerose og gennemsnitlig sygdomsaktivitet (førstelinjebehandling)?*
- *Hvilken værdi har ozanimod sammenlignet med fingolimod for patienter med attakvis multipel sklerose og høj sygdomsaktivitet (andenlinjebehandling)?*

Hence the protocol specifies the following populations

Population		Comparator
P1	RRMS patients in first line	Dimethyl fumarate (DMF)
P2	RRMS patients in second line	Fingolimod

DMF Dimethyl fumarate; RRMS relapsing-remittent multiple sclerosis

The clinical assessment of ozanimod have been conducted according to the protocol in the two population.

Ozanimod was investigated in two phase III studies, the 2-year RADIANCE and the 1-year SUNBEAM both with interferon beta-1a as comparator. [2, 3]

Participants were aged 18–55 years, had multiple sclerosis according to 2010 McDonald criteria, a relapsing clinical course, brain MRI lesions consistent with multiple sclerosis, an expanded disability status scale score of 0·0–5·0, and either at least one relapse within 12 months before screening or at least one relapse within 24 months before screening plus at least one gadolinium-enhancing (GdH) lesion within 12 months before randomisation. [2, 3]

For the pooled data from the RADIANCE and SUNBEAM studies ozanimod 1 mg demonstrated a statistically significant and clinically meaningful reduction of the adjusted annualised relapse rate (ARR; the primary endpoint) compared to interferon beta-1a 30 µg once weekly (Rate Ratio 0.62 (0.51 to 0.77; p<0.0001)). Similar statistically significant effects were seen for the secondary endpoints, adjusted mean number of new or enlarging T2 lesions per scan over 24 months and adjusted mean number of GdH lesions at month 24. The proportion of participants with confirmed disability progression at 3 months (CDP3) was not significantly different between treatment groups. Fewer treatment emergent adverse events (TEAEs) were reported in the ozanimod group than in the interferon beta-1a group in both studies, while the frequency of serious TEAEs was similar between the groups. [2, 3]

As no head to head clinical studies comparing ozanimod with fingolimod and dimethyl fumarate (DMF) respectively, exists, a network meta-analysis (NMA) was conducted including studies with at least 12 months follow-up. The analysis was based on the DEFINE[4] and CONFIRM [5] studies for dimethyl fumarate and the FREEDOMS[6], FREEDOMS II [7] and TRANSFORMS [8] studies for fingolimod with inclusion of the BRAVO study (interferon beta 1a vs placebo) [9] to complete the network (see clinical dossier section 4.4.1).

The NMA results for comparison between ozanimod and dimethyl fumarate showed no statistically significant difference with regard to ARR (rate ratio: 0.85; 95% credibility interval (CrI): 0.5-1.58), CDP3 (hazard ratio (HR): 1.32; 95% CrI: 0.48-3.25), frequency of serious adverse

events (SAEs) (relative risk (RR): 0.92; 95% CrI: 0.37-2.23) and frequency of adverse events (AEs) (RR: 0.98; 95% CrI: 0.92-1.04) (see clinical dossier section 5.1.3).

The NMA results for comparison between ozanimod and fingolimod (clinical dossier section 5.2.3) showed no statistically significant difference with regard to ARR (rate ratio: 0.98; 95% CrI: 0.61-1.69), CDP3 (HR: 1.11 95% CrI: 0.48-2.44), frequency of SAEs (RR: 0.81; 95% CrI: 0.37-1.73) and frequency of AEs (RR: 0.99; 95% CrI: 0.93-1.03)

A comprehensive review of the safety profile has been provided (clinical dossier 5.3). Overall, the frequency of TEAEs is comparable between the ozanimod, dimethyl fumarate and fingolimod. However, ozanimod seems to have a favourable safety profile as compared to fingolimod regarding frequency of severe leukopenia and herpes virus infections, frequency of first dose cardiac AEs like bradycardia, skin malignancies and increases of liver enzymes.

Overall, the clinical assessment concludes that ozanimod is a relevant new treatment option with efficacy and safety comparable to dimethyl fumarate in P1 and efficacy comparable to and safety profile more favourable than fingolimod (P2).

An economic model has been developed to assess the cost per patient of ozanimod in each of the populations as well as the five-year regional budget impact of introducing ozanimod as standard treatment in each of the populations defined in the protocol. The analysis has been conducted from a partial societal perspective.

2 Cost analysis

Scope of analysis

The main outcome studied is the incremental cost per patients. The scope of analysis is limited to cost associated with choice of treatment (ozanimod, DMF or fingolimod) and exclude cost elements that are likely to be unaffected by choice of treatment.

A limited societal perspective was applied in costing.

A time horizon was set to 5 years in the base case to reflect average treatment duration (see section 'Treatment duration'). In sensitivity analysis up to 10 years of treatment can be tested.

Cost elements directly associated with choice of treatment include cost of drug and drug monitoring.

Excluded cost elements include cost of drug administration given the treatments are administrated orally. Furthermore, costs of side effects were omitted because there is no evidence to suggest that the intervention is associated with statistically significant or clinically relevant differences in safety.

2.1 Resource use and unit costs

Cost of medicine

An overview of the dosing of ozanimod and comparators included is provided in Table 1. Information on dosage, drug administration, and treatment schedules obtained using the respective SmPC and the Medicine Council protocol.

Drug wastage was included as a number of packs wasted at the end of the time-horizon where patients are discontinuing treatment. The same number of packs are added to each arm as there is no reason to expect drug wastage to differ between products. All treatments are

available in pack sizes for 28 days of maintenance treatment. In the base case it is assumed that on average half of the pack is wasted. Drug waste is added to the drug cost.

Table 1: Dosing of RRMS treatments included in the analysis

Product	Population	Recommended dosing
Ozanimod[11]	P1/ P2	Days 1 – 4: 0.23 mg once daily Days 5 – 7: 0.46 mg once daily Days 8 and thereafter: 0.92 mg once daily
Dimethyl fumarate[12]	P1	The starting dose is 120 mg twice a day. After 7 days, the dose should be increased to the recommended maintenance dose of 240 mg twice a day
Fingolimod[13]	P2	In adults, the recommended dose is one 0.5 mg capsule taken orally once daily

Table 2 Available strengths and pack sizes and price per pack (PPP)

Product	Strength and pack size	Pack price
Ozanimod	0.23/0.46 mg 7 capsules* 0.92 mg 28 capsules	2,907.84† 11,631.36†
Dimethyl fumarate[14]	120 mg 14 capsules 240 mg 56 capsules	2,541,43‡ 11,087.00‡
Fingolimod[14]	0.5 mg 28 capsules	11,337.60

Abbreviations: PPP pharmacy purchase price. Medicinpriser.dk (price period 02.11.2020-15.11.2020)
* Initiation pack with 4×0.23mg capsules and 3×0.46mg capsules for first week dosing
† PPP valid from 30th of November 2020
‡ Based on PPP of AMGROS tender winners for each strength

Cost of drug administration

As outline in the scope of analysis above, the cost of drug administration was omitted from the analysis based on all interventions being oral treatment administrated by the patients. Cost of monitored first administration (where applicable) is included in the cost of monitoring.

Cost of monitoring

The number of contacts associated with treatment monitoring for the standard patients was sourced from the Medicines Council background documentation for it's treatment recommendation[10].

In the cost analysis the following assumptions was made:

- All patients will have MRI at diagnosis.[10] The requirement for a recent MRI for patients starting treatment with DMF is hence conservatively excluded.

- All patients will have at three regular outpatient follow-up visits the first year and 2 times per year the following years.[10] Monitoring requirements that according to the SmPC should be carried out on a regular basis are assumed to be performed during these contacts.

- Patient treated with DMF are assumed to have blood test every 2nd week for the first 26 and every 8th week thereafter[10]. Blood samples associated with initiation of therapy is assumed to be included in the DRG of the initiation visit.

- Patient treated with fingolimod are according to the Medicine Council background document for treatment recommendation in RRMS required to have blood test every 3-6 months. [10] We assumed that in the first year, patients would be monitored months 1, 3, 9, 12 and every 6th month thereafter.

- With respect to monitoring tests, patients treated with ozanimod are assumed to have the same scheduled test as patients treated with fingolimod (months 1, 3, 9, 12 and every 6th month thereafter). Blood samples associated with initiation of therapy is assumed to be included in the DRG of the initiation visit.

- Additional monitoring requirement (blood tests) are assumed to lead to a visit to a local care facility for blood sampling and tests. The test results are evaluated by the hospital department but do not require an outpatient visit.

- Patients with low resting heart rate, second-degree AV block or a history of AV block or heart failure is monitored after first dosing. According to the ozanimod Public Assessment Report (p 126), 105 of 2729 (4%) in the ozanimod phase 3 program had HR <55 bpm, with prolonged QTcF interval or additional risks for QT prolongation, as well as with concomitant medication known to impact cardiac conduction.[15] In the cost analysis, it was assumed that 5% of patients would require monitored first dosing.

The resulting number of health care contact for each product is shown in Table 3. A regular outpatient visit was assumed to be associated with 90 minutes patient time (total in clinical and during travel), monitored first dosing 7 hours total time. Patient time associated with blood test was assumed to be additional to outpatient visit. Blood sampling was assumed to be performed a local facility and, hence, the total patient time as assumed to be 50% of that of a regular outpatient visit.

Table 3 Monitoring applied in the cost analysis

Type of contact	Patient time	Number of monitoring visits					
		Ozanimod		Dimethyl fumarate		Fingolimod	
		1st year	2+ years	1st year	2+ years	1st year	2+ years
Outpatient visit (initiation)	90 min	95%		100%			
Daycare visit (monitored initiation)	7 hours	5%				100%	
Routine follow-up	90 min	3	2	3	2	3	2
Blood test	45 min	4	2	16.25	6.5	4	2

Table 4 presents the unit cost per health care contact applied in the model. Outpatients visits are based on DRG_{2020}.[16] This means that the same cost is applied for an ordinary outpatient visit and the longer visits associated with monitored initiation. The DRG cost applied is the tariff

for group 01MA98 *MDC01 1-dagsgruppe, pat. mindst 7 år*. [16] The direct cost associated with assessment of monitoring test results is set to value of a DRG tariff for phone or mail follow-up to a test result (DRG group 65TE01 Telefon- og e-mail- konsultation samt skriftlig kommunikation ved prøvesvar). [16]

Travel cost was calculated based on a 28 km round trip distance for all outpatients visit (@ 3.52 kr/km)[17]. Patient time costed at 179 DKK/ hour[17]. Total time and travel cost associated with regular blood test was assumed to be 50% of the cost associated with an outpatient visit based on the assumption of the patient using a local test facility.

Table 4 Unit cost applied in the cost analysis

Resource	Regional cost	Note	Patient cost
Outpatient visit (initiation)	3,375.00	DRG_{2020} 01MA98	367.06
Daycare visit (monitored initiation)	3,375.00	DRG_{2020} 01MA98	1,351.56
Routine follow-up	3,375.00	DRG_{2020} 01MA98	367.06
Blood test	129.00	DRG_{2020} 65TE01	183.53

Treatment duration

As presented above there is no evidence to suggest that there is a statistically significant and clinically meaningful difference in time to progression between the intervention and the comparators in any of the two scientific questions raised by the MC protocol[1]. Hence a common treatment duration was applied for ozanimod and comparator treatments.

In the base case analysis, a treatment duration in each population was assessed from observed real-life discontinuation rates for patients treated with DMF in clinical practice. In a US retrospective chart review was performed on all patients with RRMS follow-up for a period of 14 months following start of DMF, 20-29% of patients discontinued treatment. [18] Similar rates have been reported in a Danish retrospective study although the time of follow-up is not stated. [19] An average treatment duration can be estimated roughly assuming a constant discontinuation rate using an exponential failure distribution as (*1/r*) where the annual rate (*r*) is estimated assuming a 14 month discontinuation rate of 20% (*-ln(80%)/14*12*). This gives an average treatment duration of 5.2 years. Based on this observation, a 5-year average treatment duration (and time horizon) was pragmatically chosen as a relevant time horizon for the base case analysis in both populations. In scenario analyses, the duration was varied from 1 to 10 years.

One year was assumed to consist of 365.25 days (in the calculation of yearly medicines consumption) and 12 months (in the calculation of monitoring costs)

Cost of side-effects

The base case analysis was designed on the premise that treatment with ozanimod is clinically equivalent with respect to outcomes in the Medicine Council assessment for both comparators and in both populations. Consequently, the costs of side-effects were excluded from the analysis.

Patient cost

Patient costs were calculated based on patient time spend in connection with travel and clinic visits as well as the cost of travel associated with drug monitoring (Table 3 and Table 4).

Discounting

Costs accrued after year 1 was discounted by 4% per year.

2.2 Results

Base case assumptions

Table 5 summarized the key base case assumption outlined above.

Table 5 Key base case assumptions

Option	Selected base case
Population	**RRMS first line patients**
Comparator	Dimethyl fumarate (DMF)
Number of patients requiring monitored initiation	Ozanimod: 5% DMF: 0%
Cost of ambulatory visit	DRG 01MA98 *MDC01 1-dagsgruppe, pat. mindst 7 år*
Drug wastage per patient	0.5 packs
Time horizon	5 years
Price	Pharmacy purchase price
Discount rate	Not applicable
Population	**RRMS first line patients**
Comparator	Fingolimod
Number of patients requiring monitored initiation	Ozanimod: 5% Fingolimod: 100%
Cost of ambulatory visit	DRG 01MA98 *MDC01 1-dagsgruppe, pat. mindst 7 år*
Drug wastage per patient	0.5 packs
Time horizon	5 years
Price	Pharmacy purchase price
Discount rate	4% per year for cost accrued after year 1

Abbreviations: DMF Dimethyl fumarate; RRMS Relapsing-remittent multiple sclerosis

Base case

Table 6 and Table 7 show the base case results by population.

Table 6 Base case results. P1 RRMS first line patients

	Ozanimod	Dimethyl fumarate
Drug cost	709,283	675,858
Monitoring	39,454	43,142
Total direct cost	748,738	719,000
Patient cost	6,249	11,446
Net present societal cost per patient	**754,986**	**730,445**
Incremental cost of ozanimod compared to dimethyl fumarate		
Incremental direct cost		29,738
Incremental societal cost		**24,541**

Table 7 Base case results. P2 RRMS patients second line patients

	Ozanimod	Fingolimod
Drug cost	709,283	691,370
Monitoring	39,454	39,454
Total direct cost	748,738	730,824
Patient cost	6,249	7,184
Net present societal cost per patient	**754,986**	**738,008**
Incremental cost of ozanimod compared to fingolimod		
Incremental direct cost		17,914
Incremental societal cost		**16,978**

Sensitivity analysis

Table 8 shows the results of a one-way sensitivity analysis of using alternative assumptions.

Table 8 Results of sensitivity analyses

Population	Scenario	Ozanimod	Comparator	Incremental cost
P1 (first line RRMS patients)	**Base case**	**754,986**	**730,445**	**24,541**
	Treatment duration 1 year	173,810	169,986	3,824
	Treatment duration 3 years	475,751	461,164	14,587
	Treatment duration 10 years	1,364,707	1,318,426	46,281
	Ozanimod monitored 1st dose 0%	754,937	730,445	24,492
	Ozanimod monitored 1st dose 10%	755,036	730,445	24,590
	Visit cost -50%	736,070	711,444	24,626
	No waste	748,183	723,960	24,223
	Full pack wasted	761,790	736,930	24,860
P2 (Second line RRMS patients)	**Base case**	**754,986**	**738,008**	**16,978**
	Treatment duration 1 year	173,810	170,767	3,044
	Treatment duration 3 years	475,751	465,468	10,283
	Treatment duration 10 years	1,364,707	1,333,109	31,598
	Ozanimod monitored 1st dose 0%	754,937	738,008	16,929
	Ozanimod monitored 1st dose 10%	755,036	738,008	17,028
	Visit cost -50%	736,070	720,695	15,375
	No waste	748,183	731,376	16,806
	Full pack wasted	761,790	744,640	17,150

3 Budget impact analysis

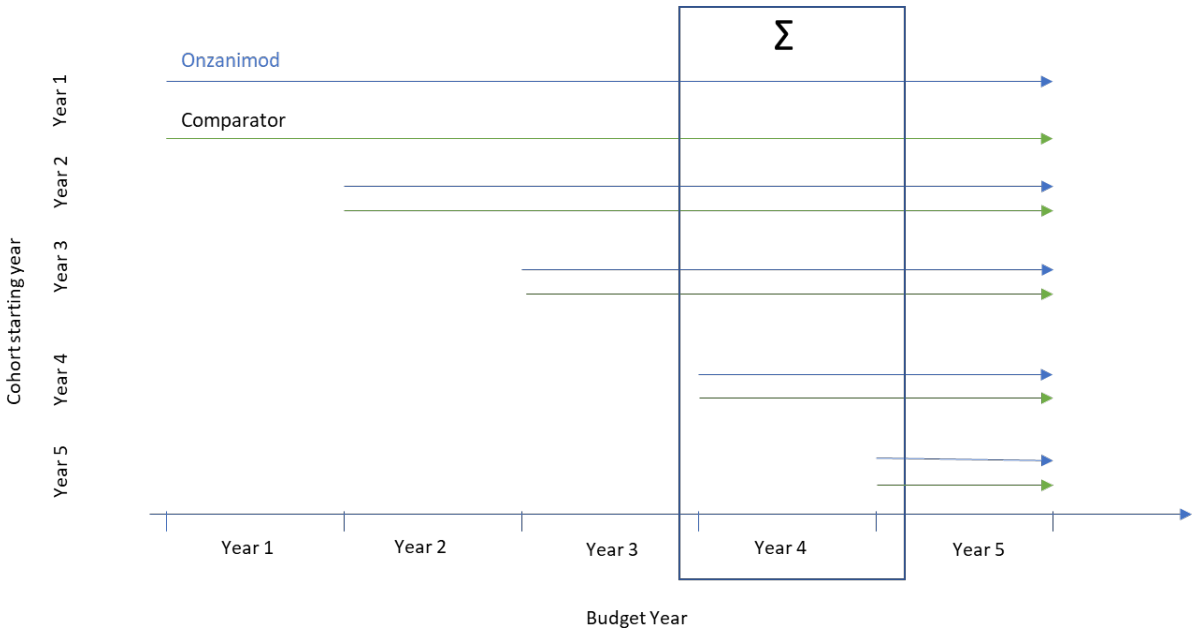
3.1 Method

The impact of introducing ozanimod as standard treatment in RRMS was calculated using a 5-year budget impact model.

The model is illustrated in Figure 1. A cohort of patients start treatment each year. In line with the cost-analysis it is assumed that each cohort of patient starting treatment in a given year (say year X) will stay on treatment until progression. Treatment duration for the two population are equal to the base case assumption in the net-present cost analysis. For each arm the costs are accrued for up to year 5. The budget impact in year X is captured as the sum in year X. Costs in the budget impact are not discounted.

The budget impact is simplified in the way that it considers a steady-state population where the share of patients on each treatment option is constant over time.

Figure 1 Illustration of budget impact model



3.2 Patient numbers and market share

The budget impact is based on population size estimations for each of the two population as described below.

P1 RRMS first line

In 2016 *Rådet for Anvendelse Dyr Sygehusmedicin* (RADS) estimated that 550 new patients per year would be diagnosed. 85 % (~470 patients) percent have MS with attacks and are thus candidates for treatment with immunomodulatory medicine.[20] Candidates for first line treatment is estimated to 90% of patients (~425) with RRMS [20]

Seventy percent of the population are women (~300). Of these one sixth (~50) is expected to have an immediate intention of pregnancy, two sixths (~100) with an intention of pregnancy within one year and the remaining three sixths (~150) have no intention of pregnancy (use contraception). [20]

The number of new patients per year relevant for treatment with ozanimod is thus approximately 275 patients among men and women using contraception with no intention of pregnancy, and 100 patients among women using contraception with intention of pregnancy within one year. [20]

In steady state, 3.3% of patients are excluded from treatment with ozanimod based on contraindication. This estimate was based on a study of comorbidities of MS patients at the time of diagnosis as recorded in in United States Department of Defense database. The population consisted of patients first diagnosed between January 2004–August 2017 with more than 1 year of pre-diagnosis history at cohort entry (diagnosis date) and at least one prescription for a MS disease-modifying treatment[21]. 3.3% of patients have a record of comorbidity of myocardial infarction, stroke/TIA, angina or heart failure. We applied this estimate for potentially contraindicated patients who would not be eligible for ozanimod.

P2 RRMS second line

The number of patients in P2 was sourced from Amgros' assessment of ocrelizumab in RRMS. The number of patients eligible for fingolimod is estimated to be 1412 of 2420 (58.3%) in 2018.

Applying to this to the number of incident patients (400-500 per year) mentioned in the same report, this means that the report is based on 233-291 incident patient per year, who would eventually be eligible for second line treatment with fingolimod. We applied the lower estimate but inflated the 2018 estimate by the growth rate of 3% per year according to Amgros, the population of patients eligible for starting fingolimod treatment in 2020 would be 248 patients ($400x1412/2420x1.03^2$).

In the budget impact analysis for ozanimod an incident population of 250 patients per year was used. It is assumed that all patients will be eligible for both products.

Market uptake

In the five-year budget analysis, it was assumed that steady state is reach in year 5. Years 1 to Year 4 the market uptake is assumed to increase linearly from 60% year 1 to 90% year 4. Table 9 and Table 10 present the patients numbers with and without recommendation in population P1 and P2, respectively.

Table 9 Patient number and without ozanimod recommendation in P1

Year:	1	2	3	4	5
Situation without ozanimod					
Ozanimod	0	0	0	0	0
Dimethyl fumarate	375	375	375	375	375
Situation with ozanimod					
Ozanimod	218	254	290	326	363
Dimethyl fumarate	157	121	85	49	12

Table 10 Patient number and without ozanimod recommendation in P2

Year:	1	2	3	4	5
Situation without ozanimod					
Ozanimod	0	0	0	0	0
Fingolimod	250	250	250	250	250
Situation with ozanimod					
Ozanimod	150	175	200	225	250
Fingolimod	100	75	50	25	0

3.3 Results

In steady state, the year five budget impact will result in increases in regional expenditure irrespective of the place in therapy (ranging from 9.2 million DKK in P1 to 3.9 million DKK in P2) when estimated using current PPP prices (Table 11).

Table 11 Result of budget impact analysis by population (DKK; pharmacy purchase prices)

P1. RRMS first line			**Budget year**		
Scenario	**1**	**2**	**3**	**4**	**5**
Situation with ozanimod	61,248,242	119,955,904	178,900,015	238,080,575	299,635,616
Situation without ozanimod	59,996,957	117,077,378	174,157,799	231,238,219	290,397,453
Budget impact	**1,251,285**	**2,878,526**	**4,742,217**	**6,842,356**	**9,238,164**
P2. RRMS second line			**Budget year**		
Scenario	**1**	**2**	**3**	**4**	**5**
Situation with ozanimod	41,052,535	80,448,870	119,941,004	159,528,939	200,651,905
Situation without ozanimod	40,477,736	79,203,471	117,929,207	156,654,943	196,797,879
Budget impact	**574,799**	**1,245,398**	**2,011,797**	**2,873,996**	**3,854,026**

4 Conclusion

The introduction of ozanimod offers a new first line treatment to patient with RRMS and is associated with an increase in societal cost over a 5-year time horizon of 24,541 DKK / patient at PPP prices. If recommended in second line treatment of RRMS, ozanimod is associated with an increase in 5-year societal cost of 16,978 DKK/patient at PPP price levels. Regional budget impact year 5 ranges from 9.2 MDKKK in first line use to 3.9 MDKK in second line when it is assumed that all eligible patients will switch to ozanimod.

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Medicinrådet

Medicinrådets protokol for vurdering af ozanimod til behandling af attakvis multipel sklerose

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om 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 metode, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, 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.

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Indhold

1 Begreber og forkortelser

AR	*Adverse Reaction*
CDP	*Confirmed Disabilty Progression*
CI	Konfidensinterval
DMT	*Disease Modifying Therapy*
EDSS	*Expanded Disability Status Scale*
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR	*Hazard ratio*
ITT	*Intention to treat*
JCV	John Cunningham virus
MS	Multipel sklerose
MSQOL-54	*Multiple Sclerosis Quality of Life-54*
OR	*Odds ratio*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PML	Progressiv multifokal leukoencefalopati
PP	*Per-protocol*
PPMS	Primær progressiv multipel sklerose
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RMS	Relapserende multipel sklerose
RR	Relativ risiko
RRMS	Recidiverende relapserende multipel sklerose
SDMT	*Symbol Digit Modality Test*
SMD	*Standardized Mean Difference*
SPMS	Sekundær progressiv multipel sklerose

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Bristol Myers Squibb på vegne af Celgene, som ønsker, at Medicinrådet vurderer ozanimod til attakvis multipel sklerose. Vi modtog den foreløbige ansøgning den 1. maj 2020.

2.1 Attakvis multipel sklerose

Multipel sklerose (MS) er en kronisk neurologisk lidelse, som hyppigst debuterer i alderen 25-45 år og forekommer ca. dobbelt så ofte hos kvinder som hos mænd. Årsagen er ukendt, men der findes flere disponerende arvelige og miljømæssige faktorer. Disse kan medvirke til en autoimmun reaktion mod molekyler på overfladen af en bestemt type celler (oligodendrocytter), som normalt beskytter og isolerer nervecellernes udløbere (aksoner) ved at omgive dem med myelinskeder. Sygdommen er karakteriseret ved spredte områder i centralnervesystemet med inflammation, demyelinisering og tab af aksoner [1]. Patienter med MS vil i varierende grad være præget af både fysiske og kognitive symptomer såsom synsnedsættelse, dobbeltsyn, spastiske lammelser af arme og/eller ben, føleforstyrrelser, dårlig balance, vandladningsforstyrrelser, forstoppelse, problemer med seksualfunktionen, smerter, træthed samt hukommelses- og koncentrationsproblemer. Patienternes livskvalitet kan være meget påvirket af både fysiske og kognitive symptomer samt træthed.

Der findes overordnet tre typer af MS: Recidiverende remitterende multipel sklerose (RRMS) eller attakvis MS, sekundær progressiv multipel sklerose (SPMS) og primær progressiv multipel sklerose (PPMS). Den hyppigste type er RRMS, som er defineret ved attakvise tilbagefald med forværring af symptomer eventuelt efterfulgt af en periode med forbedring af symptomer. RRMS kan ændre karakter, så der kommer tiltagende symptomer uden bedring og dermed gå over i et progressivt forløb kaldet SPMS [2]. Endelig bruges betegnelsen recidiverende multipel sklerose (RMS) om patienter med RRMS samt patienter med SPMS, som oplever attakker.

I Danmark har knap 16.500 personer MS, hvilket svarer til 250 pr. 100.000. Antallet af nye tilfælde har ligget nogenlunde konstant på ca. 600 personer om året siden år 2000 [3].

Udover kliniske undersøgelser bliver patienter med MS fulgt ved radiologiske undersøgelser. Fagudvalget har i Medicinrådets behandlingsvejledning for attakvis MS anbefalet magnetisk ressonansscanning en gang om året [4]. På scanningen kan klinikerne se tegn på aktiv inflammatorisk aktivitet, nye og gamle læsioner og atrofi (tab af hjernevolumen).

2.2 Ozanimod til behandling af attakvis MS

Ozanimod er en sphingosine 1-phosphate receptor modulator, som binder med høj affinitet til sphingosine 1-phosphate receptor-subtyperne 1 og 5. Ozanimod virker ved at forhindre immunforsvarets T- og B-celler i at forlade lymfeknuderne, som dermed forhindres i at infiltrere centralnervesystemet. Ozanimod begrænser derved inflammation og ledsagende vævsskade i centralnervesystemet.

Der findes to andre sphingosine 1-phosphate receptor modulatorer, som benyttes til behandling af MS. Fingolimod, som er anbefalet af Medicinrådet til andenlinjebehandling af attakvis MS (se afsnittet ”2.3 Nuværende behandling”), og siponimod, som er under vurdering til sekundær progressiv MS.

Den anbefalede vedligeholdelsesdosis af ozanimod er 0,92 mg oralt en gang dagligt. Behandlingen skal i den første uge indledes med et dosiseskaleringsprogram, som er vist i tabel 1.

Tabel 1: Dosis, eskalation

Dag 1-4	0,23 mg en gang dagligt
Dag 5-7	0,46 mg en gang dagligt
Dag 8 og vedligehold	0,92 mg en gang dagligt

2.3 Nuværende behandling

Der findes ingen behandling, som kan helbrede MS. Den nuværende behandling er delt op i symptomlindrende behandling og sygdomsmodificerende behandling (Disease Modifying Therapies (DMT's)). De nuværende DMT's er overvejende virksomme ved attakvis sygdom. Målet med behandlingen er at forsinke udvikling af fysiske og mentale funktionstab, undgå attaker og derved give patienten den bedst mulige livskvalitet.

Inddeling af patienter

Lægemidlerne til behandling af attakvis multipel sklerose er delt op i to grupper i Medicinrådets behandlingsvejledning og lægemiddelrekommandation [4][5]. De kaldes første og anden linje, men det skal ikke opfattes således, at samtlige patienter nødvendigvis vil blive behandlet med et førstelinjelægemiddel først, og dernæst med et andenlinjelægemiddel. Det skal derimod forstås således, at de mest effektive og potentielt mest bivirkningstunge lægemidler kaldes andenlinjelægemidler og forbeholdes patienter med størst sygdomsaktivitet, eller til patienter hvor førstelinjebehandling viser sig ikke at være effektiv nok.

Patienterne, som kan behandles med lægemidler fra gruppen af førstelinjepræparater, omfatter patienter med gennemsnitlig sygdomsaktivitet (defineret radiologisk og klinisk). Skift mellem lægemidler indenfor gruppen af førstelinjepræparater kan ske på grund af eksempelvis betydende bivirkninger eller ændringer i graviditetsønske.

Patienterne, som behandles med lægemidler fra gruppen af førstelinjepræparater, opdeles efter graviditets-ønske og anvendelse af antikonception. Baggrunden for dette er, at der anbefales forskellige udvaskning-sperioder for lægemidlerne inden graviditet. I den nuværende rekommandation er dimethylfumarat førstevalg til mænd, og til de kvinder som benytter antikonception [5]. I rekommandationen er denne population delt i to, men dimethylfumarat er førstevalg for begge: "Mænd og kvinder som anvender antikonception og ikke har graviditetsønske" og "kvinder som anvender antikonception og har graviditetsønske inden for ca. et år".

Patienterne, som kan behandles med lægemidler fra gruppen af andenlinjepræparater, er

- patienter med fortsat sygdomsaktivitet (defineret radiologisk og klinisk) på et førstelinjepræparat
- patienter med høj sygdomsaktivitet (defineret radiologisk og klinisk), som ikke tidligere har været behandlet.

Patienter, som behandles med lægemidler fra gruppen af andenlinjepræparater, opdeles yderligere efter, om de har antistoffer for John Cunningham virus (JCV) eller ej. Baggrunden for dette er, at behandling med nogle DMT's (hovedsageligt natalizumab) i observationelle studier har vist at kunne medføre risiko for den dødelige sygdom progressiv multifokal leukoencefalopati (PML), som forårsages af JCV [1].

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

Hvilken værdi har ozanimod sammenlignet med dimethylfumarat for patienter med attakvis multipel sklerose og gennemsnitlig sygdomsaktivitet (førstelinjebehandling)?

Population
Patienter med gennemsnitlig sygdomsaktivitet (defineret radiologisk og klinisk).

Da ozanimod er kontraindiceret hos kvinder, som kan blive gravide, omfatter populationen kun mænd samt kvinder, som benytter effektiv antikonception.

Intervention
Ozanimod.

Komparator
Dimethylfumarat er valgt, da dette lægemiddel er nuværende førstevalg i første linje til populationen i Medicinrådets lægemiddelrekommandation for attakvis multipel sklerose [5] og har en indikation, som tilsvarer ozanimods.

Effektmål
De valgte effektmål står i tabel 2.

3.2 Klinisk spørgsmål 2

Hvilken værdi har ozanimod sammenlignet med fingolimod for patienter med attakvis multipel sklerose og høj sygdomsaktivitet (andenlinjebehandling)?

Population
Patienter med høj sygdomsaktivitet (defineret radiologisk og klinisk) uanset JCV-status.

Da ozanimod og fingolimod er kontraindiceret hos kvinder, som kan blive gravide, omfatter populationen kun mænd samt kvinder, som benytter effektiv antikonception.

Intervention
Ozanimod.

Komparator
Fingolimod er valgt, da dette lægemiddel er nuværende førstevalg i anden linje til halvdelen af populationen i Medicinrådets lægemiddelrekommandation for attakvis multipel sklerose [5] og har samme virkningsmekanisme som ozanimod.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel. I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 2: Effektmål

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Vedvarende sygdomsforværring bekræftet efter 3 måneder (CPD3)	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever en ændring i CDP, der fastholdes over 3 måneder	En forskel på 10 %-point

Bivirkninger	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever en eller flere alvorlige bivirkninger	Forskel på 3 %-point
			Gennemgang af bivirkningsprofil	Narrativ vurdering
Årlig attakrate	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Antal attakker pr. patient om året	Forskel på 0,1 attakker pr. patient om året
Kognitiv funktion	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, som undgår en 10 % forværring på SDMT	En forskel på 10 %-point
Livskvalitet	*Vigtig*	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring på MSQOL54	Forskel på 0,5 SMD

For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.
CDP: Confirmed Disease Progression, SDMT: Symbol Digit Modality Test, MSQOL54: Multiple Sclerosis Quality of Life-54, SMD: Standardized Mean Difference.

3.3.1 Kritiske effektmål

Vedvarende sygdomsforværring (bekræftet efter 3 måneder)
Vedvarende sygdomsforværring (Confirmed Disabilty Progression (CDP)) defineres som en ændring i Expanded Disability Status Scale (EDSS) score på 1 eller på 0,5, hvis baseline EDSS var højere end 5,5.

EDSS er en metode til at kvantificere sygdomsforværring i MS. Måleinstrumentet måler ændringer i niveau af sygdomsforværring over tid. EDSS er det instrument, der oftest bruges, både i kliniske studier og i klinikken. EDSS-skalaen går fra 0 (fuld funktion) til 10 (død). Scorer mellem 1,0-4,5 defineres ved patienter, der stadig er i stand til at gå uden nogen hjælp, hvorimod scorer mellem 5,0-9,5 er defineret ved, at patienterne ikke kan gå. Det skal dog nævnes, at EDSS ved score ≥ 5 primært måler sygdomsforværring relateret til, om patienterne kan gå, hvorimod funktionsniveauet i overkroppen, det kognitive funktionsniveau, energiniveau og livskvalitet ikke tages i betragtning [6].

Dette effektmål er kritisk, da et centralt mål med behandlingen er at forsinke progression af sygdommen. Effektmålet CPD3 betyder, at den vedvarende sygdomsforværring opgøres som andelen af patienter, der oplever en sygdomsforværring, som fastholdes over 3 måneder. Fagudvalget forventer, at omkring 10-15 % af patienterne behandlet med nuværende dansk standardbehandling vil progrediere i løbet af to år. Den mindste klinisk relevante forskel mellem to aktive behandlinger i første linje vurderes af fagudvalget at være på 10 %-point.

Bivirkninger
Bivirkninger (adverse reactions, AR) er et kritisk effektmål, da det belyser, hvor godt patienterne tolererer ozanimod sammenlignet med komparator. Fagudvalget ønsker data på nedenstående måleenheder:

Alvorlige bivirkninger
Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere alvorlige bivirkninger, er relevant for vurderingen. Da der allerede eksisterer flere effektive behandlingsalternativer, accepterer fagudvalget ikke, at en ny behandling er markant mere bivirkningstung. Fagudvalget vurderer derfor, at den mindste klinisk relevante forskel i andelen af patienter, der får alvorlige bivirkninger, er 3 %-point.

Gennemgang af bivirkningsprofil
Fagudvalget ønsker en gennemgang af ozanimod, dimethylfumarat og fingolimods bivirkningsprofiler med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra både de kliniske studier og produktresuméet for lægemidlerne, så fagudvalget kan vurdere forskelle mellem de forskellige behandlinger.

Fagudvalget er specielt interesseret i forekomsten af alvorlige eller hyppige infektioner og i bivirkninger, der kræver hyppig monitorering såsom ændring i levertal.

Fagudvalget vægter den kvalitative gennemgang af bivirkninger højt i vurderingen af ozanimod, og ønsker at bivirkningers skal rapporteres med længst mulig tidshorisont. I vurderingsrapporten vil fagudvalget tage stilling til forhold omkring forebyggelse, monitorering og håndtering af alvorlige bivirkninger.

3.3.2 Vigtige effektmål

Årlig attakrate
Den årlige attakrate beskriver antal bekræftede attakker pr. patient om året. Fagudvalget betragter dette effektmål som vigtigt, da forebyggelse af attakker er et behandlingsmål i sig selv, da attaker kan medføre varige funktionstab, og fravær af attakker må forventes at have positiv indflydelse på patienternes livskvalitet.

Et attak defineres som nye eller forværring af eksisterende symptomer af mere end 24 timers varighed i fravær af feber eller infektion, forudgået af en stabil neurologisk tilstand i minimum 30 dage. Symptomerne skal desuden kunne tilskrives MS og skal være ledsaget af objektiv neurologisk forværring [7,8]. Fagudvalget har i tidligere protokoller vurderet, at de nuværende lægemidler, som anbefales til andenlinjebehandling af multipel sklerose, kan reducere den årlige attakrate med 0,2-0,5 pr. patient om året i forhold til placebo og 0,17 i forhold til interferon [1]. Fagudvalget har valgt at benytte en tilsvarende forskel for to aktive lægemidler til førstelinjebehandling. En gennemsnitlig forskel i den årlige attakrate på 0,1 pr. patient om året vurderes af fagudvalget at være den mindste klinisk relevante forskel mellem ozanimod og komparator. Tallet kan virke meget lavt, men da velbehandlede patienter i dansk klinisk praksis generelt har få attaker (ca. 0,1- 0,2 om året ifølge upublicerede danske registerdata, som fagudvalget har kendskab til), vil en forskel på 0,1 kunne skelne mellem to behandlingers effektivitet.

Kognitiv funktion "Symbol Digit Modality Test" (SDMT)
Fagudvalget finder, det er vigtigt at inkludere et mål for kognitiv funktion, da denne har stor betydning for patienternes trivsel og funktionsniveau. Der findes flere forskellige instrumenter, hvoraf fagudvalget har valgt SDMT-testen. I denne test skal patienterne på tid matche symboler og tal ud fra en forudbestemt nøgle. Testen er enkel, hurtig og kan med stor sensitivitet opdage kognitive skader og ændringer i kognitiv funktion over tid. Scoren bestemmes ud fra, hvor mange matchende kombinationer af symboler og tal patienterne har opnået på 90 sekunder og kan maksimalt være 110 point [9]. En ændring i test-score på 10 % betragtes som klinisk betydningsfuld, og fagudvalget vurderer, at få patienter med gennemsnitlig sygdomsaktivitet oplever en sådan ændring på dansk standardbehandling [10]. Fagudvalget vurderer, at en forskel på 10 %-point i andelen, der ikke oplever en 10 % reduktion i SDMT, er klinisk relevant.

Livskvalitet
Multiple Sclerosis Quality of Life-54 (MSQOL-54) er et sygdomsspecifikt og valideret mål for livskvalitet, der inkluderer selvrapporterede subjektive indikatorer for fysisk, emotionel og social funktionalitet og trivsel [11,12]. MSQOL-54 bygger på det hyppigt anvendte generiske instrument til måling af livskvalitet, SF-36. Det inkluderer alle domæner fra SF-36 og har derudover 18 sygdomsspecifikke domæner, som indeholder sundhedstilstand, seksuel funktion, tilfredshed med seksuel funktion, generel livskvalitet, kognitiv funktion, energi og social funktion. Skalaen går fra 0-100, hvor en højere score indikerer højere livskvalitet [13]. For helbredsrelateret livskvalitet anvendes ofte en mindste klinisk relevant forskel på 0,5 standarddeviationer

(SD), også for patienter med MS, og fagudvalget har derfor valgt at anvende en forbedring på 0,5 SD som mindste klinisk relevante forskel [14,15].

Såfremt der ikke foreligger data fra MSQOL-54, foretrækker fagudvalget data fra et andet valideret instrument, som er relevant for patienter med MS, eksempelvis de generiske SF-36 eller EQ-5D.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor ozanimod er sammenlignet direkte med dimethylfumarat eller fingolimod.

Klinisk spørgsmål 1

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem ozanimod og dimethylfumarat. Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

Klinisk spørgsmål 2

Medicinrådet har ikke fundet fuldtekstartikler, der indeholder en direkte sammenligning mellem ozanimod og fingolimod. Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

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#	Søgetermer	Kommentar
#1	Multiple Sclerosis, Relapsing-Remitting [mh:noexp]	Søgetermer for populationen
#2	RMS[tiab] OR RRMS[tiab]	
#3	relaps*[tiab] AND (multiple sclerosis[tiab] OR MS[tiab])	
#4	#1 OR #2 OR #3	
#5	ozanimod[nm]	Søgetermer for interventionen
#6	ozanimod[tiab] OR RPC1063[tiab] OR RPC-1063[tiab] OR Zeposia*[tiab]	
#7	Dimethyl Fumarate[mh]	Søgetermer for komparatorer
#8	dimethyl fumarate[tiab] OR FAG-201[tiab] OR FAG201[tiab] OR BG-00012[tiab] OR BG00012[tiab] OR BG-12[tiab] OR BG12[tiab] OR Tecfidera*[tiab] OR Fumaderm*[tiab]	
#9	Fingolimod Hydrochloride[mh]	
#10	fingolimod[tiab] OR FTY-720[tiab] OR FTY720[tiab] OR Gilen*[tiab]	
#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10	
#12	#4 AND #11	Kombination population og lægemidler
#13	(Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans[mh])	Filter til identificering af randomiserede studier
#14	#12 AND #13	

#15	(Review[pt] OR Comment[pt] OR Letter[pt] OR Case Reports[pt] OR case report[ti] OR review[ti]) NOT Randomized Controlled Trial[pt]	Eksklusion af irrelevante publikationstyper
#16	#14 NOT #15	Endelig søgning (begge kliniske spørgsmål)

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#	Søgetermer	Kommentar
#1	[mh ^"Multiple Sclerosis, Relapsing-Remitting"]	Søgetermer for populationen
#2	multiple sclerosis:kw and embase:an and relaps*:ti,ab,kw	
#3	(RMS or RRMS):ti,ab	
#4	relaps*:ti,ab and (multiple next sclerosis or MS):ti,ab	
#5	#1 or #2 or #3 or #4	
#6	(ozanimod or RPC1063 or "RPC 1063" or Zeposia*):ti,ab,kw	Søgetermer for interventionen
#7	[mh "Dimethyl Fumarate"] or "fumaric acid dimethyl ester":kw	Søgetermer for komparatorer
#8	(dimethyl next fumarate or "FAG 201" or FAG201 or "BG 00012" or BG00012 or "BG 12" or BG12 or Tecfidera* or Fumaderm*):ti,ab	
#9	[mh "Fingolimod Hydrochloride"]	
#10	(fingolimod or "FTY 720" or FTY720 or Gilen*):ti,ab,kw	
#11	#6 or #7 or #8 or #9 or #10	
#12	#5 and #11	Kombination population og lægemidler
#13	(clinicaltrials.gov or trialsearch):so	Eksklusion af irrelevante publikationstyper
#14	("conference abstract" or review):pt or (abstract or review):ti	
#15	NCT*:au	
#16	#13 or #14 or #15	
#17	#12 not #16	
#18	(Embase not Pubmed):an	Inklusion af referencer fra Embase
#19	#17 and #18 in Trials	Endelig søgning (begge kliniske spørgsmål)

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning

Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur

Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler ekskludere først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

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.
- 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).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jævnfør Appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'- og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier og vurdér, hvorvidt resultaterne er sammenlignelige.

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 fortæller, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

Fagudvalget bemærker, at indikationen for ozanimod omfatter kvinder, som anvender effektiv antikonception, men evt. har graviditetsønske på længere sigt. EMAs EPAR anbefaler, at kvinder anvender effektiv antikonception mindst 3 måneder efter endt behandling med ozanimod. Fagudvalget er bekymret for evt. *rebound* effekt, hvis behandling med ozanimod stoppes grundet graviditetsønske og beder ansøger redegøre for mulighederne for såkaldt "*bridging* terapi", altså behandlingen af kvinder med graviditetsønske, efter ozanimod er seponeret.

Grundet den farmakologiske lighed mellem de to lægemidler ønsker fagudvalget ansøgers overvejelser omkring forventningen til ozanimods langtidsbivirkningsprofil sammenlignet med fingolimods. Helt specifikt er fagudvalget interesseret i at vide, om der eksempelvis er farmakodynamiske eller -kinetiske egenskaber ved ozanimod, der gør, at sjældne, alvorlige bivirkninger ved fingolimod ikke forventes at forekomme ved behandling med ozanimod.

8 Relation til behandlingsvejledning

Fagudvalget vil i forbindelse med vurderingen af ozanimod tage stilling til, hvor det foreløbig kan placeres i Medicinrådets behandlingsvejledning for attakvis multipel sklerose.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende multipel sklerose

Formand	**Indstillet af**
Lars Kristian Storr Overlæge, speciallæge i neurologi	Lægevidenskabelige Selskaber og udpeget af Dansk Neurologisk Selskab
Medlemmer	**Udpeget af**
Kan ikke opfylde Medicinrådets habilitetskrav	Region Nordjylland
Thor Petersen Overlæge, dr.med.	Region Midtjylland
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Said Nasim Ashna Overlæge	Region Sjælland
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Kan ikke opfylde Medicinrådets habilitetskrav	Sclerosebehandlingsregistret
Kan ikke opfylde Medicinrådets habilitetskrav	Dansk Neurologisk Selskab
Marie Lynning Patient/patientrepræsentant	Danske Patienter
Malene Krüger Patient/patientrepræsentant	Danske Patienter
Preben Borring Andersen Overlæge	Inviteret af formanden
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11 Versionslog

Version	Dato	Ændring
1.0	4. august 2020	Godkendt af Medicinrådet.