Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende galcanezumab til forebyggende behandling af kronisk migræne

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 Baggrunden for Medicinrådets anbefaling

Baggrund for Medicinrådets anbefaling er en sammenfatning af lægemidlets værdi for patienterne, omkostninger for samfundet og en gengivelse af de vurderinger, der er grundlag for Medicinrådets anbefaling.

Anbefalingen er Medicinrådets vurdering af, om omkostningerne vedrørende brug af lægemidlet er rimelige, når man sammenligner dem med lægemidlets værdi for patienterne. I nogle tilfælde spiller sygdommens alvorlighed en særlig rolle i vurderingen.

Anbefalingen er et klinisk og økonomisk baseret råd til regionerne til brug for deres beslutning om at anvende et givet lægemiddel.

Læs eventuelt mere i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Godkendt af Medicinrådet 23. september 2020
Dokumentnummer 88622
Versionsnummer 1.0

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

Medicinrådet

Indhold

1 Anbefaling vedrørende galcanezumab til forebyggende behandling af kronisk migræne

Medicinrådet anbefaler galcanezumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger med mindst ét antihypertensivum og ét antiepileptikum

Vi anbefaler galcanezumab, fordi det samlet set vurderes som et ligestillet behandlingsalternativ til erenumab og fremanezumab. Samtidig vil sundhedsvæsenets omkostninger til lægemidlet være rimelige.

2 Værdi for patienterne

Der er ikke påvist en merværdi af galcanezumab sammenlignet med erenumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på to tidligere forebyggende behandlinger i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi. Derfor vurderer Medicinrådet, at galcanezumab er et klinisk ligestillet alternativ til erenumab og fremanezumab. Det betyder, at galcanezumab samlet set vurderes at være lige så effektivt og sikkert som erenumab og fremanezumab.

Der foreligger ikke direkte sammenlignende studier mellem galcanezumab, erenumab eller fremanezumab. Medicinrådets kategorisering har derfor taget udgangspunkt i en indirekte sammenligning mellem galcanezumab og erenumab. De indirekte analyser er forbundet med usikkerhed, som betyder at værdien af galcanezumab sammenlignet med erenumab ikke formelt kan kategoriseres i henhold til Medicinrådets metoder.

Kvaliteten af data for sammenligningen mellem galcanezumab og erenumab er lav. Det betyder, at nye studier med moderat sandsynlighed kan ændre konklusionen.

Høringsprocessen har ikke givet anledning til ændringer i Medicinrådets vurdering af galcanezumabs værdi (bilag 3).

Læs mere i Medicinrådets vurdering af lægemidlets værdi og den bagvedliggende protokol (bilag 4 og bilag 6).

3 Omkostninger for sundhedsvæsenet

Medicinrådet vurderer, at meromkostningerne pr. patient er ca. 2.000 kr. mindre til 4.500 kr. mere sammenlignet med standardbehandlingen over en periode på 5 år, og at budgetkonsekvenserne er ca. 600.000 i år 5. Lægemiddelvirksomhederne har dog givet en fortrolig rabat, og derfor er de reelle meromkostninger og budgetkonsekvenser anderledes.

Læs mere i den sundhedsøkonomiske afrapportering (bilag 1 og 2).

4 Alvorlighed

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

5 Anbefalingen betyder

Anbefalingen betyder, at regionerne kan bruge galcanezumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger med mindst ét antihypertensivum og ét

antiepileptik, men ikke nødvendigvis som førstevalg til alle patienter.

Medicinrådet anbefaler, at regionerne blandt galcanezumab, erenumab og fremanezumab vælger det af de tre lægemidler, der er forbundet med de laveste omkostninger.

6 Sagsbehandlingstid

Medicinrådet har brugt 10 uger og 1 dag på sit arbejde med galcanezumab til forbyggende behandling af kronisk migræne.

7 Kontaktinformation til Medicinrådet

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

8 Versionslog

Version	Dato	Ændring
1.0	23. september 2020	Godkendt af Medicinrådet.

9 Bilag

1) Medicinrådets sundhedsøkonomiske afrapportering vedr. galcanezumab, version 1.0
2) Forhandlingsnotat fra Amgros vedr. galcanezumab
3) Høringssvar fra ansøger inkl. evt. efterfølgende dialog vedr. den sundhedsøkonomiske afrapportering og lægemidlets værdi
4) Medicinrådets vurdering vedr. galcanezumab til forebyggende behandling af kronisk migræne, version 1.0
5) Ansøgers endelig ansøgning
6) Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7) Medicinrådets protokol for vurdering af galcanezumab til forebyggende behandling af kronisk migræne, version 1.0

Medicinrådet

Sundhedsøkonomisk afrapportering

Galcanezumab

Forebyggende behandling af migræne

Version 1.0

Indholdsfortegnelse

Dokumentets formål

Dette dokument indeholder en beskrivelse af den sundhedsøkonomiske analyse, som ligger til grund for ansøgningen for galcanezumab til profylaktisk behandling af migræne hos voksne, der har mindst fire migrænedage pr. måned, 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.

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 23. september 2020

Opsummering

Baggrund

Galcanezumab er induceret til profylaktisk behandling af migræne hos voksne, der har mindst fire migrænedage pr. måned. Omkring 1.200 nye patienter pr. år kandiderer årligt til behandling af den ansøgte indikation i Danmark. Sekretariatets vurdering tager udgangspunkt i dokumentation indsendt af Eli Lilly.

Analyse

Den sundhedsøkonomiske analyse estimerer de inkrementelle omkostninger pr. patient ved behandling med galcanezumab over en tidshorisont på 5 år. Galcanezumab sammenlignes med erenumab og fremanezumab som forebyggende behandling af patienter med kronisk migræne.

Inkrementelle omkostninger og budgetkonsekvenser

I det scenarie, sekretariatet mener er mest sandsynligt, er de inkrementelle omkostninger for galcanezumab ca. [redacted] DKK pr. patient sammenlignet med erenumab og ca. [redacted] DKK pr. patient sammenlignet med fremanezumab over en tidshorisont på 5 år. Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning hhv. 4.500 DKK og -2.000 DKK.

Sekretariatet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af galcanezumab som standardbehandling vil være ca. [redacted] DKK i år 5. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 600.000 DKK i år 5.

Konklusion

De inkrementelle omkostninger er udelukkende drevet af lægemiddelprisen, da analysen begrænser sig til at inkludere omkostninger til lægemidler.

Dokumentoplysninger	
Godkendelsesdato	23. september 2020
Ikrafttrædelsesdato	23. september 2020
Dokumentnummer	88717
Versionsnummer	1.0
Arbejdsgruppe	Pernille Winther Johansen, Camilla Nybo Holmberg

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
SAIP	Sygehusapotekernes indkøbspriser

1. Baggrund for den sundhedsøkonomiske analyse

Eli Lilly (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af galcanezumab og har den 14. juli 2020 indsendt en ansøgning til Medicinrådet om anbefaling af galcanezumab som mulig standardbehandling på hovedpinecentre 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).

1.1 Patientpopulation

Migræne er en udbredt lidelse, der medfører nedsat funktionsevne, tab af livskvalitet og er blandt de tre sygdomme, som er årsag til mest arbejdsfravær[1]. Lidelsen er sandsynligvis en genetisk disponeret sygdom, der vedrører både nerver og blodkar i hovedet [2,3], hvor calcitonin genrelateret protein [CGRP]-signalering menes at være en væsentlig og muligvis forårsagende faktor i sygdomsmekanismen. De egentlige årsager til migræne kendes ikke med sikkerhed.

I kliniske studier anvender man ofte en anden inddeling af migræne, nemlig "episodisk" og "kronisk" migræne. "Episodisk" migræne er defineret ved < 15 migrænedage pr.måned, og "kronisk" migræne er defineret ved hovedpine ≥ 15 dage om måneden, hvoraf mindst 8 dage er med migræne, mens resten er med anden hovedpine, f.eks. spændingshovedpine. Inddelingen skal opfattes som et kontinuerligt spektrum, hvor den enkelte patient i perioder kan gå fra episodisk til kronisk migræne og omvendt.

Fagudvalget vurderer, at antallet af patienter, der bliver behandlet for migræne på de danske hospitaler, er i omegnen af ca. 5.000-6.000 patienter årligt, men der findes ikke endelige opgørelser over det totale antal migrænepatienter, der er tilknyttet hovedpineklinikker i Danmark. Fagudvalget skønner, at flertallet af disse patienter opfylder kriterierne for forebyggende migrænebehandling.

1.1.1 Komparator

Medicinrådet har defineret erenumab og fremanezumab som komparatorer til galcanezumab, se Tabel 1.

Tabel 1: Definerede populationer og komparatorer.

Population	Komparator
Patienter, der har kronisk migræne (mindst 15 hovedpinedage pr. måned, hvoraf mindst 8 dage er med migræne) og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger.	Erenumab Fremanezumab

1.2 Problemstilling

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

Klinisk spørgsmål 1*:*

Hvad er værdien af galcanezumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika), sammenlignet med erenumab eller fremanezumab?

2. Vurdering af den sundhedsøkonomiske analyse

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

2.1 Antagelser og forudsætninger for model

Den sundhedsøkonomiske model har til formål at estimere de inkrementelle omkostninger ved forebyggende behandling af migræne. Patienternes respons på behandlingen baserer ansøger på studiet CONQUER. Dette gør sig gældende for både intervention og komparatorerne, da hele analysen bygger på en antagelse om, at lægemidlerne er klinisk ligeværdige.

2.1.1 Modelbeskrivelse

Modellen er en omkostningsminimeringsanalyse, hvor kun omkostninger til lægemidler inddrages, da dette er eneste parameter, hvor omkostningerne adskiller sig mellem intervention og komparatorer. Ansøger argumenterer for valget af denne med, at galcanezumab er klinisk ligeværdig med komparatorerne, og at galcanezumab er blevet accepteret af Medicinrådet til at blive vurderet ved 7-ugers proces.

Alle patienter, der modtager behandlingen, vil i ansøgers model blive evalueret efter tre måneder, hvor det antages, at 60 % af patienterne vil fortsætte deres behandling på baggrund af responsrater fra CONQUER-studiet. I modellen bliver patienter også evalueret i forhold til behandlingsstop efter uge 60. Derved modtager patienterne ikke nogen behandling i måned 13 og 14 efter opstart, hvilket er i overensstemmelse med Medicinrådets nationale kriterier[4]. Efter forsøg på behandlingsstop antages det, at 80 % af patienterne fortsætter behandlingen. Derved antages 48 % af startkohorten at fortsætte i behandling efter forsøg på behandlingsstop i alle 5 år.

Sekretariatets vurdering

Fagudvalget vedrørende migræne er blevet konsulteret i forhold til andelen af patienter der stopper behandling efter tre måneder og også i forhold til andelen af patienter der genoptager behandlingen efter evaluering af behandlingsstop efter 60 uger. Fagudvalget mente, at ansøgers estimat af antal patienter, der afslutter behandlingen på disse tidspunkter, er høje, i forhold til hvad der opleves i dansk klinisk praksis. Fagudvalget har yderligere estimeret, hvor stor en andel af patienterne der afslutter behandlingen efter tre måneder, hvilket er en lavere andel af patienterne, end ansøger har estimeret. Fagudvalget er ikke kommet med noget estimat for, hvor stor en andel af patienterne, der fortsætter behandlingen efter forsøg på behandlingsstop efter 60 måneder, da de danske

klinikker endnu ikke har nogen erfaringer med dette. Sekretariatets hovedanalyse vil blive baseret på fagudvalgets estimater for, hvor mange der afslutter behandlingen efter tre måneder og anvende ansøgers estimat for, hvor mange der genoptager behandlingen efter forsøg på behandlingsstop.

Sekretariatet ændrer andelen af patienter, der afslutter behandlingen med intervention og komparatorer efter tre måneder i egen hovedanalyse. Ansøgers andre modelantagelser accepteres.

2.1.2 Analyseperspektiv

Ansøgers omkostningsanalyse har et begrænset samfundsperspektiv, men inkluderer dog udelukkende lægemiddelomkostninger, idet alle andre parametre antages at være de samme som ved behandling med erenumab og fremanezumab, da alle tre lægemidler er klinisk ligeværdige. Analysen har en tidshorisont på fem år og er valgt af ansøger, da det argumenteres at være den tidshorisont, der er blevet anvendt, når lignende migrænemidler er vurderet i Medicinrådsprocessen.
Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 %.

Sekretariatets vurdering

Ansøger argumenterer for valget af en tidshorisont på fem år med, at dette tidligere er den længde, der er valgt i lignende analyser i Medicinrådsprocessen. Denne argumentation finder sekretariatet ikke er fyldestgørende nok i sig selv til at begrunde dette valg, da der altid skal foretages en konkret vurdering af tidshorisonten for alle lægemidler. Ansøger har dog suppleret med en følsomhedsanalyse, der undersøger omkostningerne over en længere tidshorisont, hvorfor tidshorisonten på de fem år accepteres.

Sekretariatet accepterer ansøgers valg af analyseperspektiv.

2.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af galcanezumab sammenlignet med erenumab og fremanezumab. De inkluderede omkostninger i ansøgers analyse er udelukkende lægemiddelomkostninger. Hospitalsomkostninger inkluderes ikke, da patienterne selv administrerer alle injektioner. Ansøger har valgt denne meget begrænsede tilgang ud fra argumentet,at galcanezumab er klinisk ligestillet med de to komparatorer, erenumab og fremanezumab. Ansøgers estimering af lægemiddelomkostninger bygger på AIP, hvilket sekretariatet har udskiftet med SAIP.

2.2.1 Lægemiddelomkostninger

De anvendte doser er i overensstemmelse med de respektive produkters produktresuméer (SPC'er), se Tabel 2. Erenumab kan både gives som en dosis på 70 mg og 140 mg. Ansøger antager, at alle patienter vil modtage 70 mg, eftersom hovedparten initierer behandlingen på denne dosis i Amgros' afrapportering for erenumab. Derudover

argumenterer ansøger med, at prisen for 70 mg og 140 mg er ens. Det vil således ikke have indflydelse på analysens resultat, hvis en del af patienterne modtager 140 mg.

Tabel 2: Anvendte lægemiddelpriser, SAIP, juni 2020.

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Galcanezumab	120 mg	1 stk.	[redacted]	Amgros
Galcanezumab (startpakning)	120 mg	2 stk.	[redacted]	Amgros
Erenumab	70 mg	1 stk.	[redacted]	Amgros
Erenumab (startpakning)	70 mg	3 stk.	[redacted]	Amgros
Fremanezumab	225 mg	1 stk.	[redacted]	Amgros
Fremanezumab (startpakning)	225 mg	3 stk.	[redacted]	Amgros

Sekretariatets vurdering

Tidligere afrapporteringer kan ikke anvendes som kilde i ansøgninger til Medicinrådet, da der i hver enkelt sag skal foretages en konkret vurdering. Dog findes ansøgers argument i forhold til kun at anvende den lave dosis af erenumab acceptabelt.

Sekretariatet accepterer ansøgers antagelser i forhold til lægemiddelomkostninger.

2.3 Følsomhedsanalyser

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

- 40 % af patienterne fortsætter efter første vurdering, og 20 % af patienterne fortsætter efter forsøg på behandlingsstop.
- 100 % af patienterne fortsætter efter første vurdering, og 100 % af patienterne fortsætter efter forsøg på behandlingsstop.
- Analysens tidshorisont sættes til 10 år.

De tre scenarier undersøges både ved sammenligning af galcanezumab og erenumab samt ved sammenligningen af galcanezumab og fremanezumab.

Sekretariatets vurdering

Som tidligere beskrevet vurderer fagudvalget, at ansøgers estimater af andelen af patienter, der stopper behandling efter tre måneder og efter 60 uger, er høj. Følsomhedsanalyser, hvor disse parametre varieres, er derfor yderst relevante, da der er stor usikkerhed forbundet med om disse estimater afspejler et reelt behandlingsforløb. Da analyse kun inkluderer lægemiddelomkostninger, er det dog ikke forventet, at have stor indflydelse på inkrementelle omkostning, men i højere grad omkostningernes størrelse.

Sekretariatet vælger at præsentere følsomhedsanalyserne, men baseret på sekretariatets hovedanalyse.

2.4 Opsummering af basisantagelser

I Tabel 3 opsummeres basisantagelserne for ansøgers hovedanalyse sammenlignet med de ændringer, som sekretariatet har lavet i egen hovedanalyse.

Tabel 3: Basisantagelser for ansøgers og sekretariatets hovedanalyse.

Basisantagelser	Ansøger	Sekretariatet
Tidshorisont	5 år	5 år
Diskonteringsrate	4 %	4 %
Inkluderede omkostninger	Lægemiddelomkostninger	Lægemiddelomkostninger
Behandlingslængder		
Intervention:	5 år	5 år
Komparator:	5 år	5 år
Behandlingsophør efter 3 måneder	40 %	7 %
Fortsat behandling efter forsøg på behandlingsstop i uge 60+0	80 % (48 % af start kohorte)	80 % (74 % af start kohorte)

3. Resultater

3.1 Resultatet af sekretariatets hovedanalyse

Sekretariatets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, men med følgende justeringer:

- Reduktion af andelen af patienter der afslutter behandling efter 3 måneder til at være 7 %.

Den inkrementelle omkostning pr. patient bliver ca. [redacted] DKK ved sammenligning med erenumab, mens den bliver ca. [redacted] DKK ved sammenligning med fremanezumab over en tidshorisont på 5 år i sekretariatets hovedanalyse. Udføres analysen med AIP, bliver den inkrementelle omkostning pr. patient hhv. ca. 4.500 DKK og ca. -2.000 DKK. De lavere inkrementelle omkostninger ved anvendelse af AIP skyldes, at der ikke anvendes rabatpriser for erenumab og fremanezumab, hvilket er tilfældet i analysen, der er baseret på SAIP.

Resultaterne fra sekretariatets hovedanalyse præsenteres i Tabel 4 og
Tabel 5.

Tabel 4: Resultatet af sekretariatets hovedanalyse ved sammenligning med erenumab, DKK, diskonterede tal.

	Galcanezumab	Erenumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 5: Resultatet af sekretariatets hovedanalyse ved sammenligning med fremanezumab, DKK, diskonterede tal.

	Galcanezumab	Fremanezumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

3.1.1 Resultatet af sekretariatets følsomhedsanalyser

Resultatet af sekretariatets følsomhedsanalyser præsenteres for erenumab i Tabel 6 og for fremanezumab i Tabel 7.

Tabel 6: Resultatet af sekretariatets følsomhedsanalyser for erenumab, DKK.

Scenarie	Inkrementelle omkostning
Hovedanalyse.	[redacted]
40 % af patienterne fortsætter efter første vurdering og 20 % af patienterne fortsætter efter forsøg på behandlingsstop.	[redacted]
100 % af patienterne fortsætter efter første vurdering og 100 % af patienterne fortsætter efter forsøg på behandlingsstop.	[redacted]
Analysens tidshorisont sættes til 10 år.	[redacted]

Tabel 7: Resultatet af sekretariatets følsomhedsanalyser for fremanezumab, DKK.

Scenarie	Inkrementelle omkostning
Hovedanalyse.	[redacted]
40 % af patienterne fortsætter efter første vurdering og 20 % af patienterne fortsætter efter forsøg på behandlingsstop.	[redacted]
100 % af patienterne fortsætter efter første vurdering og 100 % af patienterne fortsætter efter forsøg på behandlingsstop.	[redacted]
Analysens tidshorisont sættes til 10 år.	[redacted]

4. Budgetkonsekvenser

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

- Galcanezumab bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Galcanezumab bliver ikke anbefalet som standardbehandling.

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimat af patientantal og markedsandel

Ansøger har valgt at basere sit estimat af patientantal på afrapporteringen for fremanezumab, hvor det blev estimeret, at hovedpinecentrene ville have kapacitet til at behandle 600 nye patienter årligt.
Tabel 8 viser estimatet af antal nye patienter årligt i budgetkonsekvenserne.

Tabel 8: Ansøgers estimat af antal nye patienter pr. år.

Anbefales					
	År 1	År 2	År 3	År 4	År 5
Galcanezumab	246	246	246	246	246
Erenumab	354	354	354	354	354
Fremanezumab	0	0	0	0	0
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5
Galcanezumab	0	0	0	0	0
Erenumab	354	354	354	354	354
Fremanezumab	246	246	246	246	246

Ansøger antager de forskellige lægemidlers markedsandele på baggrund af danske salgstal fra maj 2020. På baggrund af dette antages erenumab at have 59 % af markedet, mens fremanezumab har de resterende 41 %. Ved en godkendelse af galcanezumab som standardbehandling antager ansøger, at galcanezumab vil overtage de 41 % af markedet fra fremanezumab.

Sekretariatets vurdering

Som det også beskrives af ansøger, er patientantallet forbundet med stor usikkerhed. Baseret på estimater fra fagudvalget ændres det årlige antal nye patienter fra 600 til 1.200 i sekretariatets budgetkonsekvensanalyse.

Fordelingen af markedet mellem de forskellige lægemidler, vil være påvirkelig af prisændringer på lægemidlerne, og hvilket lægemiddel der er angivet som førstevalg. På nuværende tidspunkt er fremanezumab førstevalg på sygehusene, hvorfor der er en forventning om, at dette lægemiddel på sigt vil udgøre en større del af markedet end erenumab. Derfor vil markedsandelen blive ændret i sekretariatets budgetkonsekvensanalyse, så fremanezumab har 80 % af markedet, hvis ikke galcanezumab bliver anbefalet som standardbehandling, se Tabel 9.

Tabel 9: Sekretariatets estimat af antal nye patienter pr. år.

Anbefales					
	År 1	År 2	År 3	År 4	År 5
Galcanezumab	120	120	120	120	120
Erenumab	120	120	120	120	120
Fremanezumab	960	960	960	960	960
Anbefales ikke					
	År 1	År 2	År 3	År 4	År 5
Galcanezumab	0	0	0	0	0
Erenumab	240	240	240	240	240
Fremanezumab	960	960	960	960	960

I ansøgers analyse indgår kun nye patienter og ikke patienter der, allerede modtager behandling for den omtalte indikation med enten erenumab eller fremanezumab. Det forventes ikke, at patienter vil skifte over på en anden behandling, selv om galcanezumab anbefales som mulig standard behandling, og derfor findes dette acceptabelt.

Sekretariatet udfører egen budgetkonsekvensanalyse, hvor antallet af nye patienter årligt vil være 1.200, og hvor fremanezumab har 80 % af markedet hvis ikke galcanezumab anbefales som standardbehandling.

4.2 Sekretariatets budgetkonsekvensanalyse

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

- Incidens af patienter, der vurderes at være kandidater til den pågældende indikation, er 1.200 personer pr. år.
- Fremanezumab har 80 % af markedet, hvis galcanezumab ikke anbefales.

Sekretariatet estimerer, at anvendelse af galcanezumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 10.

Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. 600.000 DKK i år 5.

Tabel 10: Sekretariatets analyse af totale budgetkonsekvenser, 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]

5. Diskussion

Da behandlingen med galcanezumab baseres på en antagelse om, at lægemidlet er klinisk ligestillet med begge komparatorer, er det altovervejende lægemidlernes priser, der har indflydelse på analysens resultat.

Der er stor usikkerhed forbundet med, hvor mange patienter der årligt vil være kandidater til behandling med galcanezumab, hvorfor resultatet af budgetkonsekvensanalysen er behæftet med stor usikkerhed. Da der allerede er to anbefalede produkter til samme indikation (erenumab og fremanezumab) vil de økonomiske konsekvenser for regionerne dog være begrænsede, hvis prisen på galcanezumab ikke overstiger det billigste af de tre migrænemidler.

5.1 Usikkerheder

Analysens resultat ændres, hvis andelen af patienter, der stopper behandling, ændres. Men da analysen alene baseres på lægemiddelpriser, og denne andel formentlig vil være ens for de tre ligestillede lægemidler, vil dette forhold ikke ændre på, hvilken af behandlingsalternativerne der vil være mest omkostningseffektiv.

6. Referencer

1. Flachs E, Eriksen L, Koch M, Ryd J, Dibba E, Skov-Ettrup L et al. Sygdomsbyrden i Danmark. 2015.
2. Bendtsen L, Møller Hansen J MR. Migræne og anden hovedpine - information til sundhedsfaglige - Medicin.dk [internet]. [citeret 20. august 2020]. Tilgængelig fra: https://pro.medicin.dk/sygdomme/sygdom/318362
3. Dansk Hovedpine Selskab. Referenceprogram-Diagnostik og behandling af hovedpinesygdomme og ansigtssmerter. 2010;
4. Medicinrådet. Nationale kriterier for opstart, opfølgning og seponering ved behandling med anti-CGRPantistof til forebyggende behandling af migræne. 2019;(uge 0):1–2.

7. Bilag

7.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK ved sammenligning med erenumab og [redacted] DKK ved sammenligning med fremanezumab, over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 11 og Tabel 12.

Tabel 11: Resultatet af ansøgers hovedanalyse ved sammenligning med erenumab, DKK, diskonterede tal.

	Galcanezumab	Erenumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 12: Resultatet af ansøgers hovedanalyse ved sammenligning med fremanezumab, DKK, diskonterede tal.

	Galcanezumab	Fremanezumab	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Totale omkostninger	[redacted]	[redacted]	[redacted]

7.2 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, at anvendelse af galcanezumab vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5.
Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 13.

Tabel 13: Ansøgers hovedanalyse for totale budgetkonsekvenser, 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]

Medicinrådet

Medicinrådets sekretariat
Medicinrådet Dampfærgevej 27-29, 3. th
2100 København Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	7 ugers proces
Leverandør	Eli Lilly
Lægemiddel	Galcanezumab (Emgality)
EMA-indikation	Galcanezumab er indiceret til profylaktisk behandling af migræne hos voksne, der har mindst fire migrænedage pr. måned.

Forhandlingsresultat

Amgros har opnået følgende pris på galcanezumab:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Emgality	120 mg	1 stk.	3.416,00	[redacted]	[redacted]
Emgality	120 mg	2 stk.	6.832,00	[redacted]	[redacted]

Aftalen løber som udgangspunkt indtil 31.12.2021. Hvis der publiceres en behandlingsvejledning før det, vil der laves en ny kontrakt baseret på udbuddet hertil. Medicinrådet har i november 2019 påbegyndt processen om udarbejdelsen af en ny behandlingsvejledning.

[redacted]

Vurdering af forhandlingsresultatet

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

[redacted]

Konklusion

Amgros vurderer, at prisen for galcanezumab er i niveau med de andre CGRP-antistoffer; erenumab og fremanezumab.

[redacted]

[redacted]

Relation til markedet

Markedsvilkår og konkurrence

[redacted]

Sammenligning af lægemiddelomkostninger for erenumab, fremanezumab og galcanezumab

Lægemiddel	Styrke/pakning	Antal dosis pr. år	AIP	SAIP	Første 12 måneders behandling (inkl. startbeh.)	Efterfølgende 12 måneders behandling	24 måneders behandling (inkl. startbeh.)
Aimovig (eranumab)	1 stk. 70 eller 140 mg	13	2.550	[redacted]		[redacted]	[redacted]
Aimovig startpakning	3 stk. a 70 eller 140 mg		9.340	[redacted]	[redacted]		
Ajovy (fremanezumab)	1 stk. 225 mg	12	3.550	[redacted]		[redacted]	[redacted]
Ajovy startpakning	3 stk. a 225 mg		10.650	[redacted]	[redacted]		
Emgality (galcanezumab)	1 stk. 120 mg	12	3.416	[redacted]		[redacted]	[redacted]
Emgality startpakning	2 * 2 stk. a 120 mg		13.664	[redacted]	[redacted]		

Perspektiv til andre lande

[redacted]

Jesper Skov Neergaard

Fra: Jeppe Schultz Christensen <jeppe_sc@lilly.com>
Sendt: 25. august 2020 14:05
Til: Jesper Skov Neergaard
Cc: Pernille Winther Johansen; Jane Skov
Emne: RE: Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for galcanezumab

Kategorier: GO: saved

Kære Jesper

Tak for hurtigt arbejde med vurderingen.

Vi har ikke kommentarer til kategoriseringen af værdien af Emgality.

Mvh
Jeppe Schultz Christensen
Pricing Reimbursement and Access Manager, Denmark
PhD
Eli Lilly and Company
Lyskær 3EF, 2730 Herlev, Denmark
+45 31 70 75 20 (mobile)
jeppe_sc@lilly.com
www.eli-lilly.dk

From: Jesper Skov Neergaard <JNE@medicinraadet.dk>
Sent: 25. august 2020 10:28
To: Jeppe Schultz Christensen <jeppe_sc@lilly.com>
Cc: Pernille Winther Johansen <pwj@medicinraadet.dk>; Jane Skov <JSK@medicinraadet.dk>; Jesper Skov Neergaard <JNE@medicinraadet.dk>
Subject: [EXTERNAL] Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for galcanezumab

Kære Jeppe

Sekretariatet fremsender hermed udkast til Medicinrådets vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for galcanezumab.

7-ugersprocessen forudsætter, at I kan svare på høringen i løbet af **5 arbejdsdage**. **Jeres frist for at indgive høringssvar med eventuelle bemærkninger til kategoriseringen af lægemidlets værdi og den**

sundhedsøkonomiske afrapportering er derfor den 1. september 2020. I må også gerne meddele, hvis I ikke har kommentarer til kategoriseringen. I denne periode skal I også forhandle en pris med Amgros.

Medicinrådet drøfter herefter kategorisering og endelig anbefaling i en skriftlig proces. I får besked fra sekretariatet, når Rådet er kommet frem til en afgørelse.

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

Mvh
Jesper

Jesper Skov Neergaard
Sundhedsvidenskabelig specialkonsulent og informationsspecialist
Cand.pharm, PhD
jne@medicinraadet.dk
+45 40 22 31 03

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

Medicinrådet

Medicinrådet

Medicinrådets vurdering vedrørende galcanezumab til forebyggende behandling af kronisk migræne

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 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 sammenfatter vi 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.

Godkendt af Medicinrådet 23. september 2020
Dokumentnummer 84390
Versionsnummer 1.0

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

Indhold

1 Medicinrådets konklusion

Der er ikke påvist en merværdi af galcanezumab sammenlignet med erenumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på to tidligere forebyggende behandlinger i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi. Derfor vurderer Medicinrådet, at galcanezumab er et klinisk ligestillet alternativ til erenumab og fremanezumab. Det betyder, at galcanezumab samlet set vurderes at være lige så effektivt og sikkert som erenumab og fremanezumab.

Der foreligger ikke direkte sammenlignende studier mellem galcanezumab, erenumab eller fremanezumab. Medicinrådets kategorisering har derfor taget udgangspunkt i en indirekte sammenligning mellem galcanezumab og erenumab. De indirekte analyser er forbundet med usikkerhed, som betyder at værdien af galcanezumab sammenlignet med erenumab ikke formelt kan kategoriseres i henhold til Medicinrådets metoder.

Kvaliteten af data for sammenligningen mellem galcanezumab og erenumab er lav.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

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

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

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

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

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

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

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

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

CGRP	*Caltitonin gene-related peptide* (calcitonin genralateret protein)
CI	Konfidensinterval
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*
OR	*Odds ratio*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP	*Per-protocol*
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR	Relativ risiko
SMD	*Standardized Mean Difference*

3 Introduktion

Formålet med Medicinrådets vurdering af galcanezumab til forebyggende behandling af kronisk migræne er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Eli Lilly. Vi modtog ansøgningen den 14. juli 2020.

Ansøger har tilkendegivet, at galcanezumab efter deres vurdering hverken er bedre eller dårligere end erenumab til hele den godkendte indikation og dermed kan indgå i Medicinrådets hurtigere proces på syv uger. Medicinrådet har accepteret, at galcanezumab på den baggrund kan vurderes i Medicinrådets hurtigere proces på syv uger. Ansøger påtager sig ansvaret for, at lægemidlet under processen kan kategoriseres anderledes og i så fald skal indgå i et sædvanligt procesforløb på 12 uger.

De(t) kliniske spørgsmål er:

Hvad er værdien af galcanezumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med erenumab eller fremanezumab?

3.1 Migræne

Migræne er en udbredt lidelse, der medfører nedsat funktionsevne, tab af livskvalitet og er blandt de tre sygdomme, som er årsag til mest arbejdsfravær [1]. Lidelsen er sandsynligvis en genetisk disponeret sygdom, der vedrører både nerver og blodkar i hovedet [2,3], hvor calcitonin genrelateret protein [CGRP]-signalering menes at være en væsentlig og muligvis forårsagende faktor i sygdomsmekanismen. De egentlige årsager til migræne kendes ikke med sikkerhed.

I klinisk praksis skelnes almindeligvis mellem migræne med eller uden "aura" (forbigående neurologiske forstyrrelser, f.eks. forstyrrelser af syns- eller følesans i op til 60 minutter før selve migrænehovedpinen starter) [1–3]. Migrænehovedpine kendetegnes ved anfaldsvis hovedpine typisk henover 4-72 timer (ubehandlet eller behandlet uden succes) af dunkende karakter, moderat til svær intensitet og forværring ved almindelig fysisk aktivitet. Ved anfald følger typisk kvalme, opkast og overfølsomhed overfor lys og lyd.

I kliniske studier anvender man ofte en anden inddeling af migræne, nemlig "episodisk" og "kronisk" migræne. "Episodisk" migræne er defineret ved < 15 migrænedage/måned, og "kronisk" migræne er defineret ved hovedpine ≥ 15 dage om måneden, hvoraf mindst 8 dage er med migræne, resten med anden hovedpine, f.eks. spændingshovedpine. Inddelingen skal opfattes som et kontinuerligt spektrum, hvor den enkelte patient i perioder kan gå fra episodisk til kronisk migræne og omvendt.

En migrænedag defineres som en kalenderdag med mindst fire på hinanden følgende timer med migræne eller hovedpine (uafhængig af varighed) behandlet med migrænespecifik akut anfaldsbehandling (triptaner eller ergotaminer). En hovedpinedag defineres som en kalenderdag, hvor patienten oplever migrænehovedpine eller non-migrænehovedpine med en varighed på mindst fire på hinanden følgende timer, eller en hovedpine (uafhængig af varighed), hvor patienten har behov for akut anfaldsbehandling (triptaner, ergotaminer eller anden smertestillende medicin). Dette betyder, at en migrænedag pr. definition også er en hovedpinedag, mens det modsatte ikke er tilfældet. En hovedpinedag uden karakteristiske migrænesymptomer, og som ikke kræver migrænespecifik anfaldsbehandling, er ikke en migrænedag.

Migræne er udbredt i alle aldersgrupper. Den debuterer hyppigst inden 40-årsalderen og ofte allerede i barndom eller ungdom [1,2]. Der er flere kvinder end mænd, der lider af migræne. Studier viser, at mellem 24-32 % af alle danske kvinder og mellem 5-17 % af alle danske mænd oplever migræne mindst én gang i deres liv [1]. Langt de fleste migrænepatienter bliver behandlet i primærsektoren, men ved utilfredsstillende

behandlingseffekt kan patienten blive henvist til en hovedpineklinik/-center på sygehuset. Fagudvalget vurderer, at antallet af patienter, der bliver behandlet for migræne på de danske hospitaler, er i omegnen af ca. 5.000-6.000 patienter årligt, men der findes ikke endelige opgørelser over totalt antal migrænepatienter, der er tilknyttet hovedpineklinikker i Danmark. Fagudvalget skønner, at flertallet af disse patienter opfylder kriterierne (jf. afsnit 4.1) for forebyggende migrænebehandling.

3.2 Galcanezumab

Galcanezumab er et humaniseret monoklonalt antistof, der selektivt binder til det vasodilaterende neuropeptid calcitonin genrelaterede peptid (CGRP), hvorved CGRP forhindres i at binde til CGRP-receptoren. Dette fører til en hæmning af den CGRP-inducerede karudvidelse, reduktion af den neurologisk medierede immunreaktion samt hæmning af smertesignaler. Galcanezumab administreres subkutant og indgives én gang om måneden. Initielt gives en støddosis på 240 mg og derefter 120 mg én gang om måneden.

3.3 Nuværende behandling

Medicinsk behandling af migræne inddeles i anfaldsbehandling (smertestillende og kvalmestillende) og forebyggende behandling. Forebyggende behandling tilbydes for at reducere sværhedsgrad og frekvens af hovedpineanfald til patienter, der har mindst to svære migræneanfald pr. måned med dårlig effekt af anfaldsmedicin og heraf forringet livskvalitet [3]. Forebyggende behandling er succesfuld, når patienten oplever forbedret livskvalitet samt fald i migrænens hyppighed og sværhedsgrad. Mange patienter oplever spontan forbedring over tid. Det er derfor meget individuelt, hvor lang tid en patient har brug for profylaktisk behandling, og nuværende kliniske anbefalinger angiver derfor, at medicinen forsøges afsluttet hver 6.-12. måned for at sikre, at der fortsat er behov for og effekt af medicinen [3]. Det er vigtigt at notere, at der findes en del patienter, som har såkaldt ”medicinoverforbrugshovedpine” (migræne/hovedpine pga. overforbrug af smertestillende), hvor behandlingen først og fremmest består af udtrapning af deres medicinoverforbrug og ikke yderligere tillæg af forebyggende behandling.

Mange af de lægemidler, der tilbydes som forebyggende behandling af migræne, er oprindeligt udviklet til andre formål, f.eks. antihypertensiva (blodtryksmedicin), antiepileptika (medicin mod epilepsi) og antidepressiva (medicin mod depression). Disse lægemidler har vist sig også at have effekt på forebyggelse af migræne, og visse er siden blevet godkendt til dette formål. Indenfor de seneste to år er flere nye lægemidler, de såkaldte CGRP-antistoffer, blevet godkendt til forebyggende behandling af migræne. Lægemidler, der er godkendt til forebyggende behandling af migræne i Danmark, er: metoprolol/propranolol (betablokkere), flunarizin (calciumantagonist), topiramat (antiepileptika), pizotifen (aminantagonist), clonidin (alfa2-receptor- samt imidazolinreceptoragonist) samt amitriptylin (tricyklisk antidepressivum). CGRP-antistofferne erenumab, fremanezumab og galcanezumab er alle godkendt som forebyggende behandling hos voksne der har mindst 4 migrænedage pr. måned. Derudover er botulinum type A toxin godkendt til patienter med kronisk migræne. Ikke alle lægemidler, der fremgår af de eksisterende danske behandlingsvejledninger, er blevet godkendt til forebyggelse af migræne, men bruges til formålet som ”off-label” (ikke godkendt til indikationen).

Der er ikke enighed, hverken nationalt eller internationalt, om disse lægemidlers indbyrdes placering i behandlingsalgoritmen til forebyggelse af migræne. Der er i øvrigt en meget stor individuel variation i de enkelte lægemidlers effekt og bivirkninger på den enkelte patient. Valget af, hvilket præparat en patient tilbydes, baseres således på en individuel vurdering af bl.a. patients risikoprofil, andre sygdomme og tidligere erfaring.

Der er generelt en stor enighed om, at betablokkere (metoprolol/propranolol) opfattes som førstevalgspræparater. Det er i øvrigt fagudvalgets skøn, at topiramat og de to ”off-label”-præparater

candesartancilexetil og lisinopril (pga. den relativt gunstige bivirkningsprofil) anvendes i så stor en udstrækning, at de sammen med betablokkere udgør førstevalgspræparaterne ved forebyggende behandling af migræne. Fagudvalget skønner således, at de fleste patienter, som tager forebyggende migrænebehandling, behandles med et af disse præparater.

Ved behandlingssvigt (enten i form af suboptimal effekt eller uacceptable bivirkninger) eller kontraindikationer tilbydes patienterne typisk behandling med amitriptylin/nortriptylin eller valproat – for patienter med kronisk migræne eventuelt botulinum type A toxin – som andetvalgslægemidler. I 2019 har Medicinrådet anbefalet erenumab og fremanezumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på mindst ét antiepileptikum og mindst ét antihypertensivum. De er dermed mulige behandlingsvalg til denne patientgruppe og dermed også egnede komparatorer for denne vurdering. I forbindelse med de tidligere vurderinger i Medicinrådet blev erenumab og fremanezumab vurderet at være klinisk ligestillede.

Ved behandlingssvigt eller kontraindikationer mod andetvalgslægemidlerne kan patienterne tilbydes behandling med andre lægemidler, som er mindre anvendt pga. mindre gunstig bivirkningsprofil, f.eks. lamotrigin og pizotifen.

4 Metode

Medicinrådets protokol for vurdering af galcanezumab til forebyggende behandling af migræne beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan vi vil vurdere lægemidlets værdi for patienterne.

De(t) kliniske spørgsmål er:

*Hvad er værdien af galcanezumab til patienter med **kronisk migræne**, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med erenumab eller fremanezumab?*

Population
Patienter der har kronisk migræne (mindst 15 hovedpinedage/måned hvoraf mindst 8 dage er med migræne) og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger.

Intervention
Galcanezumab 240 mg som støddosis efterfulgt af 120 mg subkutant én gang om måneden.

Komparator
Erenumab 70 mg eller 140 mg subkutant hver 4. uge.
eller
Fremanezumab 225 mg subkutant 1 gang om måneden eller 675 mg subkutant 1 gang hver tredje måned.

Medicinrådet betragter de to komparatorer som ligeværdige valg i dansk klinisk praksis, og ansøger opfordres til at vælge den komparator, som giver det bedste sammenligningsgrundlag.

Effektmål

Tabel 1. Oversigt over valgte effektmål. For alle effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskelsamt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål*	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Frekvens af migrænedage	Kritisk	Alvorlige symptomer og bivirkninger	Reduktion af månedlige migrænedage	10 %-point
	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patientpopulation, som opnår ≥ 50 % reduktion af månedlige migrænedage	5 %-point
Livskvalitet	Kritisk	Livskvalitet	Gennemsnitlig ændring fra baseline på MSQ	MSQ-RF: 5 point MSQ-FF: 5 point MSQ-EF: 8 point
Frekvens af hovedpinedage	Vigtig	Alvorlige symptomer og bivirkninger	Reduktion af månedlige hovedpinedage	10 %-point
Anfalds-sværhedsgrad	Vigtig	Alvorlige symptomer og bivirkninger	Reduktion af antal dage med anfaldsbehandling pr. måned	10 %-point
Bivirkninger	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter som oplever bivirkninger, der medfører behandlingsophør	5 %-point
			Kvalitativ gennemgang af bivirkninger	-

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Den minimale opfølgningstid til vurdering af forebyggende migrænebehandling er tre måneder, hvilket skyldes, at man i klinisk praksis normalt venter 3 måneder, inden man vurderer behandlingsresponsen hos den enkelte patient.

5 Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt seks studier, som blev vurderet egnet til besvarelse af det kliniske spørgsmål. Resultaterne fra studierne er publiceret i 17 fuldtekstartikler som angivet i tabel 2. Ansøger har vurderet, at ikke alle publikationer indeholder data, som er relevant for vurderingen. I overensstemmelse med protokollen har ansøger redegjort for deres valg af komparator, som var defineret som den af komparatorerne erenumab eller fremanezumab, der havde det bedste datagrundlag. De to komparatorer vurderes af fagudvalget som klinisk ligestillede. Ansøger har valgt at sammenligne med erenumab, da denne komparator giver det bedste sammenligningsgrundlag for patientpopulationen med kronisk migræne, som har oplevet to tidligere behandlingssvigt. Fagudvalget er enige i denne vurdering.

Tabel 2: Oversigt over de udvalgte studier. Publikationer som indeholder data, som er anvendt i vurderingen, er markeret med **fed**. Studier med fremanezumab er markeret med grå, da disse ikke indgår i vurderingen.

Lægemiddel	Studienavn og NCT-nummer	Titel
Galcanezumab	REGAIN NCT02614261	Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies[4]
		Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure[5]
		Analysis of Initial Nonresponders to Galcanezumab in Patients With Episodic or Chronic Migraine: Results From the EVOLVE-1, EVOLVE-2, and REGAIN Randomized, Double-Blind, Placebo-Controlled Studies[6]
		Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study[7]
	CONQUER NCT03559257	**Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial**[8]
Erenumab	Study 295 NCT02066415	Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial[9]
		Early onset of efficacy with erenumab in patients with episodic and chronic migraine[10]
		Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study[11]
		Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study[12]
Fremanezumab	HALO CM NCT02621931	Fremanezumab for the preventive treatment of chronic migraine[13]
		Early Onset of Efficacy With Fremanezumab for the Preventive Treatment of Chronic Migraine[14]
	Bigal 2015 NCT02021773	Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind placebo-controlled, phase 2b study[15]
		TEV-48125 for the preventive treatment of chronic migraine: Efficacy at early time points[16]
		Fremanezumab as Add-On Treatment for Patients Treated With Other Migraine Preventive Medicines[17]
		Fremanezumab for preventive treatment of migraine: Functional status on headache-free days[18]
		Sustained reductions in migraine days, moderate-to-severe headache days and days with acute medication use for HFEM and CM patients taking fremanezumab: Post-hoc analyses from phase 2 trials[19]
	FOCUS NCT03308968	Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial[20]

Populationerne i de inkluderede studier for galcanezumab og erenumab vurderes at være sammenlignelige. En undtagelse er, at der observeres en forskel i antal dage med behov for akut anfaldsmedicin mellem galcanezumab- og erenumabstudierne (tabel 3). Dette skyldes forskelle i definitionen af, hvad der betragtes som akut anfaldsmedicin snarere end en forskel mellem studiepopulationerne. Dette diskuteres i afsnittet nedenfor.

En del af patienterne i de inkluderede studier har såkaldt ”medicinoverforbrugshovedpine” (migræne/hovedpine pga. overforbrug af smertestillende lægemidler), hvor behandlingen i Danmark først og fremmest består af udtrapning af deres medicin fremfor yderligere tillæg af forebyggende behandling.

Jævnfør retningslinjerne fra International Headache Society (IHS) er det acceptabelt at inkludere disse patienter i kliniske studier, som undersøger effekten af et migræneforebyggende lægemiddel. I studie 295 og REGAIN fremgår det, at randomiseringen er stratificeret ift. medicinoverforbrug. I CONQUER fremgår der ikke information om stratificering på denne parameter, men der observeres sammenlignelige andele i de to behandlingsarme. I studie 295 har 45 % af patienterne med kronisk migræne og behandlingssvigt på to tidligere forebyggende behandlinger et overforbrug af smertestillende medicin. I REGAIN og CONQUER gælder det ca. 65 % af patienterne. Det er ikke muligt at afgøre, om denne forskel mellem studierne har betydning for sammenligningen. I erenumabstudiet, er det tidligere undersøgt, om effekten er forskellig hos patienter med og uden medicinoverforbrug [21]. Her er de observerede behandlingseffekter ens hos patienter med og uden medicinoverforbrug. Den observerede forskel mellem studierne vurderes derfor ikke at påvirke de indirekte analyser.

Relevante baselinekarakteristika er angivet i tabel 3 nedenfor.

Tabel 3: Baselinekarakteristika fra de inkluderede studier.

Studie	N	Alder (mean, SD)	Kvinder (n, %)	Månedlige migrænedage (mean, SD)	Dage med akut anfaldsmedicin pr. måned (mean, SD)	Sygdomsvarighed (mean, SD)
REGAIN						
Galcanezumab 120 mg	74	42,8 år (11,3)	68 (91,9)	20,0 dage (4,3)	16,6 dage (5,6)	22,6 år (13,3)
Placebo	177	43,9 år (11,8)	157 (88,7)	19,6 dage (4,7)	15,8 dage (6,0)	24,3 år (13,1)
CONQUER*						
Galcanezumab 120 mg	95	45,8 år (11,6)	83 (87,4)	19,2 dage (4,7)	15,0 dage (6,3)	24,2 år (13,9)
Placebo	98	44,8 år (13,1)	85 (86,7)	18,1 dage (4,7)	15,2 dage (5,9)	24,9 år (14,9)
Studie 295**						
Erenumab 70 mg	93	42,9 år (11,2)	84 (90,3)	18,0 dage (4,4)	10,5 dage (7,2)	25,2 år (13,2)
Erenumab 140 mg	92	44,2 år (10,6)	82 (89,1)	18,8 dage (4,4)	12,4 dage (6,2)	24,6 år (11,7)
Placebo	142	42,9 år (11,5)	111 (78,2)	18,3 dage (4,5)	11,4 dage (7,4)	24,0 år (12,9)

*subgruppe af patienter med kronisk migræne, **subgruppeanalyse af patienter ≥ 2 tidligere behandlingssvigt

5.1.2 Databehandling og analyse

Nedenunder beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål.

Ansøger har, i henhold til protokollen, foretaget en indirekte analyse ved brug af Buchers metode. Der er udført analyser for effektmålene: *Frekvens af migrænedage, anfaldssværhedsgrad og bivirkninger.* Der er ikke udført sammenlignende analyser for effektmålene: *Livskvalitet og frekvens af hovedpinedage*, da der ikke findes data, som muliggør dette.

Alle inkluderede studier er placebokontrolleret, dobbeltblindet, parallelgruppe RCT'er, hvad angår studiedesign, vurderes studierne at være sammenlignelige.

Definitionen af behandlingsresistens er ikke ens for Studie 295, REGAIN og CONQUER. Behandlingsresistens defineres i Studie 295 som ingen reduktion i hovedpinehyppighed, varighed eller sværhedsgrad efter behandling i mindst 6 uger ved den/de almindeligt accepterede terapeutiske dose(r). Definitionen inkluderer ikke ophør på grund af bivirkninger. I CONQUER defineres behandlingsresistens som tidligere svigt på to til fire forebyggende medicingrupper i de seneste 10 år. Det kunne være på grund af utilstrækkelig effekt og/eller tolerabilitet. I REGAIN defineres behandlingsresistens på baggrund af manglende/utilstrækkelig effekt og/eller tolerabilitet i de seneste 5 år.

Opdeling i antallet af tidligere forebyggende behandlingssvigt er også forskellige mellem studierne. I studie 295 blev antallet af forudgående forebyggende behandlingssvigt baseret på grupper af lægemidler (f.eks. topiramat, betablokkere, tricykliske antidepressiva, valproat, calciumkanalblokkere, serotonin-norepinephrin reuptakeinhibitorer, botulinumtoksin, antihypertensiva (fraset betablokkere) eller anden medicin). I REGAIN baseres opdelingen på antallet af enkelte lægemidler, hvor behandlingen er mislykkedes indenfor de seneste 5 år og er dermed ikke baseret på grupper af lægemidler. Der var ingen definition af, hvilke typer af lægemidler der kunne medregnes som en forebyggende behandling. I CONQUER blev behandlingsresistens defineret som tidligere svigt imellem to og fire grupper af forebyggende lægemidler i de sidste 10 år og svarer dermed i højere grad til opdelingen i studie 295.

Der er forskel i visse definitioner af effektmål og beregningen af effektforskelle mellem studierne. Effektmålet *anfaldssværhedsgrad*, som opgøres som antallet af dage med behov for akut anfaldsbehandling, defineres i erenumabstudiet som antal dage med behov for migrænespecifik akut anfaldsbehandling (kun triptaner eller ergotaminer), mens det i galcanezumabstudierne også inkluderer dage med behov for anden smertestillende behandling. Det betyder, at antallet af dage med behov for anfaldsbehandling er lavere for erenumab end ved galcanezumab. En ændring i forbruget af migrænespecifik anfaldsbehandling er ikke direkte forbundet med en ændring i forbruget af øvrige smertestillende behandling, idet patienter med migræne kan anvende både migrænespecifik anfaldsbehandling og øvrige smertestillende hver for sig eller samtidigt afhængigt af migræneanfaldets sværhedsgrad. Fagudvalget vurderer derfor, at tolkbarheden af effektestimaterne for anfaldssværhedsgrad fra den endelige ansøgning er yderst begrænset, da estimaterne for henholdsvis galcanezumab og erenumab udtrykker to forskellige ting.

For effektmålet *frekvens af migrænedage*, som inkluderer en opgørelse af månedlige migrænedage og 50 % responderrate, opgøres effekten i erenumabstudiet som ændringen/andel ved måned 3, mens det i galcanezumabstudierne opgøres som et gennemsnit over hele den dobbeltblindede periode fra måned 1-måned 3.

Ansøger har udført sensitivitetsanalyser for at belyse, om forskellene i opdeling på tidligere behandlingssvigt og forskellene i beregning af effektestimater påvirker den indirekte analyse. Resultaterne af disse sensitivitetsanalyser tyder ikke på, at forskellene påvirker analysens resultat og dermed kategoriseringen.

5.1.3 Evidensens kvalitet

Fagudvalget 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).

Evidensens kvalitet er **lav**, hvilket betyder, at nye studier med moderat sandsynlighed kan ændre konklusionen.

GRADE-vurderingen er udført separat for de direkte sammenligninger, der anvendes som grundlag for den indirekte sammenligning. Evidensens kvalitet for sammenligningen mellem galcanezumab og placebo er vurderet som værende moderat. Evidensens kvalitet for sammenligningen mellem erenumab og placebo er vurderet som værende lav. I denne vurdering er der bl.a. nedgraderet på domænet ”inkonsistens”, idet der kun foreligger et studie på den relevante population. For begge vurderinger er der nedgraderet på domænet ”indirekthed”, da der indgår patienter med medicinoverforbrugshovedpine i studierne. I dansk klinisk praksis vil man sikre, at disse patienter er ude af deres medicinoverforbrug, inden de kan komme i betragtning til forebyggende migrænebehandling.

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 4. Resultater for klinisk spørgsmål 1

Effektmål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Frekvens af migrænedage	Reduktion af månedlige migrænedage (MKRF: 10 %-point)	Kritisk	-4,3 %-point (-19,3; 10,6)	Kan ikke kategoriseres			Kan ikke kategoriseres
	Andel af patientpopulation, som opnår ≥ 50 % reduktion af månedlige migrænedage (MKRF: 5 %-point)	Vigtig	7,68 %-point (-13,82; 48,76)	Kan ikke kategoriseres	RR 1,20 (0,64; 2,27)	Kan ikke kategoriseres	
Livskvalitet	Gennemsnitlig ændring fra baseline på MSQ-RF (MKRF: 5 point)	Kritisk	NA*	Kan ikke kategoriseres			Kan ikke kategoriseres
	Gennemsnitlig ændring fra baseline på MSQ-FF (MKRF: 5 point)		NA*	Kan ikke kategoriseres			
	Gennemsnitlig ændring fra baseline på MSQ-EF (MKRF: 8 point)		NA*	Kan ikke kategoriseres			
Frekvens af hovedpinedage	Reduktion af månedlige Hovedpinedage (MKRF: 10 %-point)	Vigtig	NA*	Kan ikke kategoriseres			Kan ikke kategoriseres
Anfalds-sværhedsgrad	Reduktion af antal dage med anfaldsbehandling pr. måned (MKRF: 10 %-point)	Vigtig	-11,9 %-point (-35,3; 11,7)	Kan ikke kategoriseres			Kan ikke kategoriseres
Bivirkninger	Andel patienter som oplever bivirkninger, der medfører behandlingsophør (MKRF: 5 %-point)	Vigtig	2 %-point (-2; 5)	Kan ikke kategoriseres	RR 12,1 (0,13; 1103)	Kan ikke kategoriseres	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres. Fagudvalget vurderer, at galcanezumab samlet set er hverken bedre eller dårligere end erenumab, hvad angår effekt og sikkerhed.					
Kvalitet af den samlede evidens		Lav					

CI = konfidensinterval, RR = relativ risiko, Grå celle: kan ikke beregnes. *ingen sammenlignende analyse.

Frekvens af migrænedage

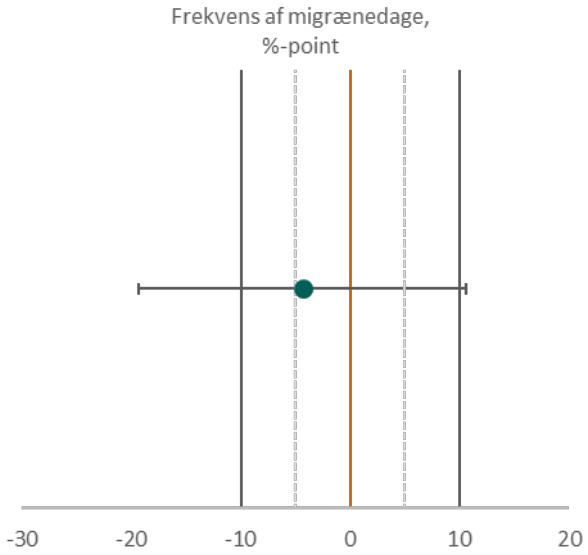
Månedlige migrænedage

Som beskrevet i protokollen er effektmålet *månedlige migrænedage* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det er et af de primære behandlingsmål med forebyggende behandling, nemlig at reducere frekvensen af migræneanfald.

Grundlaget for den indirekte sammenligning er effektestimaterne fra de placebokontrollerede studier, hvor galcanezumab, på tværs af de to inkluderede studier, gav en ændring af månedlige migrænedage på -4,03 dage [-5,28; -2,78] sammenlignet med placebo. Behandling med erenumab medførte en ændring på -3,5 dage [-2,82; -2,17]. Det indirekte effektestimat viser, at behandling med galcanezumab reducerer frekvensen af månedlige migrænedage med 0,53 dage [-1,29; 2,36] yderligere i forhold til erenumab. Dette estimat er omregnet til procentuel ændring ved hjælp af en antaget hændelsesrate for patienter behandlet med erenumab. Den antagede hændelsesrate er, på baggrund af effekten i erenumabstudiet, beregnet til 12,2 dage.

Punktestimatet for den absolutte effektforskel på -4,3 %-point (-19,3; 10,6) 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 galcanezumab vedr. *månedlige migrænedage* ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i figur 1 nedenfor.



Figur 1: Punktestimat og 95 % konfidensinterval for den absolutte forskel for reduktion af månedlige migrænedage. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Idet der er tale om et kontinuert effektmål, findes der ikke data på den relative effektforskel, og effektmålet kategoriseres derfor udelukkende på baggrund af de absolutte effektforskelle.

Andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage

Som beskrevet i protokollen er effektmålet *andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage* vigtigt for vurderingen af lægemidlets værdi for patienterne.

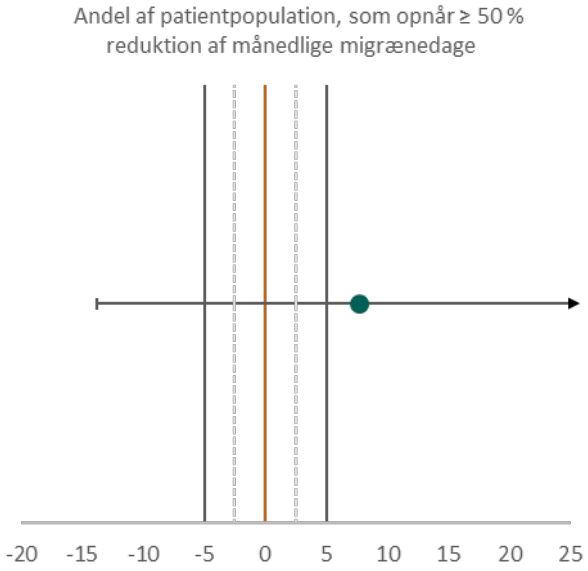
Grundlaget for beregning af det indirekte effektestimat er de placebokontrollerede studier. Galcanezumab gav, på tværs af de to inkluderede studier, en relativ øgning i 50 % responderrate på RR 3,28 [2,1; 5,19]

sammenlignet med placebo. Behandling med erenumab medførte en øgning i RR på 2,72 [1,75; 4,25]. Det indirekte effektestimat er en RR på 1,20 [0,64; 2,27] til fordel for galcanezumab.

Den absolutte effektforskel er beregnet ud fra det relative effektestimat fra den indirekte sammenligning. Den absolutte effektforskel er angivet som en procentuel forskel og er beregnet ved hjælp af en antaget hændelsesrate for erenumab. Den antagede hændelsesrate er beregnet til på baggrund af effekten fra erenumabstudiet, hvor andelen af patientpopulationen, som opnår mindst 50 % reduktion af månedlige migrænedage, er 38,4 %.

Punktestimatet for den absolutte effektforskel på 7,68 %-point (-13,82; 48,76) afspejler en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af galcanezumab vedr. *andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage* ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i figur 2 nedenfor.



Figur 2: Punktestimat og 95 % konfidensinterval for den absolutte forskel for andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Baseret på den relative effektforskel (RR 1,20 (0,64; 2,27), som fremgår af tabel 4, kan galcanezumab foreløbigt ikke kategoriseres vedr. *andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage*.

Samlet vurdering af frekvens af migrænedage

Fagudvalget vurderer, at værdien af galcanezumab på aggregeret niveau ikke kan kategoriseres. Dette skyldes hovedsageligt brede konfidensintervaller, som indeholder både positiv og negativ værdi. Hvad angår reduktionen af månedlige migrænedage og andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage vurderer fagudvalget at effekten af galcanezumab er i samme størrelsesorden som erenumab.

Livskvalitet

Som beskrevet i protokollen er effektmålet *livskvalitet* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi livskvaliteten hos kroniske migrænepatienter i høj grad påvirkes under de hyppige anfald.

Ansøger har ikke indsendt data på livskvalitet; derfor kan kategorien af galcanezumab vedr. livskvalitet ikke kategoriseres.

Frekvens af hovedpinedage

Som beskrevet i protokollen er effektmålet *frekvens af hovedpinedage* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienter med kronisk migræne ofte også er plaget af anden hovedpine foruden migræne.

Ansøger har ikke indsendt data på frekvens af hovedpinedage; derfor kan kategorien af galcanezumab vedr. frekvens af hovedpinedage ikke kategoriseres.

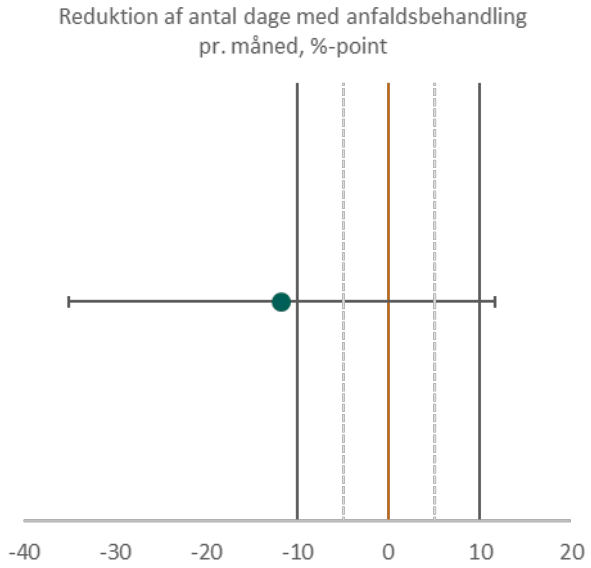
Anfaldssværhedsgrad

Som beskrevet i protokollen er effektmålet *anfaldssværhedsgrad* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi en forebyggende behandling ikke alene sigter mod at nedbringe antallet af migrænedage, men også sværhedsgraden af migræne. Forbruget af anfaldsbehandling anvendes til at måle sværhedsgraden af et migræneanfald.

Grundlaget for den indirekte sammenligning er effektestimaterne fra de placebokontrollerede studier, hvor galcanezumab, på tværs af de to inkluderede studier, gav en ændring af antallet af dage med behov for akut anfaldsbehandling på -4,23 dage [-5,43; -3,04] sammenlignet med placebo. Behandling med erenumab medførte en ændring på -3,45 dage [-4,46; -2,43]. Det indirekte effektestimat viser, at behandling med galcanezumab reducerer antallet af dage med behov for akut anfaldsbehandling med -0,79 dage [-2,35; 0,78] yderligere i forhold til erenumab. Dette estimat er omregnet til procentuel ændring ved hjælp af en antaget hændelsesrate for patienter behandlet med erenumab. Den antagede hændelsesrate er, på baggrund af effekten i erenumabstudiet, beregnet til 6,7 dage.

Punktestimatet for den absolutte effektforskel på -11,9 %-point (-35,3; 11,7) afspejler 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 galcanezumab vedr. anfaldssværhedsgrad ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i figur 3 nedenfor.



Figur 3: Punktestimat og 95 % konfidensinterval for den absolutte forskel for reduktion af antal dage med anfaldsbehandling. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Idet der er tale om et kontinuert effektmål, findes der ikke data på den relative effektforskel, og effektmålet kategoriseres derfor udelukkende på baggrund af de absolutte effektforskelle.

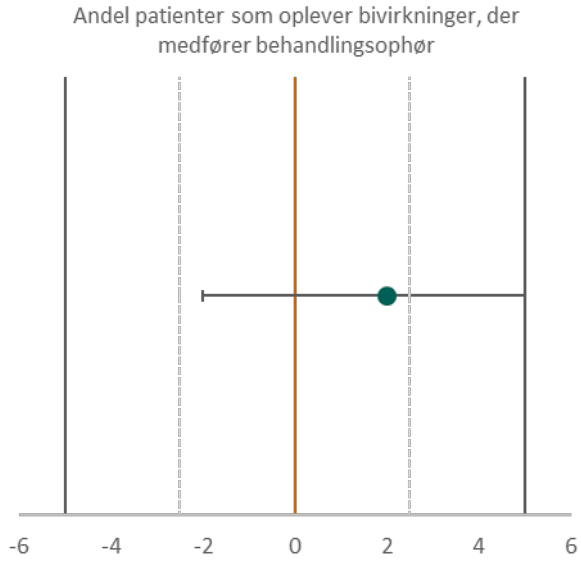
Fagudvalget vurderer, at værdien af galcanezumab på aggregeret niveau ikke kan kategoriseres. Dette skyldes den usikkerhed, der er forbundet med den indirekte sammenligning. Samtidig er der for dette effektmål en forskel mellem studierne på galcanezumab og erenumab, som gør tolkbarheden af analysen yderst begrænset. På trods af usikkerheden tyder det på, at effekten af galcanezumab og erenumab er i samme størrelsesorden.

Bivirkninger

Som beskrevet i protokollen er effektmålet *bivirkninger* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi den traditionelle forebyggende behandling af migræne ofte afbrydes på grund af bivirkninger.

Punktestimatet for den absolutte effektforskel på 2 %-point (-2; 5) 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 galcanezumab vedr. andel patienter, som oplever bivirkninger, der medfører behandlingsophør, ikke kategoriseres efter Medicinrådets metoder.

Den absolutte forskel er afbildet i figur 4 nedenfor.



Figur 4: Punktestimat og 95 % konfidensinterval for den absolutte forskel for andel patienter som oplever bivirkninger, der medfører behandlingsophør. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af den mindste klinisk relevante forskel.

Baseret på den relative effektforskel (RR 12,1 (0,13; 1103)), som også fremgår af tabel 4, har kan galcanezumab foreløbigt ikke kategoriseres vedr. bivirkninger. Dette skyldes, at de meget få hændelser og den deraf afledte store usikkerhed.

Kvalitativ gennemgang af bivirkningsprofil
Begge behandlinger er generelt forbundet med få bivirkninger. Bivirkningsprofilerne er sammenlignelige. For begge behandlinger er den hyppigst rapporterede bivirkning reaktioner på injektionsstedet. Andre hyppige bivirkninger inkluderer forstoppelse og kløe. For erenumab er en anden hyppig bivirkning muskelkramper, mens svimmelhed er angivet som en hyppig bivirkning ved galcanezumab.

De fleste reaktioner var lette eller moderate i sværhedsgrad for både erenumab og galcanezumab.

Incidensen af anti-drug-antistoffer i de dobbeltblindede behandlingsfaser er også sammenlignelige. For galcanezumab var incidensen 4,8 %, mens den er mellem 2,6 % og 6,3 % for erenumab. For begge behandlinger havde udvikling af anti-drug-antistoffer ingen indvirkning på hverken effekt eller sikkerhed.

Samlet vurdering af bivirkninger
Fagudvalget vurderer, at galcanezumab aggregeret ikke kan kategoriseres vedr. bivirkninger. Analysen for behandlingsophør er forbundet med usikkerhed, som særligt er knyttet til det relative effektestimat. De to behandlinger har sammenlignelige bivirkningsprofiler, og der observeres få hændelser for begge behandlinger. Der er dermed ikke noget, der indikerer, at der skulle være forskel mellem galcanezumab of erenumab.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at den samlede værdi af galcanezumab sammenlignet med erenumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på to tidligere forebyggende behandlinger, ikke kan kategoriseres i henhold til Medicinrådets metoder.

For det kritiske effektmål *livskvalitet* og det vigtige effektmål *frekvens af hovedpinedage* foreligger der ikke data til at foretage en sammenlignende analyse. For de øvrige effektmål *frekvens af migrænedage, anfaldssværhedsgrad* og *bivirkninger* er de indirekte analyser forbundet med betydelig usikkerhed, som er medvirkende til, at galcanezumab ikke kan kategoriseres i henhold til Medicinrådets metoder. Data for disse effektmål tyder ikke på, at galcanezumab er afgørende bedre eller dårligere end erenumab.

På baggrund af virkningsmekanisme, effekt og sikkerhed vurderer fagudvalget derfor at galcanezumab er et ligestillet behandlingsalternativ sammenlignet med erenumab.

6 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning. Fagudvalget vurderer, at galcanezumab er et klinisk ligestillet alternativ til erenumab og fremanezumab.

7 Referencer

1. Flachs E, Eriksen L, Koch M, Ryd J, Dibba E, Skov-Ettrup L, et al. Sygdomsbyrden i Danmark. København; 2015 dec.
2. Bendtsen L, Møller Hansen J, Maargaard R. Migræne [internet]. Pro.medicin. 2018 [citeret 16. august 2018]. Tilgængelig fra: https://pro.medicin.dk/Sygdomme/Sygdom/318362
3. Dansk Hovedpine Selskab. Diagnostik og behandling af hovedpinesygdomme og ansigtssmerter. 2010.
4. Bangs ME, Kudrow D, Wang S, Oakes TM, Terwindt GM, Magis D, et al. Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies. BMC Neurol. 2020;20(1):25.
5. Ruff DD, Ford JH, Tockhorn-Heidenreich A, Sexson M, Govindan S, Pearlman EM, et al. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure. Cephalalgia. 2019;39(8):931–44.
6. Nichols R, Doty E, Sacco S, Ruff D, Pearlman E, Aurora SK. Analysis of Initial Nonresponders to Galcanezumab in Patients With Episodic or Chronic Migraine: Results From the EVOLVE-1, EVOLVE-2, and REGAIN Randomized, Double-Blind, Placebo-Controlled Studies. Headache. 2019;59(2):192–204.
7. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology. 2018;91(24):e2211–21.
8. Mulleners WM, Kim B-K, Láinez MJA, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol. 2020;19(10):814–25.
9. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425–34.
10. Schwedt T, Reuter U, Tepper S, Ashina M, Kudrow D, Broessner G, et al. Early onset of efficacy with erenumab in patients with episodic and chronic migraine. J Headache Pain. 2018;19(1):92.
11. Ashina M, Tepper S, Brandes JL, Reuter U, Boudreau G, Dolezil D, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia. 2018;38(10):1611–21.
12. Lipton RB, Tepper SJ, Reuter U, Silberstein S, Stewart WF, Nilsen J, et al. Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study. Neurology. 2019;92(19):e2250–60.
13. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017;377(22):2113–22.
14. Winner PK, Spierings ELH, Yeung PP, Aycardi E, Blankenbiller T, Grozinski-Wolff M, et al. Early Onset of Efficacy With Fremanezumab for the Preventive Treatment of Chronic Migraine. Headache. 2019;59(10):1743–52.
15. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings ELH, Diener H-C, et al. Safety,

tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015;14(11):1091–100.

16. Bigal ME, Dodick DW, Krymchantowski A V, VanderPluym JH, Tepper SJ, Aycardi E, et al. TEV-48125 for the preventive treatment of chronic migraine: Efficacy at early time points. Neurology. 2016;87(1):41–8.

17. Cohen JM, Dodick DW, Yang R, Newman LC, Li T, Aycardi E, et al. Fremanezumab as Add-On Treatment for Patients Treated With Other Migraine Preventive Medicines. Headache. 2017;57(9):1375–84.

18. VanderPluym J, Dodick DW, Lipton RB, Ma Y, Loupe PS, Bigal ME. Fremanezumab for preventive treatment of migraine: Functional status on headache-free days. Neurology. 2018;91(12):e1152–65.

19. Halker Singh RB, Aycardi E, Bigal ME, Loupe PS, McDonald M, Dodick DW. Sustained reductions in migraine days, moderate-to-severe headache days and days with acute medication use for HFEM and CM patients taking fremanezumab: Post-hoc analyses from phase 2 trials. Cephalalgia. 2019;39(1):52–60.

20. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet (London, England). 2019;394(10203):1030–40.

21. Tepper SJ, Diener H-C, Ashina M, Brandes JL, Friedman DI, Reuter U, et al. Erenumab in chronic migraine with medication overuse. Neurology. 2019;92(20):e2309–20.

8 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

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

Formand	**Indstillet af**
Thue Hjortkær Nielsen Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Medlemmer	**Udpeget af**
Udpegning i gang	Region Nordjylland
Kan ikke opfylde Medicinrådets habilitetskrav	Region Midtjylland
Unni Jeppesen Praktiserende speciallæge	Region Syddanmark
Benedikte Wancsher Overlæge	Region Sjælland
Gine Stobberup Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Jon Andersen Overlæge	Dansk Selskab for Klinisk Farmakologi
Anne Bülow-Olsen Patient/patientrepræsentant	Danske Patienter
Christian Hansen Patient/patientrepræsentant	Danske Patienter
Flemming Winther Bach Professor, overlæge	Inviteret af formanden
Dagmar Beier Overlæge	Inviteret af formanden

Medicinrådets sekretariat

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

9 Versionslog

Version	Dato	Ændring
1.0	23. september 2020	Godkendt af Medicinrådet.

10 Bilag 1: Evidensens kvalitet

10.1 Cochrane, Risk of Bias

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

	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**
Studie 295	Lav	Lav	Lav	Lav	Forbehold	Lav
REGAIN	Lav	Lav	Lav	Lav	Lav	Lav
CONQUER	Lav	Lav	Lav	Lav	Lav	Lav

10.2 GRADE-profil

10.2.1 Galcanezumab vs. placebo

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Galcanezumab**	**Placebo**	**Relativ [95 % CI]**	**Absolut 95 % CI]**		
Frekvens af migrænedage, reduktion af månedlige migrænedage												
2	Randomiseret forsøg	Ikke alvorlig	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ingen	165	270	-	- 4,03 dage [-5,28; -2,78]	⊕⊕⊕◯ MODERAT	KRITISK
Frekvens af migrænedage, Andel af patientpopulation, som opnår ≥ 50 % reduktion af månedlige migrænedage												
2	Randomiseret forsøg	Ikke alvorlig	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ingen	51/165 (30,9 %)	25/270 (9,3 %)	RR: 3,28 [2,10; 5,14]	-	⊕⊕⊕◯ MODERAT	VIGTIGT
Livskvalitet, Gennemsnitlig ændring fra baseline på MSQ												
2	Randomiseret forsøg	Ikke alvorlig	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ingen	165	270	-	11,8 point [6,6; 17,0]	⊕⊕⊕◯ MODERAT	KRITISK
Frekvens af hovedpinedage, reduktion af månedlige hovedpinedage												
0												VIGTIGT
Anfaldssværdhedsgrad, reduktion af antal dage med anfaldsbehandling pr. måned												
2	Randomiseret forsøg	Ikke alvorlig	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ingen	165	270	-	- 4,23 dage [-5,43; -3,04]	⊕⊕⊕◯ MODERAT	VIGTIGT
Bivirkninger, Andel patienter som oplever bivirkninger, der medfører behandlingsophør												
1	Randomiseret forsøg	Ikke alvorlig	Alvorlig[b]	Ikke alvorlig	Ikke alvorlig	Ingen	1/95 (1 %)	0/98 (0)	RR: 3,09 [0,13; 75,0]	-	⊕⊕⊕◯ MODERAT	VIGTIGT

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio.
a. Patienter med medicinoverforbrug er inkluderet i studiet.
b. Der nedgraderes ét niveau for inkonsistens, da der kun foreligger data fra et studie.

10.2.2 Erenumab vs. placebo

Kvalitetsvurdering							Antal patienter		Effekt		Kvalitet (GRADE)	Kritisk / vigtigt
Antal studier	**Studiedesign**	**Risk of bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Erenumab**	**Placebo**	**Relativ [95 % CI]**	**Absolut 95 % CI]**		
Frekvens af migrænedage, reduktion af månedlige migrænedage												
1	Randomiseret forsøg	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	185	142	-	- 3,5 dage [-4,82; -2,17]	⊕⊕◯◯ LAV	KRITISK
Frekvens af migrænedage, Andel af patientpopulation, som opnår ≥ 50 % reduktion af månedlige migrænedage												
1	Randomiseret forsøg	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	71/185 (38,4 %)	20/142 (14,1 %)	RR: 2,72 [1,75; 4,25]	-	⊕⊕◯◯ LAV	VIGTIGT
Livskvalitet, Gennemsnitlig ændring fra baseline på MSQ												
0												KRITISK
Frekvens af hovedpinedage, reduktion af månedlige hovedpinedage												
0												VIGTIGT
Anfaldssværdhedsgrad, reduktion af antal dage med anfaldsbehandling pr. måned												
1	Randomiseret forsøg	Ikke alvorlig	Alvorlig[a]	Alvorlig[b]	Ikke alvorlig	Ingen	185	142	-	- 3,45 dage [-4,46; -2,43]	⊕⊕◯◯ LAV	VIGTIGT
Bivirkninger, Andel patienter som oplever bivirkninger, der medfører behandlingsophør												
1	Randomiseret forsøg	Ikke alvorlig	Alvorlig[a]	Ikke alvorlig	Ikke alvorlig	Ingen	0/184 (0)	1/141 (0,7 %)	RR: 2,02 [0,86; 4,75]	-	⊕⊕⊕◯ MODERAT	VIGTIGT

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio.
a. Der nedgraderes ét niveau for inkonsistens, da der kun foreligger data fra et studie.
b. Patienter med medicinoverforbrug er inkluderet i studiet.

Medicinrådet

Application for the assessment of Emgality (galcanezumab) for patients with chronic migraine previously treated with two preventive treatments (antihypertensives or antiepileptics)

Contents

1 Basic information

TABLE 1.1 CONTACT INFORMATION

Name	Jeppe S. Christensen
Title	Pricing, reimbursement and access manager
Area of responsibility	Pricing, reimbursement and access
Phone	+45 31707520
E-mail	Jeppe_sc@lilly.com
Name	Kasper Dacke
Title	Pricing, reimbursement and access manager
Area of responsibility	Pricing, reimbursement and access
Phone	+45 45 26 60 00
E-mail	Dacke_kasper@lilly.com

TABLE 1.2 OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Emgality™
Generic name	Galcanezumab
Marketing authorization holder in Denmark	Eli Lilly Denmark A/S
ATC code	N02CD02
Pharmacotherapeutic group	Analgesics, calcitonin gene-related peptide (CGRP) antagonists
Active substance(s)	Galcanezumab
Pharmaceutical form(s)	Solution for injection (injection).
Mechanism of action	Galcanezumab is a humanised IgG4 monoclonal antibody that binds CGRP thus preventing its biological activity without blocking the CGRP receptor. Elevated blood concentrations of CGRP have been associated with migraine attacks. Galcanezumab binds to CGRP with high affinity (KD = 31 pM) and high specificity (>10,000-fold vs related peptides adrenomedullin, amylin, calcitonin, and intermedin).
Dosage regimen	The recommended dose of Emgality™ (galcanezumab) is 120 mg injected subcutaneously (SC) once monthly, with a 240-mg loading dose as the initial dose.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Emgality™ (galcanezumab) is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	NA

Packaging – types, sizes/number of units, and concentrations	120 mg solution for injection in prefilled pen (PFP).
Orphan drug designation	NA

2 Abbreviations

CGRP	Calcitonin gene-related peptide
CM	Chronic migraine
TEAE	Treatment-emergent adverse event
SLR	Systematic literature review
ITC	Indirect treatment comparison
RCT	Randomised controlled trial
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EM	Episodic migraine
SD	Standard deviation
NA	Not available
CFB	Change from baseline
NR	Not reported
MSQ	Migraine-Specific Quality-of-Life Questionnaire
ITT	Intention-to-treat
ADA	Anti-drug antibodies
SAE	Serious adverse event
RR	Relative risk
RD	Risk difference
DMC	Danish Medicine Council
ACR	Assumed comparator risk
CI	Confidence interval
TEAE	Treatment-emergent adverse event
ADA	Anti-drug-antibodies

3 Summary

Galcanezumab is a humanised monoclonal antibody that potently and selectively binds to and inhibits calcitonin gene-related peptide (CGRP), a vasodilatory neuropeptide in the trigeminal system that is fundamental in the pathophysiology of migraine. Targeting the biology of migraine through inhibition of CGRP suggests that galcanezumab could improve the preventive management of migraine.

The pivotal phase III trial (REGAIN) has shown that galcanezumab is associated with clear, consistent, and clinically meaningful improvements across multiple efficacy and functioning domains in patients with chronic migraine (CM). In addition, a post hoc analysis demonstrated that galcanezumab reduced the burden of migraine and lessened day-to-day functional impairment in treatment-resistant patients with CM who had previously failed ≥2 current migraine preventive medications for efficacy or tolerability reasons (contraindication was not considered) . Given the positive results of this post hoc analysis of the phase III registration trial, a dedicated study was initiated specific to the subpopulation with treatment-resistant migraine (failed two to four migraine preventive medication categories). Findings from CONQUER support and extend the results from the pivotal phase III trial demonstrating that galcanezumab was associated with clinically meaningful improvements in several relevant outcomes in patients with episodic migraine (EM) or CM and prior failure with ≥2 preventive medications.

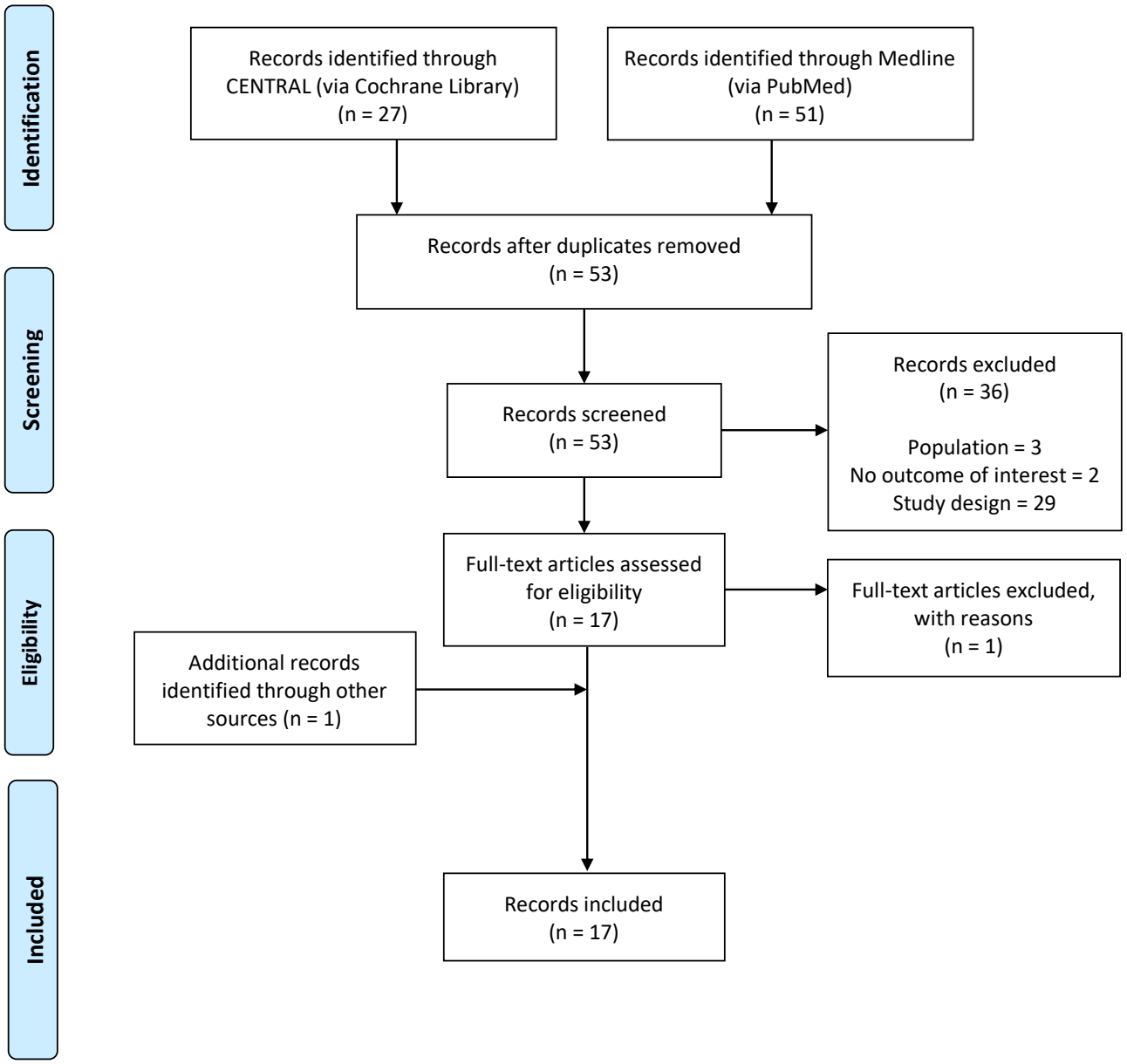
The favourable safety/tolerability profile of galcanezumab was also demonstrated in these phase III clinical trials. In general, treatment-emergent adverse events (TEAEs) were transient in nature and resolved fully, and discontinuation rates were low across all studies providing support for the tolerability of galcanezumab in patients with CM. The safety of galcanezumab has also been demonstrated in studies of up to 1 year in duration. No new safety signals were observed in the 3-month double-blind treatment phase of CONQUER indicating that galcanezumab is also well tolerated in patients with migraine and prior failure with preventive medications.

No head-to-head comparisons of the efficacy and safety of galcanezumab 120 mg compared to erenumab 70 mg or 140 mg was identified by the systematic literature review (SLR). Following a feasibility assessment on the comparability of studies for galcanezumab and erenumab, an indirect treatment comparison (ITC) was conducted on the available outcomes of interest to synthesize evidence identified. All studies included in the ITC were parallel-arm, placebo-controlled phase II or III randomized controlled trials (RCTs).

Generally, heterogeneity was low in any of the base case meta-analyses conducted for galcanezumab. Overall, across the analyses, no consistent statistically significant differences were observed between galcanezumab 120 mg and erenumab (70 + 140 mg) for all the outcomes that were assessed in the protocol. Thus, the efficacy and safety profile were found to be broadly similar. However, the limitations of these analyses must be taken into consideration in the interpretation of these results.

4 Literature search

A systematic literature review was conducted on April 24th, 2020 in the databases CENTRAL (via Cochrane Library) and Medline (via PubMed) based on the search strategy defined in the protocol. The search identified 78 publications (Medline=51 and CENTRAL=27), of which 25 were duplicates and removed. 53 publications were assessed on title and abstract level independently by two assessors and 17 publications were found eligible for full-text assessment. A total of 17 publications covering 7 clinical trials were deemed relevant in answering the clinical question. A list of references excluded after full-text screening are provided in appendix 8.1. In addition, the scientific discussion of the respective products EMA EPARs were consulted.



4.1 Relevant studies

Overall 17 publications, covering 6 individual RCTs, were identified based on the selection criteria. Out of these 6 trials, four were conducted specifically in a chronic migraine population, and three in a mixed episodic and chronic migraine population. Out of those 6 RCTs, erenumab was investigated in one trial in a chronic migraine population (subgroup, NCT02066415). Two trials REGAIN (NCT02614261) and CONQUER (NCT03559257) were identified for galcanezumab. REGAIN was performed in a population with chronic migraine. The included study results are based on a subgroup analysis of REGAIN (Ruff et al., 2019a). CONQUER was a randomized controlled trial investigating galcanezumab in episodic and chronic migraine with a history of failure to 2- 4 migraine preventive medication categories (Mulleners *et al.* 2019). Three

trials (HALO CM (NCT02621931), FOCUS (NCT03308968) and Bigal *et al.* 2015 (NCT02021773) were identified for fremanezumab. HALO CM and Bigal *et al.* 2015 was performed in a population with chronic migraine, and FOCUS was performed in a mixed episodic and chronic migraine population.

TABLE 4.1 RELEVANT STUDIES INCLUDED IN THE ASSESSMENT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies, Bangs, BMC Neurol., 2020[1]	REGAIN	NCT02614261	Start: November 30, 2015 End: March 16, 2017 (Due to an addendum in one country the completion data on clinicaltrials.gov states May 2021)
Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure, Ruff, Cephalalgia, 2019[2]			
Analysis of Initial Nonresponders to Galcanezumab in Patients With Episodic or Chronic Migraine: Results From the EVOLVE-1, EVOLVE-2, and REGAIN Randomized, Double-Blind, Placebo-Controlled Studies, Nichols R, Headache, 2019[3]			
Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study, Detke, Neurology, 2018[4]			
A Randomized, Placebo-Controlled Study of Galcanezumab in Patients with Treatment-Resistant Migraine: Double-Blind Results from the CONQUER Study (162), Mulleners, Neurology, 2020[5]	CONQUER	NCT03559257	Start: July 31, 2018 End: September 19, 2019
Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial, Tepper, Lancet Neurol., 2017[6]	Study 295	NCT02066415	Start: March 5, 2014 End: April 28, 2016
Early onset of efficacy with erenumab in patients with episodic and chronic migraine, Schwedt, J Headache Pain, 2018[7]			
Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study, Ashina, Cephalalgia, 2018[8]			
Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study, Lipton, Neurology, 2019[9]			
Fremanezumab for the preventive treatment of chronic migraine. Silberstein et al., NEJM, 2017.[10]	HALO CM	NCT02621931	Start: March 22, 2016 End: April 11, 2017
Early Onset of Efficacy With Fremanezumab for the Preventive Treatment of Chronic Migraine, Winner, Headache, 2019.[11]			
Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind,	Bigal 2015	NCT02021773	Start: January 2014 End: March 2015

placebo-controlled, phase 2b study, Bigal, Lancet Neurol., 2015[12]			
TEV-48125 for the preventive treatment of chronic migraine: Efficacy at early time points, Bigal, Neurology, 2016[13]			
Fremanezumab as Add-On Treatment for Patients Treated With Other Migraine Preventive Medicines, Cohen, Headache, 2017[14]			
Fremanezumab for preventive treatment of migraine: Functional status on headache-free days, VanderPluym, Neurology, 2018[15]			
Sustained reductions in migraine days, moderate-to-severe headache days and days with acute medication use for HFEM and CM patients taking fremanezumab: Post-hoc analyses from phase 2 trials, Halker Singh, Cephalalgia, 2019[16]			
Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial, Ferrari *et al.*, Lancet, 2019[17]	FOCUS	NCT03308968	Start: October 13, 2017 End: October 2, 2018

4.2 Main characteristics of included studies

The main characteristics of the included studies are presented in the following section and in appendix Study characteristics. As requested by the clinical expert committee in the protocol Eli Lilly have only carried out analyses and comparisons versus one of the comparators defined in the protocol. In the following analyses and comparisons erenumab have been used as comparator, as the published data available for erenumab provides the most comprehensive evidence base for the patient population of interest whereas the published data for fremanezumab on the relevant endpoints are presented in a way that makes it unfeasible to use in an ITC. For transparency study characteristics for the fremanezumab studies have been provided in Appendix 8.2.

5 Clinical questions

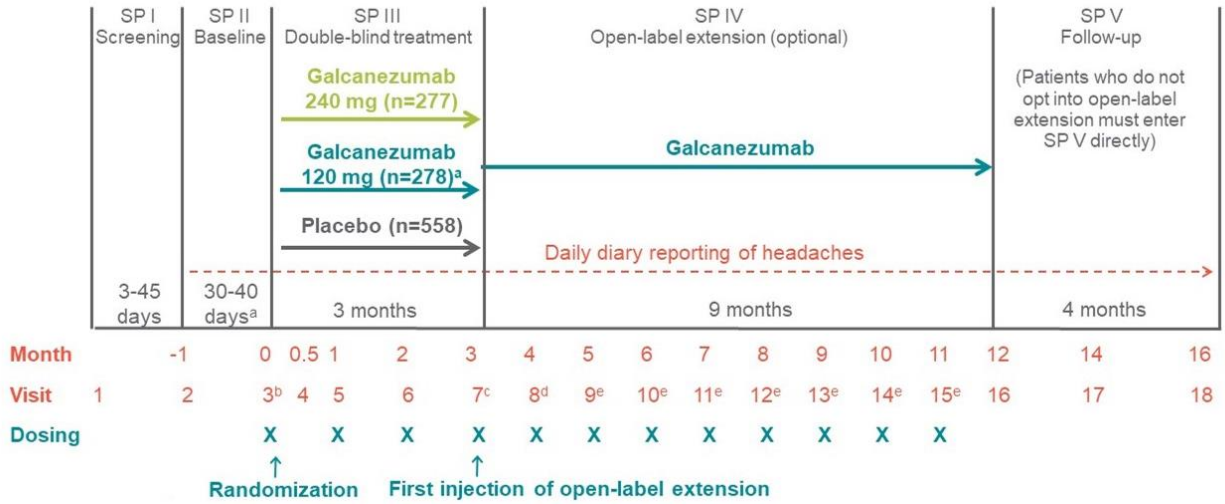
5.1 What is the clinical value of galcanezumab for patients with chronic migraine previously treated with two preventive treatments (antihypertensives or antiepileptics) compared to erenumab or fremanezumab?

5.1.1 Presentation of relevant studies

REGAIN

REGAIN (NCT02614261) was a Phase 3, multicenter, randomized, double-blind, placebo-controlled pivotal study of galcanezumab in patients suffering from chronic migraine. Chronic migraine was defined using the ICHD-3 beta guidelines[18]. Patients diagnosed with chronic migraine had a headache (≥30 minutes duration) occurring on 15 or more days per month for more than 3 months, which had the features of migraine headache on at least 8 days per month. Each month was defined as a 30-day period with migraine or headache measures normalized to a 30-day period from the actual visit intervals. In the 3-month, double-blind treatment phase, patients meeting all eligibility requirements were randomized to 1 of 3 treatment groups in a 2:1:1 ratio to receive placebo, 120 mg/month galcanezumab, or 240 mg/month galcanezumab, respectively. Patients randomized to the 120-mg dose received a loading dose of 240 mg (2 injections of 120 mg each) at visit 3 only. The primary endpoint was overall mean change from baseline in the number of monthly migraine headache days (Detke *et al*. 2018[4]). It should be noted that REGAIN excluded patients who had been unsuccessfully treated to three or more classes of migraine preventive treatments. However, as patients were allowed to have switched to other treatments within the same class, REGAIN included patients who had previously failed to three or more migraine preventive treatments. A subgroup analysis was performed on REGAIN patients with history of prior treatment failures, including patients who were unsuccessfully treated with at least 3 prior preventive migraine treatments defined as lack of efficacy and/or safety/tolerability reasons (Ruff *et al*. 2019[2]). The patients were analysed in groups of ≥1, ≥2, and ≥3 prior preventive treatment failures. The mean age ranged from 41.1 years to 45.7 years. Other baseline characteristics were comparable.

FIGURE 1 STUDY DESIGN OF REGAIN

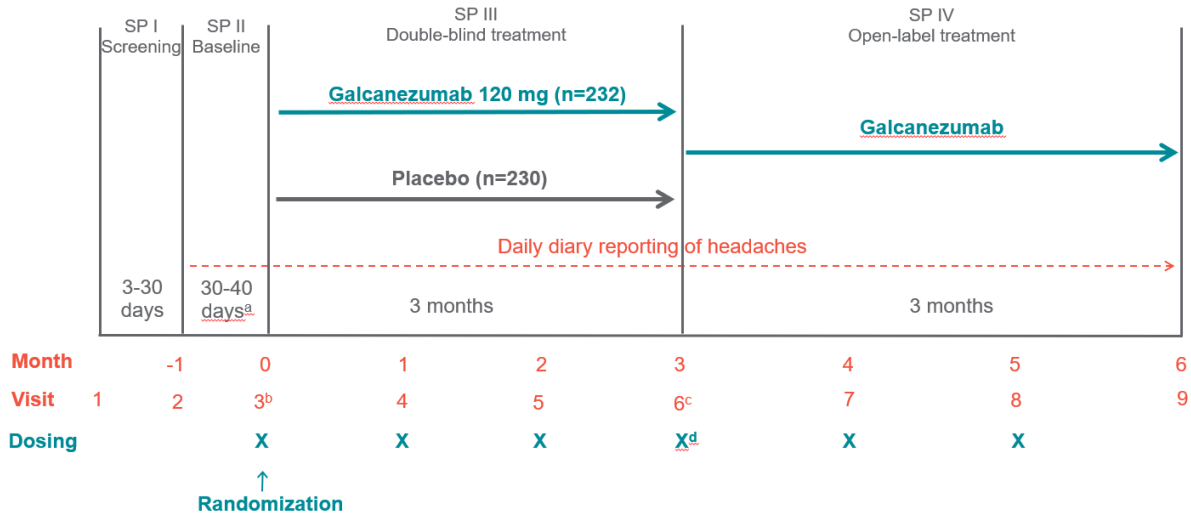


[a] Eligibility period determined between a minimum of 30 days and maximum of 40 days.
[b] Patients randomised to the 120-mg dose received a loading dose of 240 mg at the first injection only (V3).
[c] At V7, all patients entering the open-label extension received 240-mg dose.
[d] At V8, all patients received 120-mg dose.
[e] Starting at V9, dosing was flexible (120 or 240 mg) at the discretion of the investigator.
SP, study period.

CONQUER

The purpose of the CONQUER study was to assess the efficacy and safety of galcanezumab in patients with EM or CM who met study criteria for treatment resistance. Treatment resistance was defined as previous failure to between two and four standard-of-care migraine preventive medication categories in the past 10 years either due to inadequate efficacy and/or safety/tolerability reasons.

CONQUER (NCT02614261) was a Phase 3b, multicenter, randomized, double-blind, placebo-controlled study of galcanezumab in migraine patients with or without aura or chronic migraine with a history of unsuccessful treatment to 2 to 4 standard-of-care migraine preventive medication categories in the past 10 years. Treatment failure was defined as inadequate efficacy (that is, maximum tolerated dose for at least 2 months) and/or safety/tolerability reasons (Mulleners *et al*. 2019[5]). Chronic migraine was defined as having at least 8 migraine headache days and at least 15 headache days per 30-day period in the prospective baseline period. In addition, all patients had to have at least 4 migraine headache days and 1 headache-free day per 30-day period in the prospective baseline period. In the 3-month double-blind treatment phase, patients who met all eligibility requirements were randomized to 1 of 2 treatment groups in a 1:1 ratio to receive galcanezumab 120 mg/month or placebo. Patients randomized to the galcanezumab treatment group received a loading dose of 240 mg, administered as 2 injections of 120 mg each at visit 3 only. To ensure an appropriate balance of patients with episodic and chronic migraine, enrollment of patients with chronic migraine was stopped when the number of patients exceeded approximately 40%.



[a] Eligibility period determined between 30 to 40 days, with up to 5 additional days to schedule randomisation visit, if necessary.
[b] Patients randomised to galcanezumab will receive a loading dose of 240 mg at the first injection only (Visit 3).
c Patients randomised to placebo who enter SP IV will receive a loading dose of galcanezumab 240 mg at the first injection only of SP IV (Visit 6).
[d] First injection of the open-label treatment period will occur at Visit 6 once all study procedures for the double-blind period are completed.

SP, study period

Study 295

Study 295 (NCT02066415) was a Phase 2, multicenter, randomized, 3-month double-blind, placebo-controlled study of erenumab was conducted in patients suffering from chronic migraine. Patients diagnosed with chronic migraine had a headache occurring on 15 or more days per month for more than 3 months, which had the features of migraine headache on at least 8 days per month. In the 3-month, double-blind treatment phase, patients meeting all eligibility requirements were randomized to 1 of 3 treatment groups in a 3:2:2 ratio to receive placebo, erenumab 70 mg, or erenumab 140 mg once every 4 weeks, respectively. The primary endpoint was overall mean change from baseline in the number of monthly migraine headache days from baseline to the last 4 weeks of the double-blind treatment period. It should be noted that the study excluded patients who had been unsuccessfully treated with more than three preventive migraine categories (Tepper *et al.* 2018[6]). A subgroup analysis was performed in patients with a history of prior preventive treatment failures, (Ashina *et al.* 2018[8]), which form the basis for the erenumab data in this analysis.

Summary of studies included in the assessment of the clinical question

TABLE 5.1 SUMMARY OF THE INCLUDED STUDIES DESIGN

	REGAIN	CONQUER	Study 295
Study design	Phase 3 double-blind RCT	Phase 3 double-blind RCT	Phase 2 double-blind RCT
Total study population	Galcanezumab 120 mg: 278 Galcanezumab 240 mg: 277 Placebo: 558	Galcanezumab 120 mg: 232 Placebo: 230	Erenumab 70 mg: 127 Erenumab 140 mg: 126 Placebo: 200
Chronic patients ≥2 previous treatment failures	Galcanezumab 120 mg: 74 Placebo: 177	Galcanezumab 120 mg: 95 Placebo: 98	Erenumab 70 mg: 93 Erenumab 140 mg: 92 Placebo: 142
Definition of a month	30 days	30 days	28 days
Primary endpoint	Mean change from baseline in the number of monthly migraine headache days across month 1 to 3	Mean change from baseline in the number of monthly migraine headache days across month 1 to 3	Mean change from baseline in the number of monthly migraine headache days across week 9-12
Post-hoc analyses	A subgroup analysis in patients with history of prior treatment failures[2]		Subgroup analysis in patients with a history of prior preventive treatment failures[8]

In the three selected studies the patients' mean age at baseline ranged from 42.8 years in REGAIN to 45.8 years in CONQUER. The percentage of female patients ranged from 78.2% in Study 295 to 91.9% in REGAIN. Patients' mean disease duration at baseline ranged from 22.6 years in REGAIN to 25.2 years in Study 296. Selected disease characteristics of the two chronic migraine trials together with the chronic migraine subpopulation in CONQUER are presented in Table 5.2. The monthly migraine headache days at baseline were reported in all three studies, ranging from 18.0 days in Study 295 and 20.0 days in REGAIN. At baseline, the monthly migraine headache days with acute medication use for migraine or headache ranged from 10.5 in Study 295 to 16.6 in REGAIN. It is important to note that the number of monthly migraine headache days with acute medication use is generally lower in erenumab trials compared to the galcanezumab trials as abortive medication was restricted to ergot derivates and triptans only.

TABLE 5.2 OVERVIEW OF SELECTED DISEASES CHARACTERISTICS

Trial	Patients (N)	Age (mean, SD)	Female (n, %)	Number of monthly migraine headache days (mean, SD)	Monthly migraine days with acute medication^ (mean, SD)	Disease duration in years mean {SD}
REGAIN*						
Galcanezumab 120mg	74	42.8 (11.3)	68 (91.9)	20.0 (4.3)	16.6 (5.6)	22.6 (13.3)
Placebo	177	43.9 (11.8)	157 (88.7)	19.6 (4.7)	15.8 (6.0)	24.3 (13.1)
CONQUER**						
Galcanezumab 120mg	95	45.8 (11.6)	83 (87.4)	19.2 (4.7)	15.0 (6.3)***	24.2 (13.9)***
Placebo	98	44.8 (13.1)	85 (86.7)	18.1 (4.7)	15.2 (5.9)***	24.9 (14.9)***
Study 295*						
Erenumab 70 mg	93	42.9 (11.2)	84 (90.3)	18.0 (4.4)	10.5 (7.2)	25.2 (13.2)
Erenumab 140 mg	92	44.2 (10.6)	82 (89.1)	18.8 (4.4)	12.4 (6.2)	24.6 (11.7)
Placebo	142	42.9 (11.5)	111 (78.2)	18.3 (4.5)	11.4 (7.4)	24.0 (12.9)

*subgroup analysis of patients ≥2 previously treatment failures,** subgroup analysis of chronic migraine patients ***data not reported in the CONQUER publication but is based on the CSR ^abortive medication restricted to ergots and triptans only, NA - not available, SD - standard deviation

5.1.2 Results per study

Results per study are described in the following section and in appendix 8.1.6-8 for the estimates of the primary analyses as displayed in the primary manuscripts of each study. Please note that:

- Migraine headache days for REGAIN and CONQUER were reported across month 1 to month 3.
- The definitions for 50% responders differ between studies: average monthly response rate across month 1 to month 3 for the REGAIN and CONQUER study (continuous measurement), and response was assessed at month 3 for Study 295.
- The definitions for the continuous measurements differ with mean change across month 1 to month 3 for REGAIN and CONQUER, and mean change at month 3 for Study 295.

In addition to this, a sensitivity analysis which used all data points at a specific time point (i.e. at month 3 as opposed to “across” a few months) is presented in appendix 8.4.

Change from baseline of monthly migraine days

All of the studies reported change from baseline (CFB) results of the monthly migraine headache days. In the galcanezumab trials CFB where assessed mean change across month 1 to 3 and in Study 295 at month 3. The CFB in the active treatment arms ranged from -5.91 days in the galcanezumab ≥2 prior treatment failures 120 mg arm in CONQUER to -6.2 days in the erenumab 140 mg ≥2 prior treatment failures arm in Study 295. The placebo arms had a reduction in monthly migraine headache days ranging from -1.01 days in REGAIN to -2.7 days in Study 295.

TABLE 5.3 CHANGE FROM BASELINE OF MONTHLY MIGRAINE DAYS

Trial	Intervention	N	Mean CFB (95% CI)
REGAIN[2]	Galcanezumab 120 mg	72	-5.35 (-6.76; -3.93)
	Placebo	174	-1.01 (-2.07; 0.05)
CONQUER[5]	Galcanezumab 120 mg	93	-5.91 (-7.20; -4.61)
	Placebo	96	-2.21 (-3.48; -0.93)*
Study 295[8]	Erenumab 70 mg	93	-5.4 ± NR
	Erenumab 140 mg	92	-7.0 ± NR
	Pooled doses	185	-6.2 (-7.06; -5.33)**
	Placebo	142	-2.7 (-3.72; -1.68)

*subgroup analysis of chronic migraine patients, ** 70 mg and 140 mg doses were pooled as specified in the DMC protocol

The absolute efficacy differences are converted to percentage reduction using an assumed event rate (ACR) for treatment for placebo. The assumed event rate is calculated on the basis of the effect in the studies and are 18.59, 15.39 and 15.6 monthly migraine days for REGAIN. CONQUER and Study 295, respectively. The calculated percentage reduction is shown in Table 5.4.

TABLE 5.4 PERCENTAGE CHANGE FROM BASELINE OF MONTHLY MIGRAINE DAYS

Trial	Intervention	ACR	Percentage change
REGAIN[2]	Galcanezumab 120 mg	18.59	-23,3% (-36,4%;21,1%)
CONQUER[5]	Galcanezumab 120 mg	15.39	-34,5% (-12,0%; 24,7%)
Study 295[8]	Erenumab	15.6	-22,4% (-30,9%; 13,9%)

Proportion of patients with ≥50% reduction in monthly migraine days

All studies reported the ≥50% reduction in monthly migraine headache days. Responder rates of 50% were analyzed differently in the erenumab and galcanezumab trials and therefore reported differently in the available sources. In the erenumab studies, the responder outcomes are binary and calculated at month 3. In the galcanezumab studies, the responder outcomes correspond to the average of the monthly responder rates calculated across the double-blind study duration and is therefore a continuous measure. Hence, to be able to indirectly compare to the erenumab studies, the number of responders in the galcanezumab studies were re-calculated from the average of the response rates and the number of patients contributing to the analyses. Therefore, the percentage displayed in Table 5.5 might slightly differ from the average percentage reported in the available publications.

The ≥50% reduction rate in the active treatment arms ranged from 32.3% in the galcanezumab 120 mg arm in CONQUER to 41.3% in the erenumab ≥2 prior treatment failures 140 mg arm in Study 295[8]. The ≥50% reduction rate in the placebo arms ranged from 9.2% to 14.1%.

TABLE 5.5 PROPORTION OF PATIENTS WITH ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS

Trial	Intervention	N	Proportion of patients with ≥50% reduction, n (%)
REGAIN[2]	Galcanezumab 120 mg	72	21 (29.2%)
	Placebo	174	16 (9.2%)
CONQUER[5]	Galcanezumab 120 mg	93	30 (32.3%)
	Placebo	96	9 (9.4%)

Study 295[8]	Erenumab 70 mg	93	33 (35.6%)
	Erenumab 140 mg	92	38 (41.3%)
	Pooled doses	185	71 (38.4%)*
	Placebo	142	20 (14.1%)

*70 mg and 140 mg doses were pooled as specified in the DMC protocol

Mean change from baseline in MSQ

Both REGAIN and CONQUER reported on the MSQ Role function restrictive score. REGAIN compared two doses of galcanezumab with placebo. All the differences in the CFB in MSQ role function restrictive score between galcanezumab and the placebo arm were statistically significant (p<0.05). Study 295 did not report data for MSQ or sub-domains.

None of the studies reported on the MSQ total score.

TABLE 5.6 MEAN CHANGE FROM BASELINE IN MSQ

Trial	Intervention	N	Mean CFB in MSQ-RF
REGAIN[2]	Galcanezumab 120 mg	64	19.13 (13.39; 24.86)
	Placebo	160	10.67 (6.48; 14.85)
CONQUER[5]	Galcanezumab 120 mg	88	20.6 (16.97; 24.22)
	Placebo	95	6.7 (3.21; 10.18)

Mean change from baseline in monthly headache days

None of studies reported data for mean CFB in monthly headache days.

Mean CFB in migraine headache days with acute medication use

All studies reported mean CFB in migraine headache days with acute medication use. In the galcanezumab trials CFB where assessed across month 1-3 and in Study 295 at month 3. Results in the active treatment arms ranged from -4.1 in the erenumab 70 mg arm to -5.81 in the galcanezumab 120 mg arm in REGAIN. The CFB in the placebo arms were comparable.

TABLE 5.7 MIGRAINE HEADACHE DAYS WITH ACUTE MEDICATION USE

Trial	Intervention	N	Migraine headache days with acute medication use, mean (95% CI)
REGAIN[2]	Galcanezumab 120 mg	72	-5.81 (-7.18; -4.43)
	Placebo	174	-1.35 (-2.39; -0.30)
CONQUER[5]	Galcanezumab 120 mg	93	-5.40 (-6.61; -4.18)
	Placebo	96	-1.38 (-2.55; -0.20)
Study 295[8]	Erenumab 70 mg	93	-4.1 (NR)
	Erenumab 140 mg	92	-5.4 (NR)
	Pooled doses	185	-4.75 (-5.41; -4.08)*
	Placebo	142	-1.3 (-2.08; -0.51)

NR: not reported *70 mg and 140 mg doses were pooled as specified in the DMC protocol

The absolute efficacy differences are converted to percentage reduction using an assumed event rate (ACR) for treatment for placebo. The assumed event rate is calculated on the basis of the effect in the studies and are 14.45, 14.84 and 10.1 monthly migraine days for REGAIN. CONQUER and Study 295, respectively. The calculated percentage reduction is shown in Table 5.8 **Error! Reference source not found.**.

TABLE 5.8 PERCENTAGE CHANGE FROM BASELINE OF MONTHLY MIGRAINE DAYS

Trial	Intervention	ACR	Percentage change
REGAIN[2]	Galcanezumab 120 mg	14.45	-30,9% (-42,6%; -19,0%)
CONQUER[5]	Galcanezumab 120 mg	14.84	-27,1% (-38,3%; -15,8%)
Study 295[8]	Erenumab	10.1	-34,2% (-44,2%; -24,1%)

Discontinuation due to adverse events

All of the trials reported discontinuation due to adverse events. Discontinuation rates were 1.1% in the galcanezumab arm of CONQUER and 0% in both erenumab treatment arms of Study 295. In the galcanezumab 120 mg arm of REGAIN the discontinuation rate for the ITT population was 0.109%.

TABLE 5.9 DISCONTINUATION DUE TO ADVERSE EVENTS

Trial	Intervention	N	Discontinuation due to adverse events, n (%)
REGAIN[4]	Galcanezumab 120 mg	273	3 (0.109%)*
	Placebo	558	6 (0.107%)*
CONQUER[5]	Galcanezumab 120 mg	95	1 (1.1%)
	Placebo	98	0 (0%)
Study 295[8]	Erenumab 70 mg	92	0 (0%)
	Erenumab 140 mg	92	0 (0%)
	Pooled doses	184	0 (0%)**
	Placebo	141	1 (0.7%)

*Data not available for subgroup with ≥ 2 prior treatment failure. The data reported is for the total ITT population. **70 mg and 140 mg doses were pooled as specified in the DMC protocol

Narrative description of the safety profile

5.1.2.1.1 REGAIN

There were no deaths in the REGAIN study. TEAEs were reported by 50%, 58%, and 57% of patients in the placebo, galcanezumab 120 mg, and galcanezumab 240 mg groups, respectively. Most TEAEs were mild or moderate in severity. The most common TEAE was injection-site pain, but this did not differ significantly between groups (4% placebo, 6% galcanezumab 120 mg, 7% galcanezumab 240 mg). Injection-site reaction, injection-site erythema, injection-site pruritus, and sinusitis occurred more frequently in the galcanezumab 240 mg group relative to placebo, with injection-site pruritus and injection-site erythema also occurring more frequently with the 240 mg than the 120 mg galcanezumab dose. Six placebo- treated patients discontinued as a result of AEs that included abdominal pain, alopecia, headache, migraine, and myocardial infarction. Five galcanezumab-treated patients discontinued because of an AE that included increased weight in the 120 mg group and depression, increased hepatic enzymes, injection-site pain, and acute pancreatitis in the 240 mg group.

There were 10 serious AEs during the study, with 4 reported in the placebo group (alcoholic pancreatitis, epistaxis, gastritis, and myocardial infarction), 1 in the galcanezumab 120 mg group (colon cancer), and 5 in the galcanezumab 240 mg group (hypokalaemia and nephrolithiasis in 1 patient, acute pancreatitis, pulmonary embolism, and renal colic).

No clinically meaningful differences were observed between galcanezumab and placebo in laboratory values, vital signs, weight, or quantitative or qualitative ECGs. Two patients in the study had a treatment-emergent abnormal hepatic enzyme: 1 in the placebo group (1 of 558 or 0.2%) and 1 in the galcanezumab 240 mg dose group (1 of 282 or 0.4%).

During the double-blind treatment phase, treatment-emergent anti-drug-antibodies (ADA) occurred in 22 patients across the groups (1.5%, 2.7%, and 2.6% of the placebo, galcanezumab 120 mg, and galcanezumab 240 mg groups, respectively). Of these 22 patients, 13 had neutralizing ADA present (0.6%, 2.3%, and 1.5% of the placebo, galcanezumab 120 mg, and galcanezumab 240 mg groups, respectively), with a statistical difference be- tween galcanezumab 120 mg and placebo ($p < 0.05$). Maximum ADA titers among these patients ranged from 1:20 to 1: 160. There was no discernible effect of ADA on treatment efficacy or tolerability.

TABLE 5.10 TREATMENT-EMERGENT AES THAT OCCURRED IN ≥2% OF GALCANEZUMAB-TREATED PATIENTS TREATED WITH EITHER DOSE OF GALCANEZUMAB AND GREATER THAN PLACEBO, FULL SAFETY POPULATION OF REGAIN[4]

Adverse event	Placebo (n = 558), n (%)	Galcanezumab, n (%)	
		120 mg (n = 273)	240 mg (n = 282)
Patients with ≥1 event	279 (50)	159 (58)[a]	160 (57)
Injection-site pain	24 (4)	17 (6)	20 (7)
Nasopharyngitis	26 (5)	17 (6)	9 (3)
Upper respiratory tract infection	13 (2)	9 (3)	9 (3)
Injection-site reaction	10 (2)	8 (3)	15 (5)[b]
Injection-site erythema	5 (1)	4 (1)	13 (5)[c,d]
Fatigue	10 (2)	6 (2)	6 (2)
Back pain	14 (3)	9 (3)	2 (1)[d]
Urinary tract infection	7 (1)	6 (2)	4 (1)
Abdominal pain	9 (2)	6 (2)	4 (1)
Diarrhoea	9 (2)	3 (1)	6 (2)
Injection-site pruritus	1 (0)	0 (0)	7 (2)[b,d]
Migraine	5 (1)	5 (2)	4 (1)
Influenza-like illness	3 (1)	5 (2)	4 (1)
Neck pain	8 (1)	7 (3)	0 (0)[a,d]
Oropharyngeal pain	3 (1)	2 (1)	5 (2)
Sinusitis	5 (1)	4 (1)	8 (3)[a]
Arthralgia	5 (1)	1 (0)	5 (2)
Pyrexia	2 (0)	5 (2)[a]	1 (0)

Abbreviation: AE = adverse event. [a] $p < 0.05$ vs placebo. [b] $p < 0.01$ vs placebo. [c] $p < 0.001$ vs placebo. [d] $p < 0.05$ vs galcanezumab 120 mg.

5.1.2.1.2 CONQUER

Safety findings from CONQUER are consistent with those reported from the pivotal phase III trials in patients with EM and CM; galcanezumab was well tolerated and no new safety signals were observed.

Safety was only reported for the population of patients with EM and CM with prior failure with ≥2 preventive medication categories since it was not expected that there would be any differences with respect to AEs between the varying study populations. No deaths occurred during the trial and only four SAEs were reported in total (two each in the galcanezumab and placebo groups). A single patient randomized to galcanezumab discontinued the double-blind treatment period due to an AE. TEAEs occurred at a similar rate in both treatment groups and were generally mild to moderate in severity. Injection site AEs were relatively uncommon and had a greater incidence in placebo compared with galcanezumab-treated patients.

The percentage of patients reporting a TEAE was similar across the galcanezumab and placebo treatment groups. Nasopharyngitis was the most common TEAE in both treatment groups occurring in 9.13% and 6.90% of placebo- or galcanezumab-treated patients, respectively. Statistically significant differences between groups were observed for two TEAEs: injection site reactions, which occurred in six (2.61%) patients in the placebo group versus none in the galcanezumab group (p=0.0147), and insomnia, which occurred in five (2.17%) patients receiving placebo and no patients receiving galcanezumab (p=0.0299).

Most TEAEs were reported as being mild or moderate in severity, with more patients in the placebo group reporting a TEAE as severe compared with the galcanezumab group (3.5% vs 1.7%).

TABLE 5.11 TEAES REPORTED IN ≥2% OF GALCANEZUMAB-TREATED PATIENTS WITH EM OR CM AND PRIOR FAILURE WITH ≥2 PREVENTIVE MEDICATION CATEGORIES IN THE 3-MONTH, DOUBLE-BLIND TREATMENT PERIOD OF CONQUER

Adverse event	Placebo (n=230), n (%)	Galcanezumab 120 mg (n=232), n (%)
Patients with ≥1 TEAE	122 (53.04)	119 (51.29)
Nasopharyngitis	21 (53.04)	16 (6.90)
Influenza	7 (3.04)	11 (4.74)
Injection site erythema	6 (2.61)	8 (3.45)
Constipation	5 (2.17)	5 (2.16)
Injection site pain	13 (5.65)	5 (2.16)
Upper respiratory tract infection	5 (2.17)	5 (2.16)
Back pain	6 (2.61)	4 (1.72)
Bronchitis	2 (0.87)	4 (1.72)
Fatigue	1 (0.43)	4 (1.72)
Gastroenteritis	3 (1.30)	4 (1.72)
Nausea	5 (2.17)	4 (1.72)
Oropharyngeal pain	2 (0.87)	4 (1.72)
Sinusitis	5 (2.17)	4 (1.72)
CM, chronic migraine; EM, episodic migraine; TEAE, treatment-emergent adverse event.		

5.1.2.1.3 Study 295

Over one-third of patients without prior treatment failure had an incidence of AEs (30.6–37.5%). Nearly one-half of patients with prior treatment failure (42.4–57.6%) had an incidence of AEs. The incidence of AEs for placebo compared to erenumab 70 mg and erenumab 140 mg was broadly comparable. The number of SAEs and AEs leading to treatment discontinuation was low.

TABLE 5.12 ADVERSE EVENTS IN PATIENTS WITH PREVIOUSLY ≥2 FAILED PRIOR MEDICATIONS

Adverse event	Placebo (n=141), n (%)	Erenumab 70 mg (n=92), n (%)	Erenumab 140 mg (n=92), n (%)
Any AE	62 (44.0)	39 (42.4)	53 (57.6)
Grade 2	35 (24.8)	17 (18.5)	26 (28.3)
Grade 3	7 (5.0)	5 (5.4)	3 (3.3)
Any SAE	4 (2.8)	3 (3.3)	1 (1.1)
AE leading to treatment discontinuation	1 (0.7)	0 (0.0)	0 (0.0)

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required; Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

5.1.3 Comparative analyses

No head-to-head comparisons of the efficacy and safety of galcanezumab 120 mg compared with erenumab 70 mg or 140 mg were identified by the SLR. Following a feasibility assessment on the comparability of studies for galcanezumab and erenumab, an ITC was conducted on the available outcomes of interest to synthesize evidence identified. All studies included in the ITC were parallel-arm, placebo-controlled phase III RCTs.

Indirect treatment comparisons are a possible option to assess the comparative efficacy and safety of interventions of interest, which are not compared through head-to-head studies. The feasibility assessment included two important steps:

1. An evaluation to assess whether there was data from a comparable outcome for at least one study for galcanezumab and erenumab.
2. An assessment of the similarity assumption of the studies to be pooled and potential issues of heterogeneity in treatment modifier variables are identified.

Based on the findings from the SLR, data was available for the outcomes displayed in Table 5.13.

TABLE 5.13 OUTCOME MAP BY COMPARATOR

	Galcanezumab 120 mg vs Erenumab 70 mg	Galcanezumab 120 mg vs Erenumab 140 mg
Mean CFB in monthly migraine days	X	X
Proportion of patients with ≥50% reduction in monthly migraine days	X	X
Mean CFB in MSQ-RF		
Mean CFB in MSQ-PF		
Mean CFB in MSQ-EF		
Mean CFB in monthly headache days		
Mean CFB in migraine headache days with acute medication use	X	X
Discontinuation due to AE	X	X

Indirect treatment comparisons can only be conducted if the similarity assumption holds, i.e. the studies have to be similar enough to allow the treatment effects to be pooled. Note that ITC results may still hold when study characteristics differ as long as they are not treatment effect modifiers. We qualitatively assessed the comparability with respect to baseline characteristics between the limited number of studies included in the ITC.

Full details on the baseline characteristics of the included erenumab and galcanezumab studies are provided in Table 5.2 and 8.2. Generally, the study design was comparable with one difference being how the month was defined (28 days in erenumab trials, 30 days in galcanezumab trials).

The baseline characteristics of the identified studies are reported in Table 5.2. It is important to note that the number of monthly migraine headache days with acute medication use is generally lower in erenumab trials compared to the galcanezumab trials as abortive medication was restricted to ergot derivates and triptans only. Overall, the identified studies for galcanezumab and erenumab were deemed comparable with the potential exception of the outcome definition for acute medication use, which was more restricted in terms of the permitted abortive medication in the erenumab trials, thus results need to be interpreted with caution.

Though the studies were deemed to be comparable, the results from REGAIN were based on post-hoc analyses of treatment resistant patients while in CONQUER and Study 295 the analyses was pre-specified. Additionally, the definition of treatment resistant patients was not identical for REGAIN and CONQUER. As a result of these discrepancies, we conducted sensitivity analyses excluding the results of the REGAIN study to ensure that REGAIN data did not affect the overall conclusions (see section 8.4).

Indirect treatment comparison

The ITC is a statistical method used to pool results across a number of trials with comparable patient populations linked by common comparators. The technique is based on the assumption that, on a suitable scale, one can add and subtract the within-study estimates of relative treatment effects. For example, direct data comparing treatment A with C and B with C can be used to indirectly compare A and B. This is under the assumption that the following relationship between the estimated treatment effects holds:

(A–B) = (A–C)–(B–C).

Health care decision-makers require comparisons of specific competing interventions. ITC meets the needs of decision-makers where direct data may not exist between all relevant treatments.

The underlying methodology for the ITC is the Bucher *et al*. 1997 [19] method, which is a frequentist approach to evidence synthesis. Continuous outcomes were assessed in terms of weighted mean difference. Binary outcomes were assessed in terms of relative risk (RR) and risk difference (RD). For binary outcomes in terms of relative risk (RR), the treatment effect of the indirect comparison of active treatments A and B via common comparator baseline treatment C is estimated as the difference of the treatment effects of the direct comparisons on the log scale as

$$\ln(OR_{AB}) = ln(OR_{AC}) - ln(OR_{BC}).$$

The corresponding variance is the sum of the variance of the treatment effects of the direct comparisons, estimated as

$$\mathrm{Var}(lnOR_{AB}) = Var(lnOR_{AC}) + Var(lnOR_{BC}),$$

The equations in terms of RR are equivalent. To estimate relative effects in terms of risk difference (RD) or weighted mean difference (WMD), a log transformation is not necessary, and pooled RD or WMD is estimated as

$$RD_{AB} = RD_{AC} - RD_{BC},$$

with variance

$$\mathrm{Var}(RD_{AB}) = Var(RD_{AC}) + Var(RD_{BC}),$$

If more than one study is available the corresponding treatment effect and variance considered in the equations of the Bucher method is a pooled estimator obtained through meta-analysis using for binary outcome the Mantel-Haenszel method. Pooling of continuous outcome is conducted by assigning inverse variance weights to the individual studies. The inverse variance refers to the relative effect of each individual study which is considered in the pooling. The random effects are calculated using the DerSimonian- Laird method as the estimator for tau for both a continuous and binary outcome.

The heterogeneity between the studies on each direct treatment comparison was assessed through the inconsistency parameter (I^2) statistic and the p-value of the Q-statistic. The I^2 can be interpreted as the proportion of total variability attributed to heterogeneity rather than chance. The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (for example, p-value from the chi-squared test, or a confidence interval for I^2).

The heterogeneity statistic Q, which follows a central chi-squared distribution with degrees of freedom of the number of studies minus 1, was used. The test depends on the number of studies and has a low power when few studies and a high power when many studies. Therefore, this p-value was interpreted with caution and in light of the number of studies included in the meta-analysis. In the absence of heterogeneity, the results of fixed effects (FE) and random effects (RE) models are expected to be identical. Between studies variance τau^2, with 95% CI and p-value were reported.
The ITC analyses were performed using the Cheetah-tool (Indirect Comparison on results from 2 Meta-Analyses version 1.1), a Lilly developed program based on R package Meta. Treatment effects are estimated, following the approach proposed by Bucher *et al*. 1997[19] henceforth referred to as the Bucher method.

In the base case analyses the predefined estimates for each study were used. The predefined estimates corresponded to an overall estimate across the full duration of the double-blind treatment period of the galcanezumab studies (e.g. REGAIN and CONQUER) and an estimate at a time point for Study 295.

For the continuous endpoints, the results and interpretation provided around the results refer to the mean differences and 95% CI since the used outcomes are defined and reported in a similar manner in the publicly available disclosures and therefore easy to interpret.

For both types of endpoint, the text reports the RE model estimates and associated 95% confidence interval (CI) to take into account potential heterogeneity between studies.

Significance of treatment effect for the frequentist method are determined by the two-sided 95%CI and tests with two-sided p-values less than 0.05 are referred to as being statistically significant.

Regarding the data used for the responder analyses, responder rates (50%) were analyzed differently in the erenumab and galcanezumab studies and therefore reported differently in the source documents.

Hence, to be able to indirectly compare to the erenumab study, the number of responders in the galcanezumab studies were re-calculated from the average of the response rates and the number of patients contributing to the analyses. Therefore, the percentage displayed in the indirect comparison analyses might slightly differ from the average percentage reported in source documents.

For studies where no events were observed in one or both arms, a fixed value of 0.5 was added to all cells of study results (to avoid computing error while dividing by '0'). Whilst this correction meets the objective of avoiding computational errors, it usually has the undesirable effect of biasing study estimates towards no difference and overestimating variances of study estimates (consequently down-weighting inappropriately their contribution to the meta-analysis).

Change from baseline of monthly migraine days

Table 5.14 show the individual study results and the pooled results obtained through the indirect comparison for the change from baseline in monthly migraine headache days in terms of mean difference presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab (70 mg + 140 mg) and placebo. No statistically significant difference is seen between galcanezumab and erenumab (70 mg + 140 mg) for the mean difference in change from baseline in monthly migraine headache days for the random effect model (erenumab 70 mg + 140 mg: -0.53 (95% CI: (-2.36, 1.29; p=0.568). Identical results are observed for the fixed effects model.

TABLE 5.14 ITC CHANGE FROM BASELINE IN MHD

Trial	**Galcanezumab 120 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
REGAIN	72, -5.35 (6.02)	174, -1.01 (7.12)	-4.34 (-6.09, -2.59)
CONQUER	93, -5.91 (6.27)	96, -2.21 (6.27)	-3.7 (-5.49, -1.91)
Pooled data	165, -5.67 (6.15)	270, -1.44 (6.84)	
FE Meta-analysis		-4.03 (-5.28, -2.78) P<0.001	
RE Meta-analysis		-4.03 (-5.28, -2.78) P<0.001	
tau^2		0	
I^2		0 (NA, NA)	
Test of heterogeneity: Q (df)		0.25 (1) P=0.616	
Trial	**Erenumab 70 mg + 140 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
Study 295	185, -6.2 (5.98)	142, -2.7 (6.15)	-3.5 (-4.82, -2.17)
FE Meta-analysis		-3.5 (-4.82, -2.17) P<0.001	
RE Meta-analysis		-3.5 (-4.82, -2.17) P<0.001	
tau^2		NA	
I^2		NA (NA, NA)	
Test of heterogeneity: Q (df)		0 (0) P=1	
FE Indirect Comparison		-0.53 (-2.36, 1.29) P=0.568	
RE Indirect Comparison		-0.53 (-2.36, 1.29) P=0.568	

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

The absolute efficacy differences are converted to percentage reduction using an assumed event rate (ACR) for treatment with erenumab. The assumed event rate is calculated on the basis of the mean effect in the studies and is 12.2 monthly migraine days. The calculated percentage reduction is shown in Table 5.4.

TABLE 5.15 PERCENTAGE CHANGE FROM BASELINE OF MONTHLY MIGRAINE DAYS

Intervention	Mean difference	ACR	Percentage change
Galcanezumab 120 mg vs. Erenumab 70mg + 140 mg	-0.53 (-2.36, 1.29)	12.2	-4.3% (-19.3%; 10.6%)

Proportion of patients with ≥50% reduction in monthly migraine days

Table 5.16 show the individual study results and the pooled results obtained through the indirect comparison for the percentage of patients with a 50% or greater reduction in monthly migraine headache days in terms of RR and RD, each presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab 70 mg + 140 mg and placebo. The ITC random effects model comparing galcanezumab to erenumab 70 mg + 140 mg results in a RR of 1.20 (95% CI: 0.64, 2.27; p=0.563). Similar results are observed for the fixed effects model. The absolute treatment difference (RD) was calculated based on the RR according to the DMC methods guideline (RD=ACR*RR-ACR). The assumed comparator risk (ACR) was assumed to equal to the erenumab arm (38.4%). The absolute risk difference was estimated to 7.68% (95% CI: - 13.82; 48.76).

TABLE 5.16 ITC PROPORTION OF PATIENTS WITH ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS

Trial	**Galcanezumab 120 mg** n/N (%)	**Placebo n/N (%)**	**Risk ratio (95% CI)**
REGAIN	21/72 (29.2)	16/174 (9.2)	3.17 (1.76, 5.72)
CONQUER	30/93 (32.3)	9/96 (9.4)	3.44 (1.73, 6.85)
Pooled data	51/165 (30.9)	25/270 (9.3)	
FE Meta-analysis			3.3 (2.1, 5.19) P<0.001
RE Meta-analysis			3.28 (2.1, 5.14) P<0.001
tau^2			0
I^2			0 (NA, NA)
Test of heterogeneity: Q (df)			0.03 (1) P=0.859
Trial	**Erenumab 70 mg + 140 mg** n/N (%)	**Placebo** n/N (%)	
Study 295	71/185 (38.4)	20/142 (14.1)	2.72 (1.75, 4.25)
FE Meta-analysis			2.72 (1.75, 4.25) P<0.001
RE Meta-analysis			2.72 (1.75, 4.25) P<0.001
tau^2			NA
I^2			NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1
FE Indirect Comparison			1.21 (0.64, 2.29) P=0.553
RE Indirect Comparison			1.20 (0.64, 2.27) P=0.563

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

Mean CFB in migraine headache days with acute medication use

Table 5.17 show the individual study results and the pooled results obtained through the indirect comparison for the change from baseline in monthly migraine headache days with acute medication use in terms of mean difference presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab (70 mg + 140 mg)

and placebo. No statistically significant difference was observed between galcanezumab 120 mg and Erenumab 70 mg + 140 mg (mean difference: -0.79 (95% CI: -2.35, 0.78; p=0.324) in reducing overall migraine headache days with acute medication use. Identical results are observed for the fixed effects model. It must be noted that the permitted acute medications in the erenumab trials were restricted to ergots and triptans, whereas a broader definition was applied in the galcanezumab studies. Hence, the results of this variable must be interpreted with caution.

TABLE 5.17 ITC MEAN CFB IN MIGRAINE HEADACHE DAYS WITH ACUTE MEDICATION USE

Trial	**Galcanezumab 120 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
REGAIN	72, -5.81 (5.85)	174, -1.35 (6.99)	-4.02 (-5.68, -2.36)
CONQUER	93, -5.4 (5.88)	96, -1.38 (5.78)	-4.46 (-6.17, -2.75)
Pooled data	165, -5.58 (5.86)	270, -1.36 (6.58)	
FE Meta-analysis		-4.23 (-5.43, -3.04) P<0.001	
RE Meta-analysis		-4.23 (-5.43, -3.04) P<0.001	
tau^2		0	
I^2		0 (NA, NA)	
Test of heterogeneity: Q (df)		0.13 (1) P=0.717	
Trial	**Erenumab 70 mg + 140 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
Study 295	185, -4.75 (4.57)	142, -1.3 (4.72)	-3.45 (-4.46, -2.43)
FE Meta-analysis		-3.45 (-4.46, -2.43) P<0.001	
RE Meta-analysis		-3.45 (-4.46, -2.43) P<0.001	
tau^2		NA	
I^2		NA (NA, NA)	
Test of heterogeneity: Q (df)		0 (0) P=1	
FE Indirect Comparison		-0.79 (-2.35, 0.78) P=0.324	
RE Indirect Comparison		-0.79 (-2.35, 0.78) P=0.324	

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

The absolute efficacy differences are converted to percentage reduction using an assumed event rate (ACR) for treatment with erenumab. The assumed event rate is calculated on the basis of the mean effect in the studies and is 6.65 monthly migraine days. The calculated percentage reduction is shown in Table 5.18.

TABLE 5.18 PERCENTAGE CHANGE FROM BASELINE OF MIGRAINE HEADACHE DAYS WITH ACUTE MEDICATION USE

Intervention	**Mean difference**	**ACR**	**Percentage change**
Galcanezumab 120 mg vs. Erenumab 70mg + 140 mg	-0.79 (-2.35, 0.78)	6.65	-11.9% (-35.3%; 11.7%)

Discontinuation due to adverse events

Table 5.19 show the individual study results and the pooled results obtained through the indirect comparison for the outcome: discontinuation due to adverse events in terms of RR and RD, each presented with corresponding 95% CI and p-value. The ITC random effects model comparing galcanezumab to erenumab 70 + 140 mg results in an RR of 12.1 (95% CI: 0.13, 1102.98), indicating that the risk of patients discontinuing due to adverse events is increased in patients receiving galcanezumab when compared to

erenumab 70 + 140 mg; however, this difference is not statistically significant (p=0.279). Similar results are observed for the fixed effects model. However, these results need to be interpreted with caution given that no event was observed in the active treatment arm of the erenumab study or the control arm in the galcanezumab study. Only one event was reported in the galcanezumab arm in CONQUER and one in the control arm of the erenumab study.

Table 5.19 ITC discontinuation due to AE

Trial	**Galcanezumab 120 mg** n/N (%)	**Placebo n/N (%)**	**Risk ratio (95% CI)**	**Risk difference (95% CI)**
CONQUER	1/95 (1)	0/98 (0)	3.09 (0.13, 75.02)	0.01 (-0.02, 0.04)
FE Meta-analysis			3.09 (0.13, 75.02) P=0.487	0.01 (-0.02, 0.04) P=0.469
RE Meta-analysis			3.09 (0.13, 75.02) P=0.487	0.01 (-0.02, 0.04) P=0.469
tau^2			NA	NA
I^2			NA (NA, NA)	NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1	0 (0) P=1
Trial	**Erenumab 70 mg + 140 mg** n/N (%)	**Placebo** n/N (%)	**Risk ratio (95% CI)**	**Risk difference (95% CI)**
Study 295	0/184 (0)	1/141 (0.7)	0.26 (0.01, 6.23)	-0.01 (-0.03, 0.01)
FE Meta-analysis			0.26 (0.01, 6.23) P=0.402	-0.01 (-0.03, 0.01) P=0.45
RE Meta-analysis			0.26 (0.01, 6.23) P=0.402	-0.01 (-0.03, 0.01) P=0.45
tau^2			NA	NA
I^2			NA (NA, NA)	NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1	0 (0) P=1
FE Indirect Comparison			**12.1 (0.13, 1102.98) P=0.279**	**0.02 (-0.02, 0.05) P=0.308**
RE Indirect Comparison			**12.1 (0.13, 1102.98) P=0.279**	**0.02 (-0.02, 0.05) P=0.308**

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

6 Conclusion

Galcanezumab is a humanised monoclonal antibody that potently and selectively binds to and inhibits calcitonin gene-related peptide (CGRP), a vasodilatory neuropeptide in the trigeminal system that is fundamental in the pathophysiology of migraine. Targeting the biology of migraine through inhibition of CGRP suggests that galcanezumab could improve the preventive management of migraine.

The pivotal phase III trial (REGAIN) has shown that galcanezumab is associated with clear, consistent, and clinically meaningful improvements across multiple efficacy and functioning domains in patients with chronic migraine (CM). In addition, a post hoc analysis demonstrated that galcanezumab reduced the burden of migraine and lessened day-to-day functional impairment in treatment-resistant patients with CM who had previously failed ≥2 current migraine preventive medications for efficacy or tolerability reasons (contraindication was not considered) . Given the positive results of this post hoc analysis of the phase III registration trial, a dedicated study was initiated specific to the subpopulation with treatment-resistant migraine (failed two to four migraine preventive medication categories). Findings from CONQUER support and extend the results from the pivotal phase III trial demonstrating that galcanezumab was associated with clinically meaningful improvements in several relevant outcomes in patients with episodic migraine (EM) or CM and prior failure with ≥2 preventive medications.

The favourable safety/tolerability profile of galcanezumab was also demonstrated in these phase III clinical trials. In general, treatment-emergent adverse events (TEAEs) were transient in nature and resolved fully, and discontinuation rates were low across all studies providing support for the tolerability of galcanezumab in patients with CM. The safety of galcanezumab has also been demonstrated in studies of up to 1 year in duration. No new safety signals were observed in the 3-month double-blind treatment phase of CONQUER indicating that galcanezumab is also well tolerated in patients with migraine and prior failure with preventive medications.

No head-to-head comparisons of the efficacy and safety of galcanezumab 120 mg compared to erenumab 70 mg or 140 mg was identified by the systematic literature review (SLR). Following a feasibility assessment on the comparability of studies for galcanezumab and erenumab, an indirect treatment comparison (ITC) was conducted on the available outcomes of interest to synthesize evidence identified. All studies included in the ITC were parallel-arm, placebo-controlled phase II or III randomized controlled trials (RCTs).

Generally, heterogeneity was low in any of the base case meta-analyses conducted for galcanezumab. Overall, across the analyses, no statistically significant differences were observed between galcanezumab 120 mg and erenumab (70 + 140 mg) for all the outcomes that were assessed in the protocol. Thus, the efficacy and safety profile were found to be broadly similar. However, the limitations of these analyses must be taken into consideration in the interpretation of these results.

7 References

1. Bangs ME, Kudrow D, Wang S, Oakes TM, Terwindt GM, Magis D, et al. Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies. BMC Neurol [Internet]. 2020 Dec 17;20(1):25. Available from: https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-020-1609-7

2. Ruff DD, Ford JH, Tockhorn-Heidenreich A, Sexson M, Govindan S, Pearlman EM, et al. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure. Cephalalgia [Internet]. 2019 Jul 19;39(8):931–44. Available from: http://journals.sagepub.com/doi/10.1177/0333102419847957

3. Nichols R, Doty E, Sacco S, Ruff D, Pearlman E, Aurora SK. Analysis of Initial Nonresponders to Galcanezumab in Patients With Episodic or Chronic Migraine: Results From the EVOLVE-1, EVOLVE-2, and REGAIN Randomized, Double-Blind, Placebo-Controlled Studies. Headache [Internet]. 2019 Feb;59(2):192–204. Available from: http://doi.wiley.com/10.1111/head.13443

4. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine. Neurology [Internet]. 2018 Dec 11;91(24):e2211–21. Available from: http://www.neurology.org/lookup/doi/10.1212/WNL.0000000000006640

5. Mulleners W, Kim B, Láinez MJ, Lanteri-Minet M, Aurora SK, Nichols RM, et al. A phase 3 placebo-controlled study of galcanezumab in patients with treatment-resistant migraine: Results from the 3-month double-blind treatment phase of the conquer study. J Neurol Sci [Internet]. 2019 Oct;405(162):128. Available from: https://n.neurology.org/content/94/15_Supplement/162.abstract

6. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol [Internet]. 2017 Jun;16(6):425–34. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1474442217300832

7. Schwedt T, Reuter U, Tepper S, Ashina M, Kudrow D, Broessner G, et al. Early onset of efficacy with erenumab in patients with episodic and chronic migraine. J Headache Pain [Internet]. 2018 Dec 1;19(1):92. Available from: https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-018-0923-6

8. Ashina M, Tepper S, Brandes JL, Reuter U, Boudreau G, Dolezil D, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia [Internet]. 2018 Sep 8;38(10):1611–21. Available from: http://journals.sagepub.com/doi/10.1177/0333102418788347

9. Lipton RB, Tepper SJ, Reuter U, Silberstein S, Stewart WF, Nilsen J, et al. Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study. Neurology [Internet]. 2019 May 7;92(19):E2250–60. Available from: http://www.neurology.org/lookup/doi/10.1212/WNL.0000000000007452

10. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med [Internet]. 2017 Nov 30;377(22):2113–22. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1709038

11. Winner PK, Spierings ELH, Yeung PP, Aycardi E, Blankenbiller T, Grozinski-Wolff M, et al. Early Onset

of Efficacy With Fremanezumab for the Preventive Treatment of Chronic Migraine. Headache J Head Face Pain [Internet]. 2019 Nov;59(10):1743–52. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/head.13654

12. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings ELH, Diener H-C, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol [Internet]. 2015 Nov;14(11):1091–100. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1474442215002458

13. Bigal ME, Dodick DW, Krymchantowski A V, VanderPluym JH, Tepper SJ, Aycardi E, et al. TEV-48125 for the preventive treatment of chronic migraine. Neurology [Internet]. 2016 Jul 5;87(1):41–8. Available from: http://www.neurology.org/lookup/doi/10.1212/WNL.0000000000002801

14. Cohen JM, Dodick DW, Yang R, Newman LC, Li T, Aycardi E, et al. Fremanezumab as Add-On Treatment for Patients Treated With Other Migraine Preventive Medicines. Headache J Head Face Pain [Internet]. 2017 Oct;57(9):1375–84. Available from: http://doi.wiley.com/10.1111/head.13156

15. VanderPluym J, Dodick DW, Lipton RB, Ma Y, Loupe PS, Bigal ME. Fremanezumab for preventive treatment of migraine. Neurology [Internet]. 2018 Sep 18;91(12):e1152–65. Available from: http://www.neurology.org/lookup/doi/10.1212/01.wnl.0000544321.19316.40

16. Halker Singh RB, Aycardi E, Bigal ME, Loupe PS, McDonald M, Dodick DW. Sustained reductions in migraine days, moderate-to-severe headache days and days with acute medication use for HFEM and CM patients taking fremanezumab: Post-hoc analyses from phase 2 trials. Cephalalgia [Internet]. 2019 Jan 3;39(1):52–60. Available from: http://journals.sagepub.com/doi/10.1177/0333102418772585

17. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet [Internet]. 2019 Sep;394(10203):1030–40. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673619319464

18. Olesen J. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia [Internet]. 2018 [cited 2020 Jun 15];38(1):1–211. Available from: www.uk.sagepub.com

19. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997;50(6):683–91.

8 Appendices

8.1 Studies excluded at full-text screening

Reference (title, author, journal, year)	Reason for exclusion
Positive response to galcanezumab following treatment failure to onabotulinumtoxinA in patients with migraine: post hoc analyses of three randomized double-blind studies, Ailani, Eur J Neurol., 2020	Post-hoc analyses; After onabotulinumtoxinA failure

Main characteristics of included studies

8.2 Study characteristics

8.2.1 REGAIN

Trial name	REGAIN
NCT number	NCT02614261
Objective	The main purpose of this study is to evaluate the efficacy of the study drug known as galcanezumab in participants with chronic migraine.
Publications – title, author, journal, year	Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies, Bangs, BMC Neurol., 2020 Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure, Ruff, Cephalalgia, 2019[2] Analysis of Initial Nonresponders to Galcanezumab in Patients With Episodic or Chronic Migraine: Results From the EVOLVE-1, EVOLVE-2, and REGAIN Randomized, Double-Blind, Placebo-Controlled Studies, Nichols R, Headache, 2019[3] Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study, Detke, Neurology, 2018[4]
Study type and design	REGAIN was a Phase 3, multicentred, randomized, double-blind, placebo-controlled study of galcanezumab in patients suffering from chronic migraine. Chronic migraine was defined using the ICHD-3 beta guidelines. In the 3-month, double-blind treatment phase, patients meeting all eligibility requirements were randomized to 1 of 3 treatment groups in a 2:1:1 ratio to receive placebo, 120 mg/month galcanezumab, or 240 mg/month galcanezumab, respectively. Patients randomized to the 120-mg dose received a loading dose of 240 mg (2 injections of 120 mg each) at visit 3 only.
Follow-up time	3-month double-blind treatment phase, an optional 9-month open-label extension
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Have a diagnosis of chronic migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines, with a history of migraine headaches of at least 1 year prior to screening, and migraine onset prior to age 50. Exclusion Criteria: • Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. • Current use or prior exposure to galcanezumab or another calcitonin gene-related peptide (CGRP) antibody.

<table>
<tr><td></td><td>

- Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab.
- History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta.

</td></tr>
<tr><td>Intervention</td><td>

Total population (ITT):
N=1113
galcanezumab 120 mg SC, once monthly (with 240-mg loading dose) n=278
galcanezumab 240 mg SC, once monthly n=277
placebo SC, once monthly n=558

≥2 previously failed preventive treatment subgroup:
Galcanezumab 120 mg: 74
Placebo: 177

</td></tr>
<tr><td>Baseline characteristics</td><td>

	Placebo (n = 558)	**Galcanezumab 120 mg (n = 278)**	**Galcanezumab 240 mg (n = 277)**
Age, years	41.6 (12.1)	39.7 (11.9)[a]	41.1 (12.4)
Females, n (%)	483 (87)	237 (85)	226 (82)
BMI, kg/m^2	26.9 (5.6	26.4 (5.5)	26.7 (5.2)
Years since migraine diagnosis	21.9 (12.9	20.4 (12.7	20.1 (12.7)[a]
Migraine with aura, n (%)	310 (56)	153 (55)	141 (51)
Number of monthly MHDs	19.6 (4.6)	19.4 (4.3)	19.2 (4.6)
Number of monthly MHD with acute medication use	15.5 (6.6)	15.1 (6.3	14.5 (6.3)[a]
Number of monthly headache days	21.5 (4.1)	21.2 (4.0)	21.4 (4.1)
Prior preventive treatment in past 5 y, n (%)	435 (78)	211 (76)	220 (79)
Failed ≥2 preventives in past 5 y, n (%)	163 (29)	68 (24)	97 (35)b
Acute headache medication overuse, n (%)	353 (63)	178 (64)	177 (64)
Concurrent preventive treatment, n (%)	82 (15)	37 (13)	43 (16)
MIDAS total score	68.7 (57.4)	62.5 (49.5)	69.2 (64.1)
MSQ RF-R score	38.4 (17.2)	39.3 (17.3)	38.9 (17.3)
MSQ RF-P score	55.0 (20.8)	55.5 (22.0)	57.1 (20.5)
MSQ EF score	44.2 (26.0)	45.3 (25.8)	45.7 (27.4)
PGI-S score	4.9 (1.2)	4.8 (1.2)	4.9 (1.3)

EF = Emotional Function; MHD = migraine headache days; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire version 2.1; PGI-S = Patient Global Impression-Severity of Illness; RF-P = Role Function-Preventive; RF-R = Role Function-Restrictive Data are mean (SD) unless otherwise indicated.
[a]p ≤ 0.05 vs placebo.
[b]p ≤ 0.01 vs galcanezumab 120 mg.

</td></tr>
</table>

Primary and secondary endpoints	The primary endpoint was overall mean change from baseline in the number of monthly migraine headache days *Secondary endpoints* Change from baseline in number of monthly: • MHDs with triptan use • MHDs with NSAID/aspirin use • MHDs with acetaminophen/paracetamol use • Headache days • Moderate-to-severe headache days • ICHD MHDs • Migraine attacks • Migraine headache hours • Headache hours Changes from baseline in: • MSQ Role Function–Preventive domain score • MSQ Emotional Function domain score • MSQ total score • PGI-I • MIDAS total score Responder analysis: • 30% response rate • Based on PGI-S • Based on MSQ Role Function–Restrictive • Based on MIDAS
Method of analysis	The primary analysis was performed using a restricted maximum likelihood-based mixed models repeated measures (MMRM) technique and includes the fixed categorical effects of treatment, pooled country, medication overuse (yes/no), concomitant prophylaxis use (yes/no), month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of migraine headache days and baseline number of migraine headache days-by-month interaction. Visit wise binary efficacy variables were analysed using a generalized linear mixed model (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis. Safety analyses were conducted in the safety population, which included data from all randomised patients who received ≥1 dose of investigational product, with analyses based on modal treatment received by the patient during the double-blind treatment phase. Categorical safety measures were analysed using Fisher's exact test. An MMRM model (including effects of treatment, month, and treatment-by-month interaction as fixed categorical variables and baseline value and baseline-by-month interaction as continuous fixed covariates) was used to analyse change from baseline in vital signs. Change from baseline to last observation carried forward endpoint in laboratory and electrocardiogram (ECG) parameters was analysed by analysis of covariance.
Subgroup analyses	A subgroup analysis was performed on REGAIN patients with history of prior treatment failures, including patients who were unsuccessfully treated with at least 2 prior preventive migraine treatments defined as lack of efficacy and/or safety/tolerability reasons (Ruff et al. 2019[2]).

8.2.2 CONQUER

Trial name	CONQUER / CGAW

<table>
<tr><td>NCT number</td><td>NCT03559257</td></tr>
<tr><td>Objective</td><td>The purpose of this study is to assess the safety and efficacy of galcanezumab in people with treatment-resistant episodic or chronic migraine</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>A Randomized, Placebo-Controlled Study of Galcanezumab in Patients with Treatment-Resistant Migraine: Double-Blind Results from the CONQUER Study (162), Mulleners, Neurology, 2020[5]</td></tr>
<tr><td>Study type and design</td><td>CONQUER (CGAW) was a phase IIIb, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial. Patients who met all criteria for enrolment were randomised to treatment groups based on a computer-generated random sequence using an interactive web-response system. Patients, investigators and the sponsor were all blinded to treatment allocation.</td></tr>
<tr><td>Follow-up time</td><td>3-month double-blind randomised period, followed by a 3-month open-label treatment period</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Patients with episodic or chronic migraine who had failed 2 to 4 standard-of-care migraine preventive medication categories in the past 10 years due to inadequate efficacy and/or safety/tolerability reasons.

Inclusion Criteria:
• Have a diagnosis of migraine or chronic migraine.
• History of migraine headaches at least 1 year prior to screening, with onset prior to age 50.
• Have failed previous migraine preventive medications in the past 10 years due to inadequate efficacy or tolerability.

Exclusion Criteria:
• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product.
• Current use or prior exposure to galcanezumab or another calcitonin gene-related peptide (CGRP) antibody.
• History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine).
• Pregnant or nursing.</td></tr>
<tr><td>Intervention</td><td>Total population (CM+EM):
N=462
galcanezumab 120 mg SC, once monthly (with 240-mg loading dose) n=232
placebo SC, once monthly n=230

CM subpopulation:
N=193
galcanezumab 120 mg SC, once monthly (with 240-mg loading dose) n=95
placebo SC, once monthly n=98

Open-label period (3 months):
Galcanezumab 120 mg SC, once monthly (patients previously assigned to placebo will receive initial loading dose of galcanezumab 240 mg)</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>EM only population (n=269)</th><th>CM only population (n=193)</th><th>EM/CM combined (n=462)</th></tr>
<tr><td>Age, years</td><td>46.09 (11.46)</td><td>45.32 (12.36)</td><td>45.77 (11.83)</td></tr>
</table>
</td></tr>
</table>

	Females, n (%)	229 (85.13)	168 (87.05)	397 (85.93)
	BMI, kg/m^2	25.71 (5.24)	25.84 (5.91)	25.76 (5.52)
	Years since migraine diagnosis	22.30 (12.88)	24.56 (14.35)	23.24 (13.54)
	Migraine with aura, n (%)	120 (44.61)	84 (43.52)	204 (44.16)
	Number of monthly MHDs	9.34 (2.82)	18.65 (4.69)	13.23 (5.91)
	Number of monthly days with acute medication use	9.53 (3.66)	16.22 (6.43)	12.33 (5.99)
	Number of monthly headache days	10.77 (2.80)	20.91 (4.43)	15.01 (6.15)
	Number of monthly ICHD MHDs[a]	7.20 (3.67)	14.28 (6.92)	10.16 (6.32)
	Number of monthly migraine attacks	5.69 (1.76)	6.10 (2.18)	5.86 (1.95)
	MSQ Role Function–Restrictive domain score	47.56 (15.95)	41.15 (18.41)	44.89 (17.29)
	PGI-S rating	4.44 (1.10)	4.87 (1.31)	4.62 (1.21)
	MIDAS total score	39.26 (30.60)	67.18 (56.97)	50.93 (45.68)
	Prior migraine preventive medication categories failed in past 10 years, n (%)[b]			
	Failed 1	2 (0.74)	5 (2.59)	7 (1.52)
	Failed 2	167 (62.08)	102 (52.85)	269 (58.23)
	Failed 3	78 (29.00)	61 (31.61)	139 (30.09)
	Failed 4	22 (8.18)	24 (12.44)	46 (9.96)
	Failed 5	0 (0)	1 (0.52)	1 (0.22)
	Number of prior migraine preventive medications failed in past 10 years	3.06 (1.32)	3.69 (1.89)	3.32 (1.61)

Data are mean (SD) unless otherwise stated.
[a]Definition does not include probable migraine.
[b]Medication categories include those listed in study inclusion criteria: propranolol or metoprolol; topiramate; valproate or divalproex; amitriptyline; flunarizine; candesartan; onabotulinumtoxin A or B; medication locally approved for prevention of migraine.
BMI, body mass index; CM, chronic migraine; EM, episodic migraine; ICHD, International Classification of Headache Disorders; MHD, migraine headache days; MIDAS, Migraine Disability Assessment; MSQ, Migraine-Specific Quality of Life Questionnaire; PGI-S, Patient's Global Impression of Severity.

Primary and secondary endpoints	The primary endpoint was overall mean change from baseline in the number of monthly MHDs during the 3-month double-blind treatment period in the total population (combined EM and CM) Key secondary endpoints: All key secondary endpoints were tested both in the total population (episodic and chronic migraine) and in the episodic and chronic subpopulations, unless otherwise specified.

	• The overall mean change from baseline in the number of monthly headache days during the 3-month double-blind treatment phase
	• The percentage of patients with ≥50% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
	• The mean change from baseline in the Role Function-Restrictive domain score of the MSQ v2.1 at Month 3
	• The percentage of patients with ≥75% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
	• The percentage of patients with 100% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase
	
	Other secondary endpoints
	• Changes from baseline at month 3 on the following measures:
	  ○ MIDAS total score and individual items
	  ○ MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores
	  ○ HCRU and Employment Status
	  ○ EQ-5D-5L
	  ○ MIBS-4
	• WPAI
	• Mean change from baseline in the PGI-S until the LOCF endpoint
	• The overall mean change from baseline in the number of monthly migraine attacks during the 3-month double-blind treatment phase in patients with episodic migraine
	• The percentage of chronic migraine patients with ≥30% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
	Analysis of: TEAEs, SAEs, discontinuation due to AEs, discontinuation rates, vital signs and weight, ECGs, laboratory measurements

Method of analysis	Analyses were conducted on the ITT population, which included data from all randomised patients who received ≥1 dose of study medication and was based on the treatment to which the patient was randomised regardless of whether they received a different treatment. Continuous efficacy variables with repeated measures were analysed using MMRM methods. The MMRM included the fixed categorical effects of treatment, baseline migraine headache day frequency category (low EM, high EM, and CM), pooled country, month, and treatment-by-month interaction; continuous fixed covariates were baseline and baseline-by-month interaction. For the primary endpoint, the baseline migraine headache day frequency category was excluded from the covariates since the continuous baseline monthly MHD value is already in the model. Like the pivotal phase III trials, the primary and key secondary endpoints were tested using a gated testing approach to control for type 1 error. If the null hypothesis was rejected for the primary endpoint, key secondary endpoints were sequentially tested following a gatekeeping hierarchy starting with the comparison of change in migraine headache days between treatment groups based on the EM subpopulation. If the null hypothesis was rejected for that comparison, then the comparison of 50% response rate between treatment groups was tested in the total population. Rejection of the null hypothesis resulted in testing of the next comparison in the sequence (50% response rate in the EM subpopulation). The same pattern was followed until the null hypothesis is accepted for an endpoint, at which point any further testing ceased for the key secondary objectives. The gatekeeping sequence was not used for any of the other secondary or tertiary endpoints.

	Safety analyses were conducted on the safety population, which included all randomised patients who received ≥1 dose of study medication. Analysis was conducted based on the treatment the patient received.
Subgroup analyses	Subgroups from the ITT population, episodic subpopulation, chronic subpopulation, high frequency episodic (HFEM) subpopulation, and pooled HFEM and chronic subpopulation were included in the subgroup analysis. *ITT episodic subpopulation*: All patients with episodic migraine who were randomized and received at least 1 dose of investigational product *ITT chronic subpopulation*: All patients with chronic migraine who were randomized and received at least 1 dose of investigational product

8.2.3 Study 295

Trial name	Study 295
NCT number	NCT02066415
Objective	To evaluate the effect of erenumab compared to placebo on the change from baseline in the number of monthly migraine days in adults with chronic migraine.
Publications – title, author, journal, year	Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial, Tepper, Lancet Neurol., 2017[6] Early onset of efficacy with erenumab in patients with episodic and chronic migraine, Schwedt, J Headache Pain, 2018[7] Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study, Ashina, Cephalalgia, 2018[8] Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study, Lipton, Neurology, 2019[9]
Study type and design	This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2 study. Enrolled patients were assigned 3:2:2 to placebo, erenumab 70 mg or erenumab 140 mg monthly for 3 months (12 weeks) via interactive response technology. The investigators, patients and sponsor were masked to treatment assignment. Participants who completed the 12-week double-blind treatment phase of Study 20120295 were eligible to enrol in an open-label extension study (Study 20130255; NCT02174861). The study is completed.
Follow-up time	Patients were followed up for safety for 12 weeks after end of treatment. Results from the 12-week double-blind phase of the study are presented here.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • History of at least 5 attacks of migraine without aura and/or migraine with visual sensory, speech and/or language, retinal or brainstem aura. • History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine day. • ≥ 4 distinct headache episodes, each lasting ≥ 4 hours OR if shorter, associated with use of a triptan or ergot-derivative on the same calendar day based on the eDiary calculations. • Demonstrated at least 80% compliance with the eDiary. Exclusion Criteria: • History of cluster headache or hemiplegic migraine headache

<table>
<tr><td></td><td>

Unable to differentiate migraine from other headaches
Failed > 3 medication categories due to lack of efficacy for prophylactic treatment of migraine.
Received botulinum toxin in head or neck region within 4 months prior to screening.
Used a prohibited migraine prophylactic medication, device or procedure within 2 months prior to the start of the baseline phase

</td></tr>
<tr><td>Intervention</td><td>656 patients were randomly assigned to placebo (n=281), erenumab 70 mg (n=188) and erenumab 140 mg (n=187). Participants received subcutaneous injections on day 1 and at weeks 4 and 8 by in the double-blind treatment phase.
609 patients continued in the follow up study, where all patients received erenumab by subcutaneous injections.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo (n=286)</th><th>Erenumab 70 mg (n=191)</th><th>Erenumab 140 mg (n=190)</th></tr>
<tr><td>Age (Years)</td><td>42.1 (11.3)</td><td>41.4 (11.3)</td><td>42.9 (11.1)</td></tr>
<tr><td>Range</td><td>18.66*</td><td>18.64</td><td>18.64</td></tr>
<tr><td>Sex</td><td></td><td></td><td></td></tr>
<tr><td>Women</td><td>226 (79%)</td><td>166 (87%)</td><td>160 (84%)</td></tr>
<tr><td>Men</td><td>60 (21%)</td><td>25 (13%)</td><td>30 (16%)</td></tr>
<tr><td>Body-mass index (kg/m2)</td><td>26.3 (5.1)</td><td>26.0 (5.3)</td><td>26.0 (5.4)</td></tr>
<tr><td>Age at migraine onset (years)</td><td>20.4 (10.0)</td><td>21.1 (10.5)</td><td>21.5 (10.6)</td></tr>
<tr><td>Disease duration (years)</td><td>22.2 (12.6)</td><td>20.7 (12.8)</td><td>21.9 (11.8)</td></tr>
<tr><td>History of migraine with aura</td><td>124 (43%)</td><td>81 (42%)</td><td>71 (73%)</td></tr>
<tr><td>Medication overuse</td><td>117 (41%)</td><td>79 (41%)</td><td>78 (41%)</td></tr>
<tr><td>History of previous preventive treatment failure</td><td></td><td></td><td></td></tr>
<tr><td>No drug failures ±</td><td>86 (30%)</td><td>64 (34%)</td><td>64 (34%)</td></tr>
<tr><td>Failure of >1 drugs ⌊</td><td>200 (70%)</td><td>127 (67%)</td><td>126 (66 %)</td></tr>
<tr><td>Failure of >2 drugs ⌊</td><td>142 (50%)</td><td>93 (49%)</td><td>92(48%)</td></tr>
<tr><td>Previous use of preventive drug topiramate</td><td>150 (52%)</td><td>89 (47%)</td><td>97 (51%)</td></tr>
<tr><td>Previous use of onabotulinum toxin</td><td>65 (23%)</td><td>50 (26%)</td><td>43 (23%)</td></tr>
<tr><td>Baseline period</td><td></td><td></td><td></td></tr>
<tr><td>Monthly migraine days</td><td>18.2 (4.7)</td><td>17.9 (4.4)</td><td>17.8 (4.7)</td></tr>
<tr><td>Monthly headache hours</td><td>235.3 (126.1)</td><td>223.6 (126.6)</td><td>215.1 (123.5)</td></tr>
<tr><td>Monthly headache days</td><td>21.1 (3.9)</td><td>20.5 (3.8)</td><td>20.7 (3.8)</td></tr>
<tr><td>Monthly migraine attacks</td><td>4.2 (1.7)</td><td>4.5 (1.7)</td><td>4.3 (1.6)</td></tr>
<tr><td>Monthly acute migraine-specific drug use days</td><td>9.5 (7.6)</td><td>8.8 (7.2)</td><td>9.7 (7.0)</td></tr>
<tr><td>Acute migraine-specific drug use‖</td><td>225 (79%)</td><td>143 (75%)</td><td>149 (78%)</td></tr>
</table>
Data are mean (SD) or n (%) unless otherwise stated. Table based on randomisation analysis set. Come percentages do not total 100% because of rounding. *One patient was 65 years old at screening but turned 66 before randomisation. Ł includes native Hawaiian and other Pacific Islander, multiple ethnic origins, or other. ± includes treatment-naive patients and patients who had previous use of preceptive drugs, but who did not have treatment failure due to lack of efficacy or tolerability. ⌊Failure due to lack of efficacy or poor tolerability. ‖ Triptans and ergot derivatives only.
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary Endpoint:

Change from baseline in Monthly Migraine Days

</td></tr>
</table>

	Secondary Endpoints: • Percentage of Participants With at Least a 50% Reduction in Monthly Migraine Days from Baseline • Change from Baseline in Monthly Acute Migraine-specific Medication Treatment Days • Change from Baseline in Cumulative Monthly Headache Hours • Number of Participants with Adverse Events • Number of Participants Who Developed Antibodies to Erenumab.
Method of analysis	The randomisation analysis set included all patients who were randomly assigned to treatment or placebo in the study. The efficacy analysis set included patients in the randomisation analysis set who received at least one dose of investigational product and completed at least one post-baseline monthly electronic diary measurement. For all analyses, patients were analysed according to the randomised treatment. A sequential testing procedure, specifically the hierarchical gate-keeping procedures and Hochberg method, was used to maintain the two-sided study-wise type I error at 0.05 for the two erenumab doses and the primary and secondary endpoints. The test for erenumab superiority in the primary endpoint (change from baseline in mean monthly migraine days) was tested separately at a significance level of 0.04 for the erenumab 70 mg group and 0.01 for the erenumab 140 mg group. If the primary endpoint was significantly different from placebo at each dose level, the secondary endpoints were to be tested separately using the Hochberg method at the same significance levels. If the secondary endpoints were significantly different for an erenumab treatment group compared with placebo, the corresponding significance level was to be carried over to the hypothesis testing of the primary endpoint for the other erenumab treatment group, if it was not significantly different from placebo under the original significance level (0.04 for the 70 mg group and 0.01 for the 140 mg group). If the secondary endpoints were negatively correlated, the Holm method was used for the corresponding tests rather than the Hochberg method. For the primary endpoint at week 12, the least-squares mean at each timepoint was calculated with a linear mixed effects model including treatment group, baseline monthly migraine days, stratification factors (region [North America vs Europe] and medication overuse [presence vs absence]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The continuous secondary endpoints were analysed with the same method as for the primary endpoint. We reported the least-squares mean change from baseline for each treatment group, treatment difference compared with placebo, 95% CI, and p values for pairwise comparison. For the 50% responder secondary endpoint, we used a stratified Cochran-Mantel-Haenszel test after the missing data were imputed as non-response. We reported adjusted odds ratios (OR) compared with placebo, 95% CI, and p values. The safety analysis set included all randomly assigned patients who received at least one dose of investigational product. For all analyses, patients were analysed according to the randomized treatment.
Subgroup analyses	Pre-specified (failed ≥1 and failed ≥2) and post-hoc (failed ≥ 3) subgroup analyses were conducted, based on number of prior treatment failure(s). Effect (change in monthly migraine days, MMD, and MSMD and ≥50% and ≥75 responder rates) in patients who had failed ≥1, ≥2) or ≥3 prior treatments due to lack of efficacy and/or tolerability was compared to that of the overall study population. For continuous endpoints, adjusted analyses utilized a generalized linear mixed model, which included treatment, visit, treatment by visit interaction, the two stratification factors (region and medication overuse status) and baseline value as covariates, and assumed a first-order autoregressive covariance structure. Observed data were used in analyses without imputation for missing data. For dichotomous endpoints, odds ratios were estimated from a stratified Cochran- Mantel-Haenszel test after imputation of missing data as nonresponse. The main study was not designed or powered to compare differences in efficacy between subgroups. A post-hoc analysis was conducted, based on responders versus non-responders (response defined as ≥50% reduction in MMD). Effect (MMDs, migraine-specific medication treatment days (MSMD), the Headache Impact Test (HIT-6™) scores, Migraine Disability Assessment

	(MIDAS) scores, and Migraine-Specific Questionnaire (MSQ) scores) was compared between responders and non-responders. Furthermore, a subgroup analysis was performed in patients with medication overuse at baseline. Data were presented in congress abstracts.

8.2.4 HALO CM

Trial name	HALO CM
NCT number	NCT02621931
Objective	The purpose of this study is to evaluate the efficacy, safety, and tolerability of monthly and quarterly subcutaneous (sc.) injections of fremanezumab compared with s.c injections of placebo in patients with chronic migraine (CM).
Publications – title, author, journal, year	Fremanezumab for the preventive treatment of chronic migraine. Silberstein et al., NEJM, 2017.
Study type and design	Randomized, double-blind, placebo-controlled, parallel-controlled, parallel-group trial phase 3 trial. Eligible patients were randomly assigned in a 1:1:1 ratio to receive either (1) a single higher dose of fremanezumab intended to support a quarterly dose regimen, (2) fremanezumab monthly, or (3) placebo. Patients, investigators, the sponsor, and trial staff were unaware of the trial-group assignments. The study is completed.
Follow-up time	Patients were seen at five scheduled visits for protocol-specified evaluations: at screening, baseline, weeks 4 and 8, and week 12.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Males or females aged 18 to 70 years, inclusive, with migraine onset at ≤50 years of age • Patient signs and dates the informed consent document • Patient has history of migraine according to International Classification of Headache Disorders, or clinical judgment suggests a migraine diagnosis • 85% e-diary compliance • Total body weight between 99 and 250 lbs Exclusion Criteria: • Clinically significant haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator • Evidence or medical history of clinically significant psychiatric issues, including any suicide attempt in the past, or suicidal ideation with a specific plan in the past 2 years • History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [e.g. cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism • Known infection or history of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection • Past or current history of cancer in the last 5 years, except for appropriately treated nonmelanoma skin carcinoma • Pregnant or nursing females • History of hypersensitivity reactions to injected proteins, including monoclonal antibodies

<table>
<tr><td></td><td>

- Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months prior to study drug administration or 5 half-lives, whichever is longer

</td></tr>
<tr><td>Intervention</td><td>376 participants randomized to the fremanezumab 675 mg/placebo/placebo treatment (quarterly dosing) arm received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0, and placebo as a single 1.5-mL injection on Days 28 and 56.
375 participants received matching placebo.</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics (total population)

<table>
<tr><th>Characteristic</th><th>Fremanezumab (quarterly dosing)</th><th>Fremanezumab (monthly dosing)</th><th>Placebo</th></tr>
<tr><td>Age, year</td><td>42.0 ±12.4</td><td>40.6 ±12.0</td><td>41.4 ±12.0</td></tr>
<tr><td>Body mass index</td><td>26.6 ±5.4</td><td>26.5 ±5.1</td><td>26.5 ±5.0</td></tr>
<tr><td>Female sex, n (%)</td><td>331 (88)</td><td>330 (87)</td><td>330 (88)</td></tr>
<tr><td>Disease history</td><td></td><td></td><td></td></tr>
<tr><td>Time since initial migraine diagnosis, year</td><td>19.7 ±12.8</td><td>20.1 ±12.0</td><td>19.9 ±12.9</td></tr>
<tr><td>Current use of preventive medication, n (%)</td><td>77 (2)</td><td>85 (22)</td><td>77 (21)</td></tr>
<tr><td>Current use of acute headache medication, n (%)</td><td>359 (95)</td><td>360 (95)</td><td>358 (95)</td></tr>
<tr><td>Previous use of topiramate, n (%)</td><td>106 (28)</td><td>117 (31)</td><td>117 (31)</td></tr>
<tr><td>Previous use of onabotulinumtoxinA, n (%)</td><td>66 (18)</td><td>50 (13)</td><td>49 (13)</td></tr>
<tr><td>Disease characteristics during 28-day prevention period</td><td></td><td></td><td></td></tr>
<tr><td>Headache days</td><td>13.2 ±5.5</td><td>12.8 ±5.8</td><td>13.3 ± 5.8</td></tr>
<tr><td>Days with headache of any severity and duration</td><td>20.4 ±3.9</td><td>20.3 ±4.3</td><td>20.3 ± 4.2</td></tr>
<tr><td>Migraine days</td><td>16.2 ±4.9</td><td>16.0 ±4.3</td><td>16.4 ±5.2</td></tr>
<tr><td>Days of use of any acute headache medications</td><td>13.1 ±6.8</td><td>13.1 ±7.2</td><td>13.0 ±6.9</td></tr>
<tr><td>Days of use of migraine-specific acute headache medications</td><td>11.3 ±6.2</td><td>11.1 ±6.0</td><td>10.7 ±6.3</td></tr>
<tr><td>HIT-6 score</td><td>64.3 ±4.7</td><td>64.6 ±4.4</td><td>64.1 ±4.8</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary end point was the mean change in the average number of headache days per month, comparing the baseline 28-day preintervention period with the 12-week period after the first dose of the trial regimen.
Secondary end points were

- the mean change from baseline in the average number of migraine days per month
- the percentage of patients with a reduction of at least 50% in the average number of headache days per month
- the mean change from baseline in the average number of days per month in which acute headache medication was used during the 12-week period after the first dose.

</td></tr>
</table>

	• the mean change from baseline in the number of headache days during the 4-week period after the first dose in all the patients and during the 12-week period after the first dose in patients not receiving concomitant preventive medication • • the mean change in the score on the six-item Headache Impact Test (HIT-6; scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability) 15 from baseline (day 0) to 4 weeks after administration of the last dose of the trial regimen. Safety and side-effect profiles were evaluated according to reported adverse events, vital signs (systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate), physical examination, 12-lead electrocardiography, clinical laboratory tests (serum chemical, hematologic, coagulation, and urinalysis tests), systematic assessments of local injection-site reactions (erythema, induration, ecchymosis, and pain, all evaluated both immediately and 1 hour after dose administration), concomitant medication use, and suicidal ideation and behaviour as assessed by means of scores on the electronic Columbia–Suicide Severity Rating Scale.
Method of analysis	Efficacy analyses were conducted in the modified intention-to-treat population, which included all randomly assigned patients. Safety analyses included all randomly assigned patients who received at least one dose of a trial regimen. The primary end point was analysed with the use of an analysis of covariance. The Wilcoxon rank-sum test was performed as the primary analysis if there was deviation from the normality assumption as assessed by means of the Shapiro–Wilk test. The same analyses were used for relevant secondary end points. For the percentage of patients with a reduction of at least 50% in the average number of headache days per month, the Cochran–Mantel–Haenszel test was used, with baseline use of preventive medication (yes or no) as a stratification variable.
Subgroup analyses	A small subgroup of patients (approximately 30%) was allowed to use concomitant migraine preventive medications. Analyses for the subgroup not receiving concomitant was performed; mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug in patients not receiving concomitant migraine preventive medications.

8.2.5 Bigal et al. 2015

Trial name	Assessment of LBR-101 In Chronic Migraine
NCT number	NCT02021773
Objective	The purpose of the study is to determine whether monthly subcutaneous administration of LBR-101 is safe and provides migraine prevention in patients with chronic migraine.
Publications – title, author, journal, year	Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Bigal et al., Lancet neurology, 2015 TEV-48125 for the preventive treatment of chronic migraine: Efficacy at early time points, Bigal, Neurology, 2016 Fremanezumab as Add-On Treatment for Patients Treated with Other Migraine Preventive Medicines, Cohen, Headache, 2017 Fremanezumab for preventive treatment of migraine: Functional status on headache-free days, VanderPluym, Neurology, 2018

<table>
<tr><td></td><td>Sustained reductions in migraine days, moderate-to-severe headache days and days with acute medication use for HFEM and CM patients taking fremanezumab: Post-hoc analyses from phase 2 trials, Halker Singh, Cephalalgia, 2019</td></tr>
<tr><td>Study type and design</td><td>In this multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group phase 2b study, we enrolled men and women (aged 18-65 years) from 62 sites in the USA who had chronic migraine. Using a randomisation list generated by a central computerised system and an interactive web response system, we randomly assigned patients (1:1:1, stratified by sex and use of concomitant preventive drugs) to three 28-day treatment cycles of subcutaneous TEV-48125 675/225 mg (675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles), TEV-48125 900 mg (900 mg in all three treatment cycles), or placebo. Investigators, patients, and the funder were blinded to treatment allocation. The study is completed.</td></tr>
<tr><td>Follow-up time</td><td>Time frame: 12 weeks</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion Criteria:
Males or females aged 18 to 65 years of age.
A signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study including any known and potential risks and available alternative treatments.
Chronic migraine meeting the diagnostic criteria listed in the International Classification of Headache Disorders (ICHD-III beta version, 2013)
Body Mass Index (BMI) of 17.5 to 37.5 kg/m2, and a total body weight between 50 kg and 120 kg inclusive.
Demonstrated compliance with the electronic headache diary during the run-in period headache data on a minimum of 22/28 days (80% diary compliance)
Exclusion Criteria:
Onset of chronic migraine after the age of 50 years.
Subject has received onabotulinum toxin A for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 6 months prior to study entry.
Subject is using medications containing opioids (including codeine) or barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) on more than 4 days per month for the treatment of migraine or for any other reason.
Failed > 2 medication categories or > 3 preventive medications (within two medication categories) due to lack of efficacy for prophylactic treatment of episodic or chronic migraine after an adequate therapeutic trial
Treatment with an investigational drug or device within 30 days of study entry or any prior exposure to a monoclonal antibody targeting the CGRP pathway.</td></tr>
<tr><td>Intervention</td><td>277 participants randomized to the subcutaneous LBR-101. Between Jan 8, 2014, and Aug 27, 2014, we enrolled 264 participants: 89 were randomly assigned to receive placebo, 88 to receive 675/225 mg TEV-48125, and 87 to receive 900 mg TEV-48125.</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics (total population)

<table><tr><th>Characteristic</th><th>Placebo (n=89)</th><th>TEV-48125 675/225 mg (n=88)</th><th>TEV-48125 900 mg (n=86)</th></tr><tr><td>Age, years</td><td>40·7 (11·5)</td><td>40·0 (11·6)</td><td>41·5 (12·9)</td></tr><tr><td>Height, cm</td><td>166·4 (8·1)</td><td>165·4 (8·3)</td><td>165·7 (7·6)</td></tr><tr><td>Body mass index, kg/m²</td><td>25·7 (4·5)</td><td>27·0 (5·2)</td><td>26·6 (5·3)</td></tr><tr><td>Female sex, n (%)</td><td>76 (85%)</td><td>76 (86%)</td><td>75 (86%)</td></tr></table></td></tr>
</table>

	Headache-hours of any severity per month	169·1 (113·11)	159·1 (90·73)	157·7 (108·16)
	Headache-hours of at least moderate severity per month	91·90 (74·68)	90·7 (59·71)	96·20 (94·42)
	Headache-days of at least moderate severity per month	13·9 (5·6)	13·8 (6·3)	13·1 (5·9)
	Migraine-days per month	16·8 (5·0)	17·2 (5·4)	16·4 (5·3)
	Days of acute drug use per month	15·7 (6·2)	15·1 (7·0)	16·2 (6·7)
	Days of triptan use per month	10·0 (5·3)	9·2 (5·6)	11·8 (6·0)
	Years of migraine	20·4 (13·1)	15·8 (11·2)	18·8 (12·2)
	Preventive drug use (yes)	38 (43%)	35 (40%)	33 (38%)
	Data are mean (SD) or number of patients (%)			
Primary and secondary endpoints	The primary endpoints: 1. Mean change from baseline in the number of monthly cumulative headache hours of any severity on headache days relative to the 28-day post-treatment period ending with week 12 [Time Frame: 12 weeks after first dose of blinded study drug] 2. Safety as determined by the presence of Adverse events by treatment group [Time Frame: 12 weeks after first dose of blinded study drug] Secondary efficacy endpoint: Mean change from baseline in the number of headache days of at least moderate severity relative to the 28-day post-treatment period ending with week 12. [Time Frame: 12 weeks after first dose of blinded study drug]			
Method of analysis	Sample size and power were calculated using the PASS version 11 statistical software developed by NCSS LLC (Kaysville, UT, USA). To detect with at least 80% power a mean change from baseline in the number of headache hours of at least 35 h (SD≤80), at least 30 h (SD≤60), or at least 25 h (SD≤40), we aimed to allocate at least 75 participants to each group. To impute values for missing calendar day entries in a given month, scores of months with 20–27-day entries were prorated. Scores for months with less than 10 days of diary data were estimated using a modified last observation carried forward approach, calculated as the patient's previous 28 day period mean value of day entries multiplied by the ratio of the mean for all patients in the same period and divided by the mean number of day entries for all patients in the previous 28 day period. Scores for months with 10–19 days of diary data were estimated using an average of both methods. The primary, secondary, and exploratory efficacy endpoints were analysed using the mixed-effects model repeated measurement (MMRM) analysis method. Change from baseline in the variable of interest (e.g., headache-hours) at weeks 1–4, weeks 5–8, and weeks 9–12 was the dependent variable; preventive drug use (yes or no), sex, visit number, treatment, and treatment-by-visit interaction were fixed factors; baseline value of the variable of interest and years since disease onset were covariates; and patient was treated as a random effect. We used unstructured covariance matrix for repeated findings within patients and constructed 95% CIs for the least square mean difference between groups. All statistical tests were two-sided at a type I error (α) of 0·05. We used the Hochberg approach to adjust for multiplicity for the analysis of the primary and secondary efficacy variables. All efficacy variables were analysed for the intention-to-treat population, which included all patients who were randomly assigned to treatment group, received at least one dose of study drug, and provided at least one endpoint measurement. We used SAS version 9.3 for all statistical analyses.			
Subgroup analyses	A post-hoc subgroup analysis was performed indicating that there was a significant difference in number of days on which triptans were used between the placebo group and each of the TEV-48125 dose.			

8.2.6 FOCUS

Trial name	Assessment of LBR-101 In Chronic Migraine
NCT number	NCT03308968
Objective	The purpose of this study is to evaluate the efficacy, safety, and tolerability of monthly and quarterly subcutaneous (s.c) injections of fremanezumab compared with s.c injections of placebo in participants with chronic migraine (CM) or episodic migraine (EM) who have responded inadequately to 2 to 4 classes of prior preventive treatments.
Publications – title, author, journal, year	Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial, Ferrari *et al.*, Lancet, 2019[17]
Study type and design	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study with an Open-Label Period. Approximately equal numbers of participants from each subgroup (CM and EM) are randomized in blinded-fashion 1:1:1 into one of 3 treatments for the subgroup - 2 active treatments and 1 placebo treatment- consisting of monthly injections for 3 months (up to Week 12). Then all participants continue into an open-label extension of 3 months (up to Week 24) during which everyone is administered s.c injections of fremanezumab.
Follow-up time	Time frame: 12 weeks with 12 weeks open-label extension
Population (inclusion and exclusion criteria)	Inclusion Criteria: • The participant has a diagnosis of migraine with onset at ≤50 years of age. • Body weight ≥45 kilograms. • The participant has a history of migraine for ≥12 months prior to screening. • Women of childbearing potential (WOCBP) whose male partners are potentially fertile (that is; no vasectomy) must use highly effective birth control methods for the duration of the study and the follow-up period and for 6.0 months after discontinuation of investigational medicinal product (IMP) • Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [that is; vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, acceptable birth control methods for the duration of the study and for 6.0 months after discontinuation of the investigational medicinal product (IMP). o Additional criteria apply, please contact the investigator for more information. Exclusion Criteria: • At the time of screening visit, participant is receiving any preventive migraine medications, regardless of the medical indication for more than 5 days and expects to continue with these medications. • Participant has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit. • The participant has used an intervention/device (for example, scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening. • The participant uses triptans/ergots as preventive therapies for migraine. • Participant uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (for example, 81 mg) used for cardiovascular disease prevention is allowed.
Intervention	Between Nov 10, 2017, and July 6, 2018, 838 participants with episodic (329 [39%]) or chronic (509 [61%]) migraine were randomly assigned to placebo (n=279), quarterly fremanezumab (n=276), or monthly fremanezumab (n=283)

Baseline characteristics	Baseline characteristics (total population)

	Placebo (n=279)	Quarterly fremanezumab (n=276)	Monthly fremanezumab (n=283)
Age (years)	46·8 (11·1)	45·8 (11·0)	45·9 (11·1)
Age range			
18–45 years	121 (43%)	125 (45%)	128 (45%)
46–65 years	149 (53%)	144 (52%)	149 (53%)
>65 years	9 (3%)	7 (3%)	6 (2%)
Sex			
Male	46 (16%)	47 (17%)	45 (16%)
Female	233 (84%)	229 (83%)	238 (84%)
Race			
White	262 (94%)	262 (95%)	262 (93%)
Black or African-American	2 (<1%)	2 (<1%)	4 (1%)
Asian	1 (<1%)	0	3 (1%)
American Indian or Alaska native	0	0	1 (<1%)
Other	1 (<1%)	2 (<1%)	1 (<1%)
Not reported	13 (5%)	10 (4%)	12 (4%)
Weight (kg)	71·4 (13·7)	70·7 (13·4)	71·0 (13·7)
Height (cm)	167·7 (9·0)	167·7 (8·1)	167·3 (7·7)
Body-mass index (kg/m²)	25·3 (4·1)	25·1 (4·1)	25·3 (4·3)
Time since initial migraine diagnosis (years)	24·3 (13·6)	24·3 (12·8)	24·0 (13·7)
Migraine classification			
Episodic	112 (40%)	107 (39%)	110 (39%)
Chronic	167 (60%)	169 (61%)	173 (61%)
Migraine preventive medications failed in the past 10 years			
β blockers	160 (57%)	146 (53%)	165 (58%)
Anticonvulsants	186 (67%)	213 (77%)	216 (76%)
Tricyclic antidepressants	137 (49%)	124 (45%)	127 (45%)
Flunarizine	59 (21%)	41 (15%)	45 (16%)
Candesartan	51 (18%)	53 (19%)	46 (16%)
OnabotulinumtoxinA	76 (27%)	75 (27%)	71 (25%)
Valproic acid	83 (30%)	86 (31%)	92 (33%)
Number of previous preventive medication classes failed			
2	142 (51%)	140 (51%)	133 (47%)
3	82 (29%)	85 (31%)	98 (35%)
4	54 (19%)	49 (18%)	50 (18%)
Monthly number of migraine days at baseline	14·3 (6·1)	14·1 (5·6)	14·1 (5·6)
Monthly number of headache days of at least moderate severity at baseline	12·8 (5·9)	12·4 (5·8)	12·7 (5·8)
Monthly days of use of any acute headache medication at baseline	12·3 (6·3)	12·8 (6·2)	12·2 (6·0)

Data are mean (SD) or n (%).

Primary and secondary endpoints	The primary endpoints: Change from Baseline in Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Fremanezumab

	Secondary outcomes included the change from baseline in the monthly average number of migraine days during the 4-week period after the first dose of study drug and the proportions of participants with a 50% or greater response (i.e., participants achieving a ≥50% reduction in the monthly average number of migraine days during the 4-week and 12-week periods after the first dose of study drug). Additional secondary outcomes were the change from baseline in the monthly average number of headache days of at least moderate severity during the 4-week and 12-week periods after the first dose of study drug and the change from baseline in the days of use of any acute headache medications during the 12-week period after the first dose of study drug
Method of analysis	Demographic and baseline characteristics were summarised descriptively. The primary efficacy outcome was analysed with an analysis of covariance (ANCOVA) method, with treatment, sex, region, special group of treatment failure, migraine classification, and treatment- by-migraine classification interaction as fixed effects; and baseline number of migraine days and years since onset of migraine as covariates. Sensitivity analyses were done with a mixed-effects repeated measures analysis model, including treatment, sex, region, special group of treatment failure, migraine classification, month, treatment-by-migraine classification interaction, treatment-by-month inter action, and treatment-by- migraine classification-by-month inter action as fixed effects; baseline value and years since onset of migraine as covariates; and participant as a random effect. The least-squares mean (LSM) change from baseline with standard error (SE) is presented for each treatment group, and the LSM difference versus placebo with 95% CI is presented for both fremanezumab dosing groups. Continuous secondary and exploratory efficacy outcomes were analysed similarly to the primary efficacy outcome. For the proportion of responders, a logistic regression model was used with the following effects: treatment, sex, region, special group of treatment failure (yes or no), and migraine classification (chronic or episodic). Stratification factors (as randomised) were used in the model. Participants who discontinued treatment early were considered non-responders for the overall analysis and for each month after discontinuation.
Subgroup analyses	

Results per study

8.2.7 Table A3a Results of study REGAIN

Trial name:	REGAIN										
NCT number:	NCT02614261										
				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		
Mean change from baseline in monthly migraine days	Galcanezumab	72	-5.35 (-6.76; -3.93)	-23.3%	-36.4%; 21.1%	0.0001	NA			Subgroup analyses for repeated continuous measures were conducted using restricted maximum likelihood-based mixed models with repeated measures (MMRM).	Ruff *et al.* 2019[2]
	Placebo	174	-1.01 (-2.07; 0.05)								
Proportion of patients with ≥50% reduction in monthly migraine days	Galcanezumab	72	21/72 (29.2%)	19.96	6.99;43.42	0.0001	RR: 3.17	1.76; 5.72	0.0001	Subgroup analyses for binary measures were conducted using restricted maximum likelihood-	Ruff *et al.* 2019[2]
	Placebo	174	16/174 (9.2%)								

							based mixed models with generalized linear mixed model.	
Mean change from baseline in MSQ-RF	Galcanezumab	64	19.13 (13.39; 24.86)	8.45	1.46; 15.45	0.02	NA	Subgroup analyses for repeated continuous measures were conducted using restricted maximum likelihood-based mixed models with repeated measures (MMRM).	Ruff *et al.* 2019[2]
	Placebo	160	10.67 (6.48; 14.85)						
Mean change from baseline in MSQ-PF	Galcanezumab	NR	NR	NR			NR		
	Placebo	NR	NR						
Mean change from baseline in MSQ-EF	Galcanezumab	NR	NR	NR			NR		
	Placebo	NR	NR						
Mean change from baseline in monthly headache days	Galcanezumab	NR	NR	NR			NR		
	Placebo	NR	NR						
Mean CFB in migraine headache days with acute medication use	Galcanezumab	72	-5.81 (-7.18; -4.43)	-30.9%	-42.6%; -19.0%	0.0001	NA	Subgroup analyses for repeated continuous measures were conducted	Ruff *et al.* 2019[2]
	Placebo	167	-1.35 (-2.39; -0.30)						

									using restricted maximum likelihood-based mixed models with repeated measures (MMRM).	
Discontinuation due to AE	Galcanezumab	273	3/273 (0.109%)	0.02%	-0.014; 0.015	0.97	RR: 1.02	0.25; 4.05	0.97	Cochran-Mantel-Haenszel test for between-group comparisons, adjusting for baseline medication overuse and concurrent preventive medication use	Detke *et al.* 2018[4]
	Placebo	558	6/558 (0.107%)							

*Converted to reduction in percentage by using the mean observed event rate in the placebo arm of the study. ACR in mean change from baseline in monthly migraine days = 18.59 days and in mean CFB in migraine headache days with acute medication use 14.45 days.

8.2.8 Table A3b Results of study CONQUER

Trial name:	CONQUER										
NCT number:	NCT02614261										
				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		
Mean change from baseline in monthly migraine days	Galcanezumab	93	-5.91 (-7.20; -7.20)	-34.5%*	-12.0%; 24.7%	0.0001	NA			Pre-specified subgroup analyses for repeated continuous measures were conducted using restricted maximum likelihood-based mixed models with repeated measures (MMRM).	Mulleners *et al.* 2019[5]
	Placebo	96	-2.21 (-3.48; -0.93)								
Proportion of patients with ≥50% reduction in monthly migraine days	Galcanezumab	93	30/93 (32.3)	22.94	6,86; 54.99	0.0001	RR: 3.44	1.73; 6.85	0.0004	Subgroup analyses for binary measures were conducted using restricted maximum likelihood-based mixed models with	Mulleners *et al.* 2019[5]
	Placebo	96	9/96 (9.4)								

										generalized linear mixed model.	
Mean change from baseline in MSQ-RF	Galcanezumab	88	20.6 (16.97; 24.22)	13.90	8.94; 18.85	<0.0001	NA			Post-hoc subgroup analyses for repeated continuous measures were conducted using restricted maximum likelihood-based mixed models with repeated measures (MMRM).	Mulleners *et al.* 2019[5]
	Placebo	95	6.7 (3.21; 10.18)								
Mean change from baseline in MSQ-PF	Galcanezumab	NR	NR	NR			NR				
	Placebo	NR	NR								
Mean change from baseline in MSQ-EF	Galcanezumab	NR	NR	NR			NR				
	Placebo	NR	NR								
Mean change from baseline in monthly headache days	Galcanezumab	NR	NR	NR			NR				
	Placebo	NR	NR								
Mean CFB in migraine headache days with acute medication use	Galcanezumab	93	-5.4 (-6.61; -4.18)	-27.1%*	-38.3%; -15.8%	<0.0001	NA	NA	NA	Subgroup analyses for repeated continuous measures were conducted	Mulleners *et al.* 2019[5]

	Placebo	96	-1.38 (-2.55; -0.21)							using restricted maximum likelihood-based mixed models with repeated measures (MMRM).	
Discontinuation due to AE	Galcanezumab	95	1/95 (1.1%)	-1.05%	-1.79; 3.90	0.47	RR: 3.09	0.13; 75.02 (+0.5tc)	0.487	Cochran-Mantel-Haenszel test for between-group comparisons, adjusting for baseline medication overuse and concurrent preventive medication use	Mulleners *et al.* 2019[5]
	Placebo	98	0/98 (0%)								

*Converted to reduction in percentage by using the mean observed event rate in the placebo arm of the study. ACR in mean change from baseline in monthly migraine days = 15.93 days and in mean CFB in migraine headache days with acute medication use 14.84 days.

8.2.9 Table A3c Results of Study 295

Trial name:	Study 295										
NCT number:	NCT02066415										
				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		

Mean change from baseline in monthly migraine days	Erenumab (70+140 mg)	185	-6.2 (-7.06; -5.33)	-22.4%	-30.9%; 13.9%	<0.001	NA	NA	NA	Prespecified subgroup analysis. Continuous endpoints, adjusted analyses utilized a generalized linear mixed model, which included treatment, visit, treatment by visit interaction, the two stratification factors (region and medication overuse status) and base-line value as covariates, and assumed a first-order autoregressive covariance structure.	Ashina *et al.* 2018[8]
	Placebo	142	-2.7 (-3.72; -1.68)								
Proportion of patients with ≥50% reduction in monthly migraine days	Erenumab (70+140 mg)	185	71/185 (38.4%)	24%	15.00; 33.00	<0.001	RR: 2.72	1.75; 4.25	<0.001	For dichotomous endpoints, odds ratios were estimated from a stratified Cochran-Mantel-Haenszel test after imputation of missing data as nonresponse	Ashina *et al.* 2018[8]
	Placebo	142	20/142 (14.1%)								
Mean change from baseline in MSQ-RF	Erenumab (70+140 mg)	185	NR	NR			NR				
	Placebo	142	NR								
Mean change from baseline in MSQ-FF	Erenumab (70+140 mg)	185	NR	NR			NR				
	Placebo	142	NR								
Mean change from baseline in MSQ-EF	Erenumab (70+140 mg)	185	NR	NR			NR				
	Placebo	142	NR								

Mean change from baseline in monthly headache days	Erenumab (70+140 mg) Placebo	185 142	NR NR	NR			NR			
Mean CFB in migraine headache days with acute medication use	Erenumab (70+140 mg) Placebo	185 142	-4.75 (-5.41; -4.08) -1.3 (-2.08; -0.51)	-34.2%*	-44.2%; -24.1%	<0.001	NA	NA	NA	Continuous endpoints, adjusted analyses utilized a generalized linear mixed model, which included treatment, visit, treatment by visit interaction, the two stratification factors (region and medication overuse status) and base-line value as covariates, and assumed a first-order autoregressive covariance structure.	Ashina *et al.* 2018[8]
Discontinuation due to AE	Erenumab (70+140 mg) Placebo	184 141	0/184 (0%) 1/141 (0.7%)	-0.01	-0.03; 0.01	0.45	RR: 0.26	0.01; 6.23	0.402	For dichotomous endpoints, odds ratios were estimated from a stratified Cochran-Mantel-Haenszel test after imputation of missing data as nonresponse	Ashina *et al.* 2018[8]

*Converted to reduction in percentage by using the mean observed event rate in the placebo arm of the study. ACR in mean change from baseline in monthly migraine days = 15.6 days and in mean CFB in migraine headache days with acute medication use 10.01 days.

8.3 Results per PICO (clinical question)

8.3.1 Table A4 Results referring to clinical question 1

Results per outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
		Difference	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value	
Mean CFB in monthly migraine days	3	-4.3%	-19.3%; 10.6%	0.568	NA	NA	NA	The underlying methodology for the ITC is the Bucher et al. (1997) method, which is a frequentist approach to evidence synthesis. Continuous outcomes were assessed in terms of weighted mean difference. Binary outcomes were assessed in terms of relative risk (RR) and risk difference (RD). For binary outcomes in terms of relative risk (RR)
Proportion of patients with ≥50% reduction in monthly migraine days	3	7.68	- 13.82; 48.76	NA	RR: 1.20	0.64; 2.27	0.563	The underlying methodology for the ITC is the Bucher et al. (1997) method, which is a frequentist approach to evidence synthesis. Continuous outcomes were assessed in terms of weighted mean difference. Binary outcomes were assessed in terms of relative risk (RR) and risk difference (RD). For binary outcomes in terms of relative risk (RR)
Mean CFB in MSQ-RF		NA	NA	NA	NA	NA	NA	Results for MSQ are only reported for galcanezumab, hence a comparison is not possible.
Mean CFB in MSQ-PF		NA	NA	NA	NA	NA	NA	Results for MSQ are only reported for galcanezumab, hence a comparison is not possible.
Mean CFB in MSQ-EF		NA	NA	NA	NA	NA	NA	Results for MSQ are only reported for galcanezumab, hence a comparison is not possible.
Mean CFB in monthly headache days		NA	NA	NA	NA	NA	NA	

Mean CFB in migraine headache days with acute medication use	3	-11.9%	-35.3; 11.7%	0.324				The underlying methodology for the ITC is the Bucher et al. (1997) method, which is a frequentist approach to evidence synthesis. Continuous outcomes were assessed in terms of weighted mean difference. Binary outcomes were assessed in terms of relative risk (RR) and risk difference (RD). For binary outcomes in terms of relative risk (RR)
Discontinuation due to AE	2	2%	-2%; 4%	0.308	12.1	0.13; 1102.98	0.279	The underlying methodology for the ITC is the Bucher et al. (1997) method, which is a frequentist approach to evidence synthesis. Continuous outcomes were assessed in terms of weighted mean difference. Binary outcomes were assessed in terms of relative risk (RR) and risk difference (RD). For binary outcomes in terms of relative risk (RR)

8.4 Sensitivity analysis based on data at week 12

The following section includes sensitivity analyses which use all data points at a specific time point, specifically at week 12 as opposed to "across" a few months, as in the base case. This approach enables a comparison with erenumab at 12 weeks.

8.4.1 Results per study

Change from baseline of monthly migraine days

All of the studies reported change from baseline (CFB) results of the monthly migraine headache days at 12 weeks. In the galcanezumab trials CFB where assessed across month 1-3 and in Study 295 across week 9-12. The CFB in the active treatment arms ranged from -5.24 days in the galcanezumab ≥2 prior treatment failures 120 mg arm in REGAIN to -7.0 days in the erenumab 140 mg ≥2 prior treatment failures arm in Study 295. The placebo arms had a reduction in monthly migraine headache days ranging from -1.05 days in REGAIN to -2.7 days in Study 295.

TABLE 8.1 CHANGE FROM BASELINE OF MONTHLY MIGRAINE DAYS AT WEEK 12

Trial	Intervention	N	Mean CFB (95% CI)
REGAIN[2]	Galcanezumab 120 mg	69	-5.24 (-6.89; -3.5)
	Placebo	167	-1.05 (-2.25; 0.15)
CONQUER[5]	Galcanezumab 120 mg	88	-6.57 (-8.08; -5.06)
	Placebo	95	-2.47 (-3.94; -1.00)*
Study 295[8]	Erenumab 70 mg	93	-5.4 ± NR
	Erenumab 140 mg	92	-7.0 ± NR
	Pooled doses	185	-6.2 (-7.06; -5.33)**
	Placebo	142	-2.7 (-3.72; -1.68)

*subgroup analysis of chronic migraine patients, ** 70 mg and 140 mg doses were pooled as specified in the DMC protocol

Proportion of patients with ≥50% reduction in monthly migraine days

Study 295 reported achievement of ≥50% and ≥75% reduction from baseline in monthly migraine days. REGAIN and CONQUER reported the mean proportion of patients with ≥50% and ≥75% reduction in monthly migraine headache days.

All studies reported the ≥50% reduction in monthly migraine headache days. Responder rates (50%, 75% or 100%) were analyzed differently in the erenumab and galcanezumab trials and therefore reported differently in the available sources. In the erenumab studies, the responder outcomes are binary and calculated at month 3. In the galcanezumab studies, the responder outcomes correspond to the average of the monthly responder rates calculated across the double-blind study duration and is therefore a continuous measure. Hence, to be able to indirectly compare to the erenumab studies, the number of responders in the galcanezumab studies were re-calculated from the average of the response rates and the number of patients contributing to the analyses. Therefore, the percentage displayed in the indirect comparison analyses might slightly differ from the average percentage reported in the available publications.

The ≥50% reduction rate in the active treatment arms ranged from 30.4% in the galcanezumab ≥ 2 prior treatment failure 120 mg arm in REGAIN to 41.3% in the erenumab ≥2 prior treatment failures 140 mg arm in Study 295[8]. The ≥50% reduction rate in the placebo arms were comparable.

TABLE 8.2 PROPORTION OF PATIENTS WITH ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS AT WEEK 12

Trial	Intervention	N	Proportion of patients with ≥50% reduction, n (%)
REGAIN[2]	Galcanezumab 120 mg	69	21 (30.4%)
	Placebo	167	24 (14.4%)
CONQUER[5]	Galcanezumab 120 mg	88	32 (36.4%)
	Placebo	95	12 (12.6%)
Study 295[8]	Erenumab 70 mg	93	33 (35.6%)
	Erenumab 140 mg	92	38 (41.3%)
	Pooled doses	185	71 (38.4%)*
	Placebo	142	20 (14.1%)

*70 mg and 140 mg doses were pooled as specified in the DMC protocol

Mean change from baseline in MSQ

Both REGAIN and CONQUER reported on the MSQ Role function restrictive score. REGAIN compared two doses of galcanezumab with placebo. All the differences in the CFB in MSQ role function restrictive score between galcanezumab and the placebo arm were statistically significant (p<0.05). Study 295 did not report data for MSQ or sub-domains.

None of the studies reported on the MSQ total score.

TABLE 8.3 MEAN CHANGE FROM BASELINE IN MSQ

Trial	Intervention	N	Mean CFB in MSQ-RF	Mean CFB in MSQ-EF
REGAIN[2]	Galcanezumab 120 mg	64	19.13 (13.39; 24.86)	21.0 (17.25; 24.74)*
	Placebo	160	10.67 (6.48; 14.85)	14.1 (10.95; 17.24)*
CONQUER[5]	Galcanezumab 120 mg	88	20.6 (16.97; 24.22)	24.38 (19.15; 29.61)
	Placebo	95	6.7 (3.21; 10.18)	11.09 (5.98; 16.19)

*Data not available for subgroup with ≥ 2 prior treatment failure. The data reported is for the total ITT population.

Mean change from baseline in monthly headache days

None of studies reported data for mean CFB in monthly headache days.

Mean CFB in migraine headache days with acute medication use

All studies reported mean CFB in migraine headache days with acute medication use. In the galcanezumab trials CFB where assessed across month 1-3 and in Study 295 across week 9-12. Results in the active treatment arms ranged from -4.1 in the erenumab 70 mg arm to -6.3 in the galcanezumab 120 mg arm in CONQUER. The CFB in the placebo arms were comparable.

TABLE 8.4 MIGRAINE HEADACHE DAYS WITH ACUTE MEDICATION USE AT WEEK 12

Trial	Intervention	N	Migraine headache days with acute medication use, mean (95% CI)
REGAIN[2]	Galcanezumab 120 mg	69	-5.64 (-7.22; -4.06)
	Placebo	167	-1.39 (-2.55; -0.23)
CONQUER[5]	Galcanezumab 120 mg	88	-6.03 (-7.42; -4.63)
	Placebo	95	-1.6 (-2.95; -0.25)
Study 295[8]	Erenumab 70 mg	93	-4.1 (NR)
	Erenumab 140 mg	92	-5.4 (NR)

	Pooled doses	185	-4.75 (-5.41; -4.08)*
	Placebo	142	-1.3 (-2.08; -0.51)

NR: not reported *70 mg and 140 mg doses were pooled as specified in the DMC protocol

Discontinuation due to adverse events

All of the trials reported discontinuation due to adverse events. Discontinuation rates were 1.1% in the galcanezumab arm of CONQUER and 0% in both erenumab treatment arms of Study 295. In the galcanezumab 120 mg arm of REGAIN the discontinuation rate for the ITT population was 0.109%.

TABLE 8.5 DISCONTINUATION DUE TO ADVERSE EVENTS

Trial	Intervention	N	Discontinuation due to adverse events, n (%)
REGAIN[4]	Galcanezumab 120 mg	273	3 (0.109%)*
	Placebo	558	6 (0.107%)*
CONQUER[5]	Galcanezumab 120 mg	95	1 (1.1%)
	Placebo	98	0 (0%)
Study 295[8]	Erenumab 70 mg	92	0 (0%)
	Erenumab 140 mg	92	0 (0%)
	Pooled doses	184	0 (0%)**
	Placebo	141	1 (0.7%)

*Data not available for subgroup with ≥ 2 prior treatment failure. The data reported is for the total ITT population. **70 mg and 140 mg doses were pooled as specified in the DMC protocol

Narrative description of the safety profile

8.4.1.1.1 REGAIN

There were no deaths in the REGAIN study. TEAEs were reported by 50%, 58%, and 57% of patients in the placebo, galcanezumab 120 mg, and galcanezumab 240 mg groups, respectively. Most TEAEs were mild or moderate in severity. The most common TEAE was injection-site pain, but this did not differ significantly between groups (4% placebo, 6% galcanezumab 120 mg, 7% galcanezumab 240 mg). Injection-site reaction, injection-site erythema, injection-site pruritus, and sinusitis occurred more frequently in the galcanezumab 240 mg group relative to placebo, with injection-site pruritus and injection-site erythema also occurring more frequently with the 240 mg than the 120 mg galcanezumab dose. Six placebo- treated patients discontinued as a result of AEs that included abdominal pain, alopecia, headache, migraine, and myocardial infarction. Five galcanezumab-treated patients discontinued because of an AE that included increased weight in the 120 mg group and depression, increased hepatic enzymes, injection-site pain, and acute pancreatitis in the 240 mg group.

There were 10 serious AEs during the study, with 4 reported in the placebo group (alcoholic pancreatitis, epistaxis, gastritis, and myocardial infarction), 1 in the galcanezumab 120 mg group (colon cancer), and 5 in the galcanezumab 240 mg group (hypokalaemia and nephrolithiasis in 1 patient, acute pancreatitis, pulmonary embolism, and renal colic).

No clinically meaningful differences were observed between galcanezumab and placebo in laboratory values, vital signs, weight, or quantitative or qualitative ECGs. Two patients in the study had a treatment-emergent abnormal hepatic enzyme: 1 in the placebo group (1 of 558 or 0.2%) and 1 in the galcanezumab 240 mg dose group (1 of 282 or 0.4%).

During the double-blind treatment phase, treatment-emergent anti-drug-antibodies (ADA) occurred in 22 patients across the groups (1.5%, 2.7%, and 2.6% of the placebo, galcanezumab 120 mg, and galcanezumab

240 mg groups, respectively). Of these 22 patients, 13 had neutralizing ADA present (0.6%, 2.3%, and 1.5% of the placebo, galcanezumab 120 mg, and galcanezumab 240 mg groups, respectively), with a statistical difference be- tween galcanezumab 120 mg and placebo ($p < 0.05$). Maximum ADA titers among these patients ranged from 1:20 to 1: 160. There was no discernible effect of ADA on treatment efficacy or tolerability.

TABLE 8.6 TREATMENT-EMERGENT AES THAT OCCURRED IN ≥2% OF GALCANEZUMAB-TREATED PATIENTS TREATED WITH EITHER DOSE OF GALCANEZUMAB AND GREATER THAN PLACEBO, FULL SAFETY POPULATION OF REGAIN[4]

Adverse event	Placebo (n = 558), n (%)	Galcanezumab, n (%)	
		120 mg (n = 273)	240 mg (n = 282)
Patients with ≥1 event	279 (50)	159 (58)[a]	160 (57)
Injection-site pain	24 (4)	17 (6)	20 (7)
Nasopharyngitis	26 (5)	17 (6)	9 (3)
Upper respiratory tract infection	13 (2)	9 (3)	9 (3)
Injection-site reaction	10 (2)	8 (3)	15 (5)[b]
Injection-site erythema	5 (1)	4 (1)	13 (5)[c,d]
Fatigue	10 (2)	6 (2)	6 (2)
Back pain	14 (3)	9 (3)	2 (1)[d]
Urinary tract infection	7 (1)	6 (2)	4 (1)
Abdominal pain	9 (2)	6 (2)	4 (1)
Diarrhoea	9 (2)	3 (1)	6 (2)
Injection-site pruritus	1 (0)	0 (0)	7 (2)[b,d]
Migraine	5 (1)	5 (2)	4 (1)
Influenza-like illness	3 (1)	5 (2)	4 (1)
Neck pain	8 (1)	7 (3)	0 (0)[a,d]
Oropharyngeal pain	3 (1)	2 (1)	5 (2)
Sinusitis	5 (1)	4 (1)	8 (3)[a]
Arthralgia	5 (1)	1 (0)	5 (2)
Pyrexia	2 (0)	5 (2)[a]	1 (0)

Abbreviation: AE = adverse event. [a] $p < 0.05$ vs placebo. [b] $p < 0.01$ vs placebo. [c] $p < 0.001$ vs placebo. [d] $p < 0.05$ vs galcanezumab 120 mg.

8.4.1.1.2 CONQUER

Safety findings from CONQUER are consistent with those reported from the pivotal phase III trials in patients with EM and CM; galcanezumab was well tolerated and no new safety signals were observed. Safety was only reported for the population of patients with EM and CM with prior failure with ≥2 preventive medication categories since it was not expected that there would be any differences with respect to AEs between the varying study populations. No deaths occurred during the trial and only four SAEs were reported in total (two each in the galcanezumab and placebo groups). A single patient randomized to galcanezumab discontinued the double-blind treatment period due to an AE. TEAEs

occurred at a similar rate in both treatment groups and were generally mild to moderate in severity. Injection site AEs were relatively uncommon and had a greater incidence in placebo compared with galcanezumab-treated patients.

The percentage of patients reporting a TEAE was similar across the galcanezumab and placebo treatment groups. Nasopharyngitis was the most common TEAE in both treatment groups occurring in 9.13% and 6.90% of placebo- or galcanezumab-treated patients, respectively. Statistically significant differences between groups were observed for two TEAEs: injection site reactions, which occurred in six (2.61%) patients in the placebo group versus none in the galcanezumab group (p=0.0147), and insomnia, which occurred in five (2.17%) patients receiving placebo and no patients receiving galcanezumab (p=0.0299).

Most TEAEs were reported as being mild or moderate in severity, with more patients in the placebo group reporting a TEAE as severe compared with the galcanezumab group (3.5% vs 1.7%).

TABLE 8.7 TEAES REPORTED IN ≥2% OF GALCANEZUMAB-TREATED PATIENTS WITH EM OR CM AND PRIOR FAILURE WITH ≥2 PREVENTIVE MEDICATION CATEGORIES IN THE 3-MONTH, DOUBLE-BLIND TREATMENT PERIOD OF CONQUER

Adverse event	Placebo (n=230), n (%)	Galcanezumab 120 mg (n=232), n (%)
Patients with ≥1 TEAE	122 (53.04)	119 (51.29)
Nasopharyngitis	21 (53.04)	16 (6.90)
Influenza	7 (3.04)	11 (4.74)
Injection site erythema	6 (2.61)	8 (3.45)
Constipation	5 (2.17)	5 (2.16)
Injection site pain	13 (5.65)	5 (2.16)
Upper respiratory tract infection	5 (2.17)	5 (2.16)
Back pain	6 (2.61)	4 (1.72)
Bronchitis	2 (0.87)	4 (1.72)
Fatigue	1 (0.43)	4 (1.72)
Gastroenteritis	3 (1.30)	4 (1.72)
Nausea	5 (2.17)	4 (1.72)
Oropharyngeal pain	2 (0.87)	4 (1.72)
Sinusitis	5 (2.17)	4 (1.72)
CM, chronic migraine; EM, episodic migraine; TEAE, treatment-emergent adverse event.		

8.4.1.1.3 Study 295

Over one-third of patients without prior treatment failure had an incidence of AEs (30.6–37.5%). Nearly one-half of patients with prior treatment failure (42.4–57.6%) had an incidence of AEs. The incidence of AEs for placebo compared to erenumab 70 mg and erenumab 140 mg was broadly comparable. The number of SAEs and AEs leading to treatment discontinuation was low.

TABLE 8.8 ADVERSE EVENTS IN PATIENTS WITH PREVIOUSLY ≥2 FAILED PRIOR MEDICATIONS AT WEEK 12

Adverse event	Placebo (n=141), n (%)	Erenumab 70 mg (n=92), n (%)	Erenumab 140 mg (n=92), n (%)
Any AE	62 (44.0)	39 (42.4)	53 (57.6)
Grade 2	35 (24.8)	17 (18.5)	26 (28.3)
Grade 3	7 (5.0)	5 (5.4)	3 (3.3)

Any SAE	4 (2.8)	3 (3.3)	1 (1.1)
AE leading to treatment discontinuation	1 (0.7)	0 (0.0)	0 (0.0)

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required; Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

8.4.2 Comparative analyses

Change from baseline of monthly migraine days

Table 8.9 show the individual study results and the pooled results obtained through the indirect comparison for the change from baseline in monthly migraine headache days in terms of mean difference presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab (70 mg + 140 mg) and placebo. No statistically significant difference is seen between galcanezumab and erenumab (70 mg + 140 mg) for the mean difference in change from baseline in monthly migraine headache days for the random effect model (erenumab 70 mg + 140 mg: -0.65 (95% CI: (-2.62, 1.31; p=0.516). Identical results are observed for the fixed effects model.

TABLE 8.9 ITC CHANGE FROM BASELINE IN MHD AT WEEK 12

Trial	**Galcanezumab 120 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
REGAIN	69, -5.24 (6.89)	167, -1.05 (7.88)	-4.19 (-6.21, -2.17)
CONQUER	88, -6.57 (7.13)	95, -2.47 (7.21)	-4.1 (-6.18, -2.02)
Pooled data	157, -5.99 (7.04)	262, -1.56 (7.66)	
FE Meta-analysis		-4.15 (-5.59, -2.7) P<0.001	
RE Meta-analysis		-4.15 (-5.59, -2.7) P<0.001	
tau^2		0	
I^2		0 (NA, NA)	
Test of heterogeneity: Q (df)		0 (1) P=0.951	
Trial	**Erenumab 70 mg + 140 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
Study 295	185, -6.2 (5.98)	142, -2.7 (6.15)	-3.5 (-4.82, -2.17)
FE Meta-analysis		-3.5 (-4.82, -2.17) P<0.001	
RE Meta-analysis		-3.5 (-4.82, -2.17) P<0.001	
tau^2		NA	
I^2		NA (NA, NA)	
Test of heterogeneity: Q (df)		0 (0) P=1	
FE Indirect Comparison		**-0.65 (-2.62, 1.31) P=0.516**	
RE Indirect Comparison		**-0.65 (-2.62, 1.31) P=0.516**	

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

The absolute efficacy differences are converted to percentage reduction using an assumed event rate (ACR) for treatment with erenumab. The assumed event rate is calculated on the basis of the mean effect in the studies and is 12.2 monthly migraine days. The calculated percentage reduction is shown in Table 8.10Table 5.4.

TABLE 8.10 PERCENTAGE CHANGE FROM BASELINE OF MONTHLY MIGRAINE DAYS

Intervention	**Mean difference**	**ACR**	**Percentage change**

Galcanezumab 120 mg vs. Erenumab 70mg + 140 mg	-0.65 (-2.62, 1.31)	12.2	-5.3% (-21.5%; 10.7%)

Proportion of patients with ≥50% reduction in monthly migraine days

Table 8.11 show the individual study results and the pooled results obtained through the indirect comparison for the percentage of patients with a 50% or greater reduction in monthly migraine headache days in terms of RR and RD, each presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab 70 mg + 140 mg and placebo. The ITC random effects model comparing galcanezumab to erenumab 70 mg + 140 mg results in a RR of 0.89 (95% CI: 0.49; 1.6; p=0.688). Similar results are observed for the fixed effects model. The absolute treatment difference (RD) was calculated based on the RR according to the DMC methods guideline (RD=ACR*RR-ACR). The assumed comparator risk (ACR) was assumed to equal to the erenumab arm (38.4%). The estimated absolute risk difference was estimated to -4.22% (95% CI: - 19.58; 23.04).

TABLE 8.11 ITC PROPORTION OF PATIENTS WITH ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS AT WEEK 12

Trial	**Galcanezumab 120 mg** n/N (%)	**Placebo n/N (%)**	**Risk ratio (95% CI)**
REGAIN	21/69 (30.4)	24/167 (14.4)	2.12 (1.27, 3.54)
CONQUER	32/88 (36.4)	12/95 (12.6)	2.88 (1.59, 5.23)
Pooled data	53/157 (33.8)	36/262 (13.7)	
FE Meta-analysis			2.46 (1.66, 3.64) P<0.001
RE Meta-analysis			2.41 (1.64, 3.56) P<0.001
tau^2			0
I^2			0 (NA, NA)
Test of heterogeneity: Q (df)			0.59 (1) P=0.441
Trial	**Erenumab 70 mg + 140 mg** n/N (%)	**Placebo** n/N (%)	
Study 295	71/185 (38.4)	20/142 (14.1)	2.72 (1.75, 4.25)
FE Meta-analysis			2.72 (1.75, 4.25) P<0.001
RE Meta-analysis			2.72 (1.75, 4.25) P<0.001
tau^2			NA
I^2			NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1
FE Indirect Comparison			**0.9 (0.5, 1.63) P=0.737**
RE Indirect Comparison			**0.89 (0.49, 1.6) P=0.688**

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

Mean CFB in migraine headache days with acute medication use

Table 8.12 show the individual study results and the pooled results obtained through the indirect comparison for the change from baseline in monthly migraine headache days with acute medication use in terms of mean difference presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab (70 mg + 140 mg) and placebo. No statistically significant difference was observed between galcanezumab 120 mg and Erenumab 70 mg + 140 mg (mean difference: -0.89 (95% CI: -2.59, 0.8; p=0.302) in reducing overall migraine headache days with acute medication use. Identical results are observed for the fixed effects model. It must be noted that the permitted acute medications in the erenumab trials were restricted to

ergots and triptans, whereas a broader definition was applied in the galcanezumab studies. Hence, the results of this variable must be interpreted with caution.

TABLE 8.12 ITC MEAN CFB IN MIGRAINE HEADACHE DAYS WITH ACUTE MEDICATION USE AT WEEK 12

Trial	**Galcanezumab 120 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
REGAIN	69, -5.64 (6.56)	167, -1.39 (7.62)	-4.25 (-6.18, -2.32)
CONQUER	88, -6.03 (6.57)	95, -1.6 (6.63)	-4.43 (-6.34, -2.52)
Pooled data	157, -5.86 (6.55)	262, -1.47 (7.27)	
FE Meta-analysis		-4.34 (-5.7, -2.98) P<0.001	
RE Meta-analysis		-4.34 (-5.7, -2.98) P<0.001	
tau^2		0	
I^2		0 (NA, NA)	
Test of heterogeneity: Q (df)		0.02 (1) P=0.897	
Trial	**Erenumab 70 mg + 140 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
Study 295	185, -4.75 (4.57)	142, -1.3 (4.72)	-3.45 (-4.46, -2.43)
FE Meta-analysis		-3.45 (-4.46, -2.43) P<0.001	
RE Meta-analysis		-3.45 (-4.46, -2.43) P<0.001	
tau^2		NA	
I^2		NA (NA, NA)	
Test of heterogeneity: Q (df)		0 (0) P=1	
FE Indirect Comparison		**-0.89 (-2.59, 0.8) P=0.302**	
RE Indirect Comparison		**-0.89 (-2.59, 0.8) P=0.302**	

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

The absolute efficacy differences are converted to percentage reduction using an assumed event rate (ACR) for treatment with erenumab. The assumed event rate is calculated on the basis of the mean effect in the studies and is 6.65 monthly migraine days. The calculated percentage reduction is shown in Table 8.13.

TABLE 8.13 PERCENTAGE CHANGE FROM BASELINE OF MIGRAINE HEADACHE DAYS WITH ACUTE MEDICATION USE

Intervention	**Mean difference**	**ACR**	**Percentage change**
Galcanezumab 120 mg vs. Erenumab 70mg + 140 mg	-0.89 (-2.59, 0.8)	6.65	-13.4% (-38.9%; 12.0%)

Discontinuation due to adverse events

Table 8.14 show the individual study results and the pooled results obtained through the indirect comparison for the outcome: discontinuation due to adverse events in terms of RR and RD, each presented with corresponding 95% CI and p-value. The ITC random effects model comparing galcanezumab to erenumab 70 + 140 mg results in an RR of 12.1 (95% CI: 0.13, 1102.98) p=0.279), indicating that the risk of patients discontinuing due to adverse events is increased in patients receiving galcanezumab when compared to erenumab 70 + 140 mg; however, this difference is not statistically significant (p=0.279). Similar results are observed for the fixed effects model. However, these results need to be interpreted with caution given that no event was observed in the active treatment arm of the erenumab study or the control arm in the galcanezumab study. Only one event was reported in the galcanezumab arm in CONQUER and one in the control arm of the erenumab study.

Table 8.14 ITC discontinuation due to AE

Trial	**Galcanezumab 120 mg** n/N (%)	**Placebo n/N (%)**	**Risk ratio (95% CI)**	**Risk difference (95% CI)**
CONQUER	1/95 (1.10)	0/98 (0)	3.09 (0.13, 75.02) /+0.5tc/	0.01 (-0.02, 0.04) /+0.5tc/
FE Meta-analysis			3.09 (0.13, 75.02) P=0.487	0.01 (-0.02, 0.04) P=0.469
RE Meta-analysis			3.09 (0.13, 75.02) P=0.487	0.01 (-0.02, 0.04) P=0.469
tau^2			NA	NA
I^2			NA (NA, NA)	NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1	0 (0) P=1
Trial	**Erenumab 70 mg + 140 mg** n/N (%)	**Placebo** n/N (%)	**Risk ratio (95% CI)**	**Risk difference (95% CI)**
Study 295	0/184 (0)	1/141 (0.7)	0.26 (0.01, 6.23)	-0.01 (-0.03, 0.01)
FE Meta-analysis			0.26 (0.01, 6.23) P=0.402	-0.01 (-0.03, 0.01) P=0.45
RE Meta-analysis			0.26 (0.01, 6.23) P=0.402	-0.01 (-0.03, 0.01) P=0.45
tau^2			NA	NA
I^2			NA (NA, NA)	NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1	0 (0) P=1
FE Indirect Comparison			12.1 (0.13, 1102.98) P=0.279	0.02 (-0.02, 0.05) P=0.308
RE Indirect Comparison			12.1 (0.13, 1102.98) P=0.279	0.02 (-0.02, 0.05) P=0.308

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom, +#tc - # added to test and control cells

8.5 Sensitivity analysis only including CONQUER data at 12 weeks

Change from baseline of monthly migraine days

Table 8.15 shows the individual study results for the change from baseline in monthly migraine headache days in terms of mean difference presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab (70 mg + 140 mg) and placebo. No statistically significant difference is seen between galcanezumab and erenumab (70 mg + 140 mg) for the mean difference in change from baseline in monthly migraine headache days for the random effect model (erenumab 70 mg + 140 mg: -0.6 (95% CI: (-3.07; 1.86; p=0.631). Identical results are observed for the fixed effects model.

TABLE 8.15 ITC CHANGE FROM BASELINE IN MHD AT WEEK 12

Trial	**Galcanezumab 120 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
CONQUER	88, -6.57 (7.13)	95, -2.47 (7.21)	-4.1 (-6.18, -2.02)
Pooled data	88, -6.57 (7.13)	95, -2.47 (7.21)	

FE Meta-analysis		4.1 (-6.18, -2.02)	
RE Meta-analysis		4.1 (-6.18, -2.02)	
tau^2		NA	
I^2		NA (NA, NA)	
Test of heterogeneity: Q (df)		0 (0) P=1	
Trial	**Erenumab 70 mg + 140 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
Study 295	185, -6.2 (5.98)	142, -2.7 (6.15)	-3.5 (-4.82, -2.17)
FE Meta-analysis		-3.5 (-4.82, -2.17) P<0.001	
RE Meta-analysis		-3.5 (-4.82, -2.17) P<0.001	
tau^2		NA	
I^2		NA (NA, NA)	
Test of heterogeneity: Q (df)		0 (0) P=1	
FE Indirect Comparison		-0.6 (-3.07, 1.86) P=0.631	
RE Indirect Comparison		-0.6 (-3.07, 1.86) P=0.631	

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

The absolute efficacy differences are converted to percentage reduction using an assumed event rate (ACR) for treatment with erenumab. The assumed event rate is calculated on the basis of the mean effect in the studies and is 12.2 monthly migraine days. The calculated percentage reduction is shown in Table 8.16.

TABLE 8.16 PERCENTAGE CHANGE FROM BASELINE OF MONTHLY MIGRAINE DAYS

Intervention	Mean difference	ACR	Percentage change
Galcanezumab 120 mg vs. Erenumab 70mg + 140 mg	-0.6 (-3.07, 1.86)	12.2	-4.9% (-25.2%; 15.2%)

Proportion of patients with ≥50% reduction in monthly migraine days

Table 8.17 shows the individual study results for the percentage of patients with a 50% or greater reduction in monthly migraine headache days in terms of RR and RD, each presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab 70 mg + 140 mg and placebo. The ITC random effects model comparing galcanezumab to erenumab 70 mg + 140 mg results in an RR of 1.06 (95% CI: 0.49; 1.6). Similar results are observed for the fixed effects model.

The absolute treatment difference (RD) was calculated based on the RR according to the DMC methods guideline (RD=ACR*RR-ACR). The assumed comparator risk (ACR) was assumed to equal to the erenumab arm (38.4%). The estimated absolute risk difference was estimated to 2.3% (95% CI: - 19.2; 46.8).

TABLE 8.17 ITC PROPORTION OF PATIENTS WITH ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS

Trial	Galcanezumab 120 mg n/N (%)	Placebo n/N (%)	Risk ratio (95% CI)
CONQUER	32/88 (36.4)	12/95 (12.6)	2.88 (1.59, 5.23)
Pooled data	32/88 (36.4)	12/95 (12.6)	
FE Meta-analysis			2.88 (1.59, 5.23)
RE Meta-analysis			2.88 (1.59, 5.23)
tau^2			NA
I^2			NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1

Trial	Erenumab 70 mg + 140 mg n/N (%)	Placebo n/N (%)	
Study 295	71/185 (38.4)	20/142 (14.1)	2.72 (1.75, 4.25)
FE Meta-analysis			2.72 (1.75, 4.25) P<0.001
RE Meta-analysis			2.72 (1.75, 4.25) P<0.001
tau^2			NA
I^2			NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1
FE Indirect Comparison			1.06 (0.5, 2.22) P=0.885
RE Indirect Comparison			1.06 (0.5, 2.22) P=0.885

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

Mean CFB in migraine headache days with acute medication use

Table 8.18 shows the individual study results for the change from baseline in monthly migraine headache days with acute medication use in terms of mean difference presented with corresponding 95% CI and p-value. The individual study results show a significant difference between galcanezumab and placebo as well as erenumab (70 mg + 140 mg) and placebo. No statistically significant difference was observed between galcanezumab 120 mg and Erenumab 70 mg + 140 mg (mean difference: -0.98 (95% CI: -3.15, 1.18; P=0.374) in reducing overall migraine headache days with acute medication use. Identical results are observed for the fixed effects model. It must be noted that the permitted acute medications in the erenumab trials were restricted to ergots and triptans, whereas a broader definition was applied in the galcanezumab studies. Hence, the results of this variable must be interpreted with caution.

TABLE 8.18 ITC MEAN CFB IN MIGRAINE HEADACHE DAYS WITH ACUTE MEDICATION USE

Trial	Galcanezumab 120 mg N, Mean (SD)	Placebo N, Mean (SD)	Mean Difference (95% CI)
CONQUER	88, -6.03 (6.57)	95, -1.6 (6.63)	-4.43 (-6.34, -2.52)
Pooled data	88, -6.03 (6.57)	95, -1.6 (6.63)	
FE Meta-analysis		-4.43 (-6.34, -2.52) P<0.001	
RE Meta-analysis		-4.43 (-6.34, -2.52) P<0.001	
tau^2		NA	
I^2		NA (NA, NA)	
Test of heterogeneity: Q (df)		0 (0) P=1	
Trial	**Erenumab 70 mg + 140 mg N, Mean (SD)**	**Placebo N, Mean (SD)**	**Mean Difference (95% CI)**
Study 295	185, -4.75 (4.57)	142, -1.3 (4.72)	-3.45 (-4.46, -2.43)
FE Meta-analysis		-3.45 (-4.46, -2.43) P<0.001	
RE Meta-analysis		-3.45 (-4.46, -2.43) P<0.001	
tau^2		NA	
I^2		NA (NA, NA)	
Test of heterogeneity: Q (df)		0 (0) P=1	
FE Indirect Comparison		-0.98 (-3.15, 1.18) P=0.374	
RE Indirect Comparison		-0.98 (-3.15, 1.18) P=0.374	

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

The absolute efficacy differences are converted to percentage reduction using an assumed event rate (ACR) for treatment with erenumab. The assumed event rate is calculated on the basis of the mean effect in the studies and is 6.65 monthly migraine days. The calculated percentage reduction is shown in Table 8.19.

TABLE 8.19 PERCENTAGE CHANGE FROM BASELINE OF MIGRAINE HEADACHE DAYS WITH ACUTE MEDICATION USE

Intervention	Mean difference	ACR	Percentage change
Galcanezumab 120 mg vs. Erenumab 70mg + 140 mg	-0.98 (-3.15, 1.18)	6.65	-14.7% (-47.4%; 17.7%)

Discontinuation due to adverse events

Table 8.20 show the individual study results for the outcome: discontinuation due to adverse events in terms of RR and RD, each presented with corresponding 95% CI and p-value. The ITC random effects model comparing galcanezumab to erenumab 70 + 140 mg results in an RR of 12.1 (95% CI: 0.13, 1102.98 p=0.279), indicating that the risk of patients discontinuing due to adverse events is increased in patients receiving galcanezumab when compared to erenumab 70 + 140 mg; however, this difference is not statistically significant (p=0.279). Similar results are observed for the fixed effects model. However, these results need to be interpreted with caution given that no event was observed in the active treatment arm of the erenumab study or the control arm in the galcanezumab study. Only one event was reported in the galcanezumab arm in CONQUER and one in the control arm of the erenumab study.

Table 8.20 ITC discontinuation due to AE

Trial	**Galcanezumab 120 mg** n/N (%)	**Placebo n/N (%)**	**Risk ratio (95% CI)**	**Risk difference (95% CI)**
CONQUER	1/95 (1.10)	0/98 (0)	3.09 (0.13, 75.02) /+0.5tc/	0.01 (-0.02, 0.04) /+0.5tc/
FE Meta-analysis			3.09 (0.13, 75.02) P=0.487	0.01 (-0.02, 0.04) P=0.469
RE Meta-analysis			3.09 (0.13, 75.02) P=0.487	0.01 (-0.02, 0.04) P=0.469
tau^2			NA	NA
I^2			NA (NA, NA)	NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1	0 (0) P=1
Trial	**Erenumab 70 mg + 140 mg** n/N (%)	**Placebo** n/N (%)	**Risk ratio (95% CI)**	**Risk difference (95% CI)**
Study 295	0/184 (0)	1/141 (0.7)	0.26 (0.01, 6.23)	-0.01 (-0.03, 0.01)
FE Meta-analysis			0.26 (0.01, 6.23) P=0.402	-0.01 (-0.03, 0.01) P=0.45
RE Meta-analysis			0.26 (0.01, 6.23) P=0.402	-0.01 (-0.03, 0.01) P=0.45
tau^2			NA	NA
I^2			NA (NA, NA)	NA (NA, NA)
Test of heterogeneity: Q (df)			0 (0) P=1	0 (0) P=1

FE Indirect Comparison	**12.1 (0.13, 1102.98) P=0.279**	**0.02 (-0.02, 0.05) P=0.308**
RE Indirect Comparison	**12.1 (0.13, 1102.98) P=0.279**	**0.02 (-0.02, 0.05) P=0.308**

SD: standard deviation, FE: Fixed effects, RE: random effects, df: degrees of freedom

Omkostnings- og budgetkonsekvensanalyse for galcanezumab (Emgality®) til forebyggende behandling af migræne

Teknisk dokument - ansøgning til Medicinrådet

23-06-2020

Version 1.2

Kontaktperson:
Jeppe S. Christensen
Pricing, Reimbursement and Access manager
✆: 31707520
✉: jeppe_sc@lilly.com

Indhold

1 Baggrund

Eli Lilly Danmark A/S ansøger om Medicinrådets anbefaling af galcanezumab (Emgality®) som mulig standardbehandling til patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) baseret på Medicinrådets protokol (Medicinrådet, 2020a).

Galcanezumab er et humaniseret monoklonalt antistof, der selektivt binder til det vasodilaterende neuropeptid calcitonin genrelaterede peptid (CGRP), hvorved CGRP forhindres i at binde til CGRPreceptoren. Dette fører til en hæmning af den CGRP-inducerede karudvidelse, reduktion af den neurologisk medierede immunreaktion samt hæmning af smertesignaler.

Galcanezumab administreres subkutant og indgives én gang om måneden. Initialt gives en støddosis på 240 mg og derefter 120 mg én gang om måneden.

I henhold til Medicinrådets protokol fremgår den relevante sammenligning til den ansøgte population af **Tabel 1:**

Tabel 1: Intervention og komparatorer

	Administration	Dosering
Intervention		
Galcanezumab	Subkutant	240 mg støddosis, herefter 120 mg én gang om måneden
Komparatorer		
Erenumab (Aimovig®)	Subkutant	70 mg eller 140 mg hver 4. uge
Fremanezumab (Ajovy®)	Subkutant	225 mg én gang om måneden eller 675 mg hver tredje måned

Produkterne administreres af patienten selv eller af pårørende. Afhængig af effekten af lægemidlerne kan behandlingen enten seponeres eller intensiveres (Medicinrådet, 2019). Erenumab og fremanezumab anses af Medicinrådet som klinisk ligeværdige.

2 Omkostningsanalyse

2.1 Tidligere analyser indenfor migræne

Amgros har publiceret to økonomiske analyser inden for forebyggende behandling af migræne, hvor hhv. erenumab og fremanezumab sammenlignes med standardbehandling (Amgros, 2019a, 2019b). Begge analyser har en tidshorisont på 5 år. I analyserne blev det antaget, at behandlingen seponeres for en betydelig del af patienterne. Amgros vurderede, at analysernes resultater er meget usikre, eftersom der er stor usikkerhed forbundet med andelen af patienter der dosisjusteres og seponeres.

2.2 Modelbeskrivelse

2.2.1 Komparatorer

I henhold til protokollen omfatter analysen både erenumab og fremanezumab som relevante komparatorer.

2.2.2 Ressourcer og omkostningsperspektiv

Eftersom der ikke er signifikante forskelle mellem galcanezumab og erenumab for de centrale effektmål jf. den indirekte sammenligning i den kliniske del af ansøgningen, antages galcanezumab derfor at være klinisk ligeværdig med komparatorerne. Denne tilgang understøttes af at Medicinrådet har accepteret at galcanezumab kan vurderes i Medicinrådets hurtige proces på 7 uger (Medicinrådet, 2020a).

Grundet den centrale antagelse om klinisk ligeværdighed er denne model udarbejdet som en omkostningsminimeringsanalyse. Eftersom lægemidlerne administreres af patienten selv, er analysen afgrænset til kun at inkludere lægemiddelomkostninger.

2.2.3 Tidshorisont

En tidshorisont på 5 år er valgt, eftersom dette er i overensstemmelse med de tidligere analyser vurderet af Amgros. Cykluslængden i modellen er en måned, da dette stemmer overens med dosishyppigheden for lægemidlerne. Omkostninger diskonteres med 4% per år i henhold til Medicinrådets metodevejledning (Medicinrådet, 2020b).

2.3 Omkostninger

2.3.1 Lægemiddelomkostninger

Enhedsomkostninger for de inkluderede lægemidler er fundet på Medicinpriser.dk og fremgår af **Tabel 2.**

Tabel 2: Anvendte lægemiddelpriser

Lægemiddel	Styrke	Pakning	Pris (AIP)*	Kilde
Galcanezumab	120 mg	1 stk.	3.416,00	Medicinpriser.dk (Emgality®)
Erenumab	70 mg	1 stk.	3.113,18	Medicinpriser.dk (Aimovig®)
	140 mg	1 stk.	3.113,18	
Fremanezumab	225 mg	1 stk.	3.550,00	Medicinpriser.dk (Ajovy®)

*Tilgået d. 21-05-2020

2.3.2 Dosering

I modellens anvendes doseringen som fremgår af Tabel 1. I modellens base-case anvendes doseringen på 70mg for erenumab, eftersom hovedparten af patienter antages at initiere behandling med denne dosis i Amgros' analyse for erenumab (Amgros, 2019a). Eftersom pakningsprisen på AIP-niveau er ens for de to styrker af erenumab, har dette valg ingen betydning for resultatet af analysen.

2.3.3 Seponering af behandling

Modellen følger Medicinrådets nationale kriterier for opstart, opfølgning og seponering ved behandling med anti-CGRP-antistof til forebyggende behandling af migræne (Medicinrådet, 2019). Her anbefales det at første evaluering sker efter 3 måneder, og evaluering af behandlingstop sker efter uge 60+0, hvilket vil sige behandlingspause måned 13 og 14 efter opstart.

I modellens base-case antages det, at 60% af patienterne fortsætter behandling efter første evaluering. Dette estimat baseres på data for responsrater fra CONQUER (Mulleners *et al.*, 2020). Det antages at 80% af patienterne, der fortsætter behandling efter evalueringen vil fortsætte behandling efter forsøg på behandlingsstop. Dette vil sige, at 48% af startkohorten antages at fortsætte i behandling efter forsøg på behandlingsstop. Dette estimat er en antagelse, eftersom der endnu ikke findes data til at besvare dette spørgsmål.

Eftersom effekten af lægemidlerne antages at være ligeværdig, forventes det ikke at der vil være forskel i seponering mellem lægemidlerne. Dermed har dette element derfor meget lille betydning for analysens resultat. Ændringer i disse antagelser belyses i scenarieanalyser.

2.4 Resultater

2.4.1 Base-case

Tabel 3 viser de samlede omkostninger for de tre lægemidler samt de inkrementelle omkostninger for erenumab og fremanezumab sammenlignet med galcanezumab over en tidshorisont på 5 år. Med brug af AIP er de samlede omkostninger 99.559,73 kr., 95.248,53 og 99.915,17 for hhv. galcanezumab, erenumab, og fremanezumab. Galcanezumab resulterer i en besparelse på 355,45 kr. sammenlignet med fremanezumab, mens galcanezumab er forbundet med en meromkostning på 4.311,20 kr. sammenlignet med erenumab.

Tabel 3: Resultatet af base-casen (AIP)

Lægemiddel	Omkostninger	Inkrementelle omkostninger vs. galcanezumab
Galcanezumab	99.559,73 kr.	
Erenumab	95.248,53 kr.	**-4.311,20 kr.**
Fremanezumab	99.915,17 kr.	**355,45 kr.**

2.4.2 Følsomhedsanalyser

Der er udarbejdet scenarieanalyser, der adresserer de to primære variabler i analysen. Dette vil sige andelen af patienter der ophører med behandling, og selve behandlingsvarigheden. **Tabel 4** og **Tabel 5** viser betydningen af ændringer i antagelserne for hhv. den parvise sammenligning med erenumab og fremanezumab. I det første scenarie antages et højere frafald end i base-casen, mens der i scenarie 2 antages et frafald på 0%. I scenarie 3 belyses betydningen af en ændring i tidshorisonten til 10 år.

Tabel 4: Scenarieanalyser for den parvise sammenligning med erenumab (AIP)

Scenarie	Inkrementelle omkostninger vs. galcanezumab	Forskel i procent
Base-case erenumab	**-4.311,20 kr.**	**-4,33%**
40% af patienter fortsætter efter første vurdering og 20% af patienter fortsætter efter forsøg på behandlingsstop	-3.878,06 kr.	-7,31%
100% af patienter fortsætter efter første vurdering og 100% af patienter fortsætter efter forsøg på behandlingsstop	-5.121,97 kr.	-2,74%
Tidshorisont på 10 år	-5.008,38 kr.	-2,87%

Tabel 5: Scenarieanalyser for den parvise sammenligning med fremanezumab (AIP)

Scenarie	Inkrementelle omkostninger vs. galcanezumab	Forskel i procent
Base-case fremanezumab	**355,45**	**0,36%**
40% af patienter fortsætter efter første vurdering og 20% af patienter fortsætter efter forsøg på behandlingsstop	-1.469,36 kr.	-2,77%
100% af patienter fortsætter efter første vurdering og 100% af patienter fortsætter efter forsøg på behandlingsstop	3.771,18 kr.	2,02%
Tidshorisont på 10 år	3.292,63 kr.	1,89%

Analyserne illustrerer, at galcanezumab er forbundet med højere omkostninger end begge komparatorer, det antages, at 40% af patienterne fortsætter efter første vurdering, og 20% af patienterne fortsætter efter forsøg på behandlingsstopr. Imidlertid er besparelserne sammenlignet med fremanezumab betydeligt højere i de resterende to scenarier. Dette skyldes højere opstartsomkostninger for galcanezumab end de to komparatorer, grundet den initiale støddosis, men en lavere månedlig omkostning end fremanezumab.

3 Budgetkonsekvensanalyse

3.1 Metode

Der er udarbejdet en simpel budgetkonsekvensanalyse, hvor de regionale omkostninger i det nuværende scenarie sammenlignes med de regionale omkostninger i scenariet hvor galcanezumab anbefales som mulig standardbehandling. Budgetkonsekvenserne opgøres per år over 5 år, og der anvendes ikke-diskonterede værdier.

3.2 Patientantal

Antallet af nye patienter, som egner sig til behandling med de tre lægemidler, i analysen er meget usikkert, og Medicinrådet angiver ikke et præcist estimat i protokollen for galcanezumab (Medicinrådet, 2020a). Derfor tages der i denne analyse udgangspunkt i Amgros' estimat i afrapporteringen for fremanezumab, hvilket vil sige knap 600 patienter per år (Amgros, 2019b). I denne analyse antages der derfor 600 nye patienter per år.

3.3 Markedsandele

I analysen for det nuværende scenarie tages udgangspunkt salgstal fra maj 2020, hvor erenumab og fremanezumab udgør hhv. 59% og 41% af alle pakninger solgte pakninger. Det antages at disse markedsandele fortsætter alle 5 år. I scenariet hvor galcanezumab anbefales, antages galcanezumab udelukkende at tage markedsandele fra fremanezumab, da det er et dyrere alternativ på AIP-niveau. Eftersom produkterne betragtes som ligeværdige, forventes markedsandelene på ethvert tidspunkt at afhænge af de konkrete tilbudspriser. Dette kan der imidlertid ikke tages højde for i analysen, da denne skal udarbejdes på AIP-niveau. De estimerede markedsandele illustreres i **Tabel 6**.

Tabel 6: Estimerede markedsandele per år i scenarierne hhv. uden anbefaling som mulig standardbehandling og med anbefaling som mulig standardbehandling

	Uden anbefaling af galcanezumab					Med anbefaling af galcanezumab				
Behandling	**År 1**	**År 2**	**År 3**	**År 4**	**År 5**	**År 1**	**År 2**	**År 3**	**År 4**	**År 5**
Galcanezumab	0%	0%	0%	0%	0%	41%	41%	41%	41%	41%
Erenumab	59%	59%	59%	59%	59%	59%	59%	59%	59%	59%
Fremanezumab	41%	41%	41%	41%	41%	0%	0%	0%	0%	0%

3.4 Resultater

3.4.1 Base case

På AIP-niveau er de estimerede budgetkonsekvenser ved anbefaling af galcanezumab som mulig standardbehandling ca. 600,000 kr. i år 1, 400.000 kr. i år 2, 200.000 kr. i år 3, 30.000 kr. i år 4, og -150.000 kr. i år 5. Initialt er galcanezumab forbundet med øgede budgetkonsekvenser grundet opstartsomkostningerne for galcanezumab, men dette udlignes over tid og resulterer i besparelser efter 5 år grundet den lavere månedlige behandlingspris for galcanezumab sammenlignet med fremanezumab. Resultaterne illustreres i Tabel 7.

Tabel 7: Resultater af base-casen: Estimerede budgetkonsekvenser per år over de næste fem år (AIP).

	År 1	År 2	År 3	År 4	År 5
Anbefales	17.473.194 kr.	27.257.229 kr.	38.998.070 kr.	50.738.911 kr.	62.479.752 kr.
Anbefales ikke	16.901.845 kr.	26.844.106 kr.	38.774.820 kr.	50.705.534 kr.	62.636.247 kr.
Totale budgetkonsekvenser	**571.350 kr.**	**413.123 kr.**	**223.250 kr.**	**33.377 kr.**	**-156.495 kr.**

3.4.2 Scenarieanalyser

Resultatet af at ændre antagelserne for markedsandele sammenlignet med basecasen er belyst i to scenarieanalyser. I den ene antages det at galcanezumab kun tager 10% markedsandele fra fremanezumab, mens galcanezumab i den anden scenarieanalyse har en markedsandel på 60% (29% tages fra erenumab og 31% tages fra fremanezumab). Resultatet præsenteres i Tabel 8.

Tabel 8: Scenarieanalyser for de estimerede budgetkonsekvenser år 5

Scenarier	**Totale budgetkonsekvenser år 5 (AIP)**
Base-case	**-156.495 kr.**
Galcanezumab har en markedsandel på 10% alle år	-38.170 kr.
Galcanezumab har en markedsandel på 60% alle år Erenumab har en markedsandel på 30% alle år Fremanezumab har en markedsandel på 10% alle år	643.417 kr.

4 Konklusion

På AIP-niveau er galcanezumab forbundet med højere omkostninger end erenumab og lavere omkostninger end fremanezumab, når analysen baseres på en tidshorisont på 5 år og det antages at 60% af patienterne fortsætter i behandling efter første evaluering og 48% af patienterne fortsætter i behandling efter forsøg på behandlingsstop. Budgetkonsekvenserne er begrænsede, eftersom populationen ikke forventes at blive udvidet som følge af introduktionen af galcanezumab.

5 Referencer

Amgros (2019a) *ERENUMAB (AIMOVIG) FOREBYGGENDE BEHANDLING AF MIGRAENE*.

Amgros (2019b) *FREMANEZUMAB (AJOVY) FOREBYGGENDE BEHANDLING AF MIGRAENE*.

Medicinrådet (2019) *Nationale kriterier for opstart, opfølgning og seponering ved behandling med anti-CGRPantistof til forebyggende behandling af migræne*.

Medicinrådet (2020a) *Medicinrådets protokol for vurdering af galcanezumab til forebyggende behandling af migraene*. Available at: www.medicinraadet.dk (Accessed: 21 May 2020).

Medicinrådet (2020b) *Metodevejledning for omkostningsanalyser af nye laegemidler og indikationer i hospitalssektoren v. 1.5*.

Mulleners, W. *et al.* (2020) 'A Randomized, Placebo-Controlled Study of Galcanezumab in Patients with Treatment-Resistant Migraine: Double-Blind Results from the CONQUER Study (162)', *Neurology*, 94(15 Supplement).

Medicinrådet

Medicinrådets protokol for vurdering af galcanezumab til forebyggende behandling af migræne

Versionsnr.: 1.0

Om Medicinrådet

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

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

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

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

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

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

Dokumentoplysninger	
Godkendelsesdato	10. februar 2020
Ikrafttrædelsesdato	10. februar 2020
Dokumentnummer	71222
Versionsnummer	1.0

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

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 10. februar 2020.

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Emgality
Generisk navn	Galcanezumab
Firma	Eli Lilly Danmark A/S
ATC-kode	N02CX08
Virkningsmekanisme	Galcanezumab er et humaniseret IgG4 monoklonalt antistof, der binder calcitonin genrelateret peptid (CGRP) og forhindrer derved dets biologiske aktivitet. Forhøjede koncentrationer i blodet af CGRP er blevet forbundet med migræneanfald.
Administration/dosis	Subkutan injektion, støddosis på 240 mg som den første dosis. Derefter 120 mg én gang om måneden.
EMA-indikation	Galcanezumab er indiceret til profylaktisk behandling af migræne hos voksne, der har mindst fire migrænedage pr. måned.
Accelerated assessment	Nej
Orhan drug	Nej
Conditional approval	Nej
Øvrige indikationer	Ingen

2 Forkortelser

CGRP:	*Caltitonin gene-related peptide* (calcitonin genralateret protein)
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
OR:	*Odds ratio*
RR:	Relativ risiko

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af galcanezumab som mulig standardbehandling af patienter med migræne. I protokollen angives en definition af population, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende galcanezumab modtaget den 10. januar 2020.

Protokollen danner grundlag for den endelige ansøgning for vurdering af galcanezumab sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem galcanezumab og erenumab eller fremanezumab af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

Ansøger har tilkendegivet, at galcanezumab efter deres vurdering hverken er bedre eller dårligere end erenumab til hele den godkendte indikation og dermed kan indgå i Medicinrådets hurtigere proces på syv uger. Medicinrådet har accepteret, at galcanezumab på den baggrund kan vurderes i Medicinrådets hurtigere proces på syv uger (www.medicinraadet.dk). Ansøger påtager sig ansvaret for, at lægemidlet under processen kan kategoriseres anderledes og i så fald skal indgå i et sædvanligt procesforløb på 12 uger.

4 Baggrund

Migræne er en udbredt lidelse, der medfører nedsat funktionsevne, tab af livskvalitet og er blandt de tre sygdomme, som er årsag til mest arbejdsfravær [1]. Lidelsen er sandsynligvis en genetisk disponeret sygdom, der vedrører både nerver og blodkar i hovedet [2,3], hvor calcitonin genrelateret protein [CGRP]-signalering menes at være en væsentlig og muligvis forårsagende faktor i sygdomsmekanismen. De egentlige årsager til migræne kendes ikke med sikkerhed.

I klinisk praksis skelnes almindeligvis mellem migræne med eller uden "aura" (forbigående neurologiske forstyrrelser, f.eks. forstyrrelser af syns- eller følesans i op til 60 minutter før selve migrænehovedpinen starter) [1–3]. Migrænehovedpine kendetegnes ved anfaldsvis hovedpine typisk henover 4-72 timer (ubehandlet eller behandlet uden succes) af dunkende karakter, moderat til svær intensitet og forværring ved almindelig fysisk aktivitet. Ved anfald følger typisk kvalme, opkast og overfølsomhed overfor lys og lyd.

I kliniske studier anvender man ofte en anden inddeling af migræne, nemlig "episodisk" og "kronisk" migræne. "Episodisk" migræne er defineret ved < 15 migrænedage/måned, og "kronisk" migræne er defineret ved hovedpine ≥ 15 dage om måneden, hvoraf mindst 8 dage er med migræne, resten med anden hovedpine, f.eks. spændingshovedpine. Inddelingen skal opfattes som et kontinuerligt spektrum, hvor den enkelte patient i perioder kan gå fra episodisk til kronisk migræne og omvendt.

En migrænedag defineres som en kalenderdag med mindst fire på hinanden følgende timer med migræne eller hovedpine (uafhængig af varighed) behandlet med migrænespecifik akut anfaldsbehandling (triptaner eller ergotaminer). En hovedpinedag defineres som en kalenderdag, hvor patienten oplever migrænehovedpine eller non-migrænehovedpine med en varighed på mindst fire på hinanden følgende timer, eller en hovedpine (uafhængig af varighed), hvor patienten har behov for akut anfaldsbehandling (triptaner, ergotaminer eller anden smertestillende medicin). Dette betyder, at en migrænedag pr. definition også er en hovedpinedag, mens det modsatte ikke er tilfældet. En hovedpinedag uden karakteristiske migrænesymptomer, og som ikke kræver migrænespecifik anfaldsbehandling, er ikke en migrænedag.

Migræne er udbredt i alle aldersgrupper. Den debuterer hyppigst inden 40-årsalderen og ofte allerede i barndom eller ungdom [1,2]. Der er flere kvinder end mænd, der lider af migræne. Studier viser, at mellem

24-32 % af alle danske kvinder og mellem 5-17 % af alle danske mænd oplever migræne mindst én gang i deres liv [1]. Langt de fleste migrænepatienter bliver behandlet i primærsektoren, men ved utilfredsstillende behandlingseffekt kan patienten blive henvist til en hovedpineklinik/-center på sygehuset. Fagudvalget vurderer, at antallet af patienter, der bliver behandlet for migræne på de danske hospitaler, er i omegnen af ca. 5.000-6.000 patienter årligt, men der findes ikke endelige opgørelser over totalt antal migrænepatienter, der er tilknyttet hovedpineklinikker i Danmark. Fagudvalget skønner, at flertallet af disse patienter opfylder kriterierne (jf. afsnit 4.1) for forebyggende migrænebehandling.

4.1 Nuværende behandling

Medicinsk behandling af migræne inddeles i anfaldsbehandling (smertestillende og kvalmestillende) og forebyggende behandling. Forebyggende behandling tilbydes for at reducere sværhedsgrad og frekvens af hovedpineanfald til patienter, der har mindst to svære migræneanfald pr. måned med dårlig effekt af anfaldsmedicin og heraf forringet livskvalitet [3]. Forebyggende behandling er succesfuld, når patienten oplever forbedret livskvalitet samt fald i migrænens hyppighed og sværhedsgrad. Mange patienter oplever spontan forbedring over tid. Det er derfor meget individuelt, hvor lang tid en patient har brug for profylaktisk behandling, og nuværende kliniske anbefalinger angiver derfor, at medicinen forsøges afsluttet hver 6.-12. måned for at sikre, at der fortsat er behov for og effekt af medicinen [3]. Det er vigtigt at notere, at der findes en del patienter, som har såkaldt ”medicinoverforbrugshovedpine” (migræne/hovedpine pga. overforbrug af smertestillende), hvor behandlingen først og fremmest består af udtrapning af deres medicinoverforbrug og ikke yderligere tillæg af forebyggende behandling.

Mange af de lægemidler, der tilbydes som forebyggende behandling af migræne, er oprindeligt udviklet til andre formål, f.eks. antihypertensiva (blodtryksmedicin), antiepileptika (medicin mod epilepsi) og antidepressiva (medicin mod depression). Disse lægemidler har vist sig også at have effekt på forebyggelse af migræne, og visse er siden blevet godkendt til dette formål. Indenfor de seneste to år er flere nye lægemidler, de såkaldte CGRP-antistoffer, blevet godkendt til forebyggende behandling af migræne. Lægemidler, der er godkendt til forebyggende behandling af migræne i Danmark, er: metoprolol/propranolol (betablokkere), flunarizin (calciumantagonist), topiramat (antiepileptika), pizotifen (aminantagonist), clonidin (alfa2-receptor- samt imidazolinreceptoragonist) samt amitriptylin (tricyklisk antidepressivum). CGRP-antistofferne erenumab, fremanezumab og galcanezumab er alle godkendt som forebyggende behandling hos voksne der har mindst 4 migrænedage pr. måned. Derudover er botulinum type A toxin godkendt til patienter med kronisk migræne. Ikke alle lægemidler, der fremgår af de eksisterende danske behandlingsvejledninger, er blevet godkendt til forebyggelse af migræne, men bruges til formålet som ”off-label” (ikkegodkendt til indikationen).

Der er ikke enighed, hverken nationalt eller internationalt, om disse lægemidlers indbyrdes placering i behandlingsalgoritmen til forebyggelse af migræne – se tabel 1 i bilag 1. Der er i øvrigt en meget stor individuel variation i de enkelte lægemidlers effekt og bivirkninger på den enkelte patient. Valget af, hvilket præparat en patient tilbydes, baseres således på en individuel vurdering af bl.a. patients risikoprofil, andre sygdomme og tidligere erfaring.

Der er generelt en stor enighed om, at betablokkere (metoprolol/propranolol) opfattes som førstevalgspræparater. Det er i øvrigt fagudvalgets skøn, at topiramat og de to ”off-label”-præparater candesartancilexetil og lisinopril (pga. den relativt gunstige bivirkningsprofil) anvendes i så stor en udstrækning, at de sammen med betablokkere udgør førstevalgspræparaterne ved forebyggende behandling af migræne. Fagudvalget skønner således, at de fleste patienter, som tager forebyggende migrænebehandling, behandles med et af disse præparater.

Ved behandlingssvigt (enten i form af suboptimal effekt eller uacceptable bivirkninger) eller kontraindikationer tilbydes patienterne typisk behandling med amitriptylin/nortriptylin eller valproat – for

patienter med kronisk migræne eventuelt botulinum type A toxin – som andetvalgslægemidler. I 2019 har Medicinrådet anbefalet erenumab og fremanezumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på mindst ét antiepileptikum og mindst ét antihypertensivum. De er dermed mulige behandlingsvalg til denne patientgruppe og dermed også egnede komparatorer for denne vurdering. I forbindelse med de tidligere vurderinger i Medicinrådet blev erenumab og fremanezumab vurderet at være klinisk ligestillede.

Ved behandlingssvigt eller kontraindikationer mod andetvalgslægemidlerne kan patienterne tilbydes behandling med andre lægemidler, som er mindre anvendt pga. mindre gunstig bivirkningsprofil, f.eks. lamotrigin og pizotifen.

4.2 Galcanezumab

Galcanezumab er et humaniseret monoklonalt antistof, der selektivt binder til det vasodilaterende neuropeptid calcitonin genrelaterede peptid (CGRP), hvorved CGRP forhindres i at binde til CGRP-receptoren. Dette fører til en hæmning af den CGRP-inducerede karudvidelse, reduktion af den neurologisk medierede immunreaktion samt hæmning af smertesignaler. Galcanezumab administreres subkutant og indgives én gang om måneden. Initielt gives en støddosis på 240 mg og derefter 120 mg én gang om måneden.

5 Kliniske spørgsmål

5.1 Klinisk spørgsmål 1

*Hvad er værdien af galcanezumab til patienter med **kronisk migræne**, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med erenumab eller fremanezumab?*

Population
Patienter der har kronisk migræne (mindst 15 hovedpinedage/måned hvoraf mindst 8 dage er med migræne) og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger.

Intervention
Galcanezumab 240 mg som støddosis efterfulgt af 120 mg subkutant én gang om måneden.

Komparator
Erenumab 70 mg eller 140 mg subkutant hver 4. uge.
eller
Fremanezumab 225 mg subkutant 1 gang om måneden eller 675 mg subkutant 1 gang hver tredje måned.

Medicinrådet betragter de to komparatorer som ligeværdige valg i dansk klinisk praksis og ansøger opfordres til at vælge den komparator, som giver det bedste sammenligningsgrundlag. Ansøger bør redegøre for valg af komparator.

Effektestimaterne for de forskellige doser af henholdsvis erenumab eller fremanezumab skal slås sammen inden de statistiske analyser. Samme fremgangsmåde blev anvendt i forbindelse med vurderingen af fremanezumab, hvor Medicinrådets sekretariat lavede en indirekte sammenligning mellem erenumab og fremanezumab. For dikotome effektmål kan resultaterne slås sammen ved at lægge antal hændelser og antal deltagere sammen for de to doser. For kontinuerte effektmål beregnes et samlet antal deltagere, en fælles middelværdi og en fælles standardafvigelse.

Effektmål
Se tabel 1.

5.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den mindste klinisk relevante forskel, som, fagudvalget vurderer, er klinisk relevant, og de valgte effektmåls kategori.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller. For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For alle effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskelsamt indplacering i de tre effektmålsgrupper (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål*	**Vigtighed**	**Effektmålsgruppe**	**Måleenhed**	**Mindste klinisk relevante forskel**
Frekvens af migrænedage	Kritisk	Alvorlige symptomer og bivirkninger	Reduktion af månedlige migrænedage	10 %-point
	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patientpopulation, som opnår ≥ 50 % reduktion af månedlige migrænedage	5 %-point
Livskvalitet	Kritisk	Livskvalitet	Gennemsnitlig ændring fra baseline på MSQ	MSQ-RF: 5 point MSQ-FF: 5 point MSQ-EF: 8 point
Frekvens af hovedpinedage	Vigtig	Alvorlige symptomer og bivirkninger	Reduktion af månedlige hovedpinedage	10 %-point
Anfalds-sværhedsgrad	Vigtig	Alvorlige symptomer og bivirkninger	Reduktion af antal dage med anfaldsbehandling pr. måned	10 %-point
Bivirkninger	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter som oplever bivirkninger, der medfører behandlingsophør	5 %-point
			Kvalitativ gennemgang af bivirkninger	-

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Den minimale opfølgningstid til vurdering af forebyggende migrænebehandling er tre måneder, hvilket skyldes, at man i klinisk praksis normalt venter 3 måneder, inden man vurderer behandlingsresponsen hos den enkelte patient.

Frekvens af migrænedage
Et af de primære behandlingsmål med forebyggende behandling er at reducere frekvensen af migræneanfald. Fagudvalget vil vurdere galcanezumabs effekt på anfaldsfrekvens ved at se på migrænedage pr. måned og

andelen af patienter, der opnår minimum 50 % reduktion i antallet af migrænedage (≥ 50 % responderrate). Begge er mål for anfaldsfrekvens, men supplerer hinanden da migrænedage pr. måned vil udtrykke den gennemsnitlige reduktion af migrænedage, mens responderraten vil indikere, om en eventuel reduktion i gennemsnitligt antal af migrænedage vil gavne en større eller mindre andel af patientpopulationen.

Frekvens af migrænedage – procentuel reduktion af månedlige migrænedage (kritisk)
Definitionen af en migrænedag følger retningslinjerne fra *International Headache Society* [4]. Definitionen kan variere lidt mellem forskellige studier, men er oftest en kalenderdag med mindst fire på hinanden følgende timer med migræne eller hovedpine (uafhængig af varighed) behandlet med migrænespecifikke akutte medikamenter (triptaner eller ergotaminer). Forebyggende migrænebehandling tilbydes normalt til patienter, der har mindst to anfald pr. måned. Ofte har patienter, der henvises til neurologiske specialcentre pga. migræne, dog en højere frekvens af migrænedage pr. måned, og det er derfor relevant at undersøge, om galcanezumab kan reducere antal migrænedage pr. måned. Idet der er stor variation blandt migrænepatienter i antal migrænedage/måned (selv for patienter med kronisk migræne), fastsættes den mindste klinisk relevante forskel i procentuel forskel i stedet for i absolutte tal. Migrænedage er et kritisk effektmål. Hos patienter med kronisk migræne og tidligere behandlingssvigt viser de kliniske studier med erenumab og fremanezumab en reduktion på ca. 4 dage fra et udgangspunkt på 18 og 14 migrænedage ved baseline [5,6]. Dette svarer til en gennemsnitlig reduktion på ca. 25 %. Fagudvalget vurderer, at en forskel på 10 %-point i antal migrænedage/måned mellem de to behandlinger, opfattes som klinisk relevant.

Frekvens af migrænedage – andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage (vigtig)
En "≥ 50 % responderrate" er et udtryk for andelen af patienter, der opnår minimum en halvering af deres migrænedage [4]. Migrænesymptomer kan være meget invaliderende for patienten, og det er mange gange svært at opnå fuldstændig symptomfrihed uden meget generende bivirkninger. Patienterne er ofte i den skole- eller erhvervsaktive alder, hvor migræne kan medføre et betydeligt fravær. Det er fagudvalgets forventning, at andelen af patienter, som opnår mindst en halvering i deres migrænedage med henholdsvis galcanezumab, erenumab og fremanezumab, er ens. De kliniske studier med erenumab og fremanezumab hos migrænepatienter med tidligere behandlingssvigt viser, at ca. 35 % af patienterne oplever minimum 50 % reduktion af deres migrænedage [5,6]. Det er fagudvalgets vurdering, at en forskel i andelen af patienter, der oplever minimum 50 % reduktion af deres migrænedage på 5 %-point, er klinisk relevant.

Livskvalitet (kritisk)
Livskvalitet er et centralt effektmål for migrænepatienter og betragtes af fagudvalget som et kritisk effektmål. Der er udviklet flere spørgeskemaer specifikt til vurdering af livskvaliteten hos migrænepatienter, herunder bl.a. "The Head Impact Test" (HIT-6), *Migraine-Specific Quality-of-Life Questionnaire* (MSQ) og *Migraine Disability Assessment questionnaire* (MIDAS). Ansøger har angivet, at HIT-6 ikke er anvendt i de studier, der undersøger effekten af galcanezumab. Ansøger kan derfor anvende *Migraine-Specific Quality-of-Life Questionnaire* (MSQ) eller *Migraine Disability Assessment questionnaire* (MIDAS) i prioriteret rækkefælge. MSQ foretrækkes fremfor MIDAS, da fagudvalget ikke har kendskab til etablerede mindste klinisk relevante forskelle for MIDAS.

MSQ er et af de mest udbredte sygdomsspecifikke værktøjer til vurdering af helbredsrelateret livskvalitet hos patienter med migræne. MSQ er valideret til patienter med episodisk migræne og patienter med kronisk migræne [7]. MSQ måler livskvaliteten indenfor de seneste 4 uger på tværs af tre subskalaer: Restriktiv funktion (MSQ-RF), forebyggende funktion (MSQ-FF) og emotionel funktion (MSQ-EF). Scoren spænder fra 0 til 100 i hvert domæne, hvor en højere score angiver forbedring i livskvalitet. Der findes mindste klinisk relevante forskelle i litteraturen, som bl.a. er bestemt ud fra studier med forebyggende migrænebehandling. De mindste klinisk relevante forskelle for hver af de tre subskalaer, som fagudvalget vil basere vurderingen på, er 5 point, 5 point og 8 point for henholdsvis MSQ-RF, MSQ-FF og MSQ-EF [8].

Hovedpinedage pr. måned (vigtig)
Patienter med kronisk migræne har ≥ 15 hovedpinedage om måneden, heraf mindst 8 dage som migrænedage. Disse patienter kan således have et betydeligt antal dage med andre non-migrænehovedpineformer, oftest spændingshovedpine. En hovedpinedag er defineret som en kalenderdag, hvor patienten oplevede en migrænehovedpine eller en non-migrænehovedpine med en varighed på mindst fire på hinanden følgende timer eller en hovedpine (uafhængig af varighed), hvor patienten har behov for akut anfaldsbehandling (triptaner, ergotaminer eller anden smertestillende medicin). Kun enkelte lægemidler, der bruges som forebyggende behandling ved migræne, har, foruden effekten på antallet af migrænedage, også en direkte effekt på reduktion af anden hovedpine. Effekten kan for andre lægemidler dog være indirekte, så en reduktion i antal migrænedage medfører en forbedring af migræne og dermed også en reduktion af øvrig non-migrænehovedpine. Ved monitorering af behandlingseffekt af den forebyggende behandling hos patienter med kronisk migræne er det derfor et centralt element at vurdere effekten af den forebyggende behandling på øvrig non-migrænehovedpine. Fagudvalget vurderer, at en forskel på 10 %-point i antal hovedpinedage pr. måned er klinisk relevant.

Forbrug af anfaldsbehandling (vigtig)
Ud over reduktion af migræneanfaldsfrekvens måles en forebyggende behandlingseffektivitet ved reduktion af sværhedsgraden af migræne [4]. Da et migræneanfald kan have forskellige sværhedsgrader i løbet af samme anfald (f.eks. mild i starten, stigende til moderat/svær og atter faldende til mild), er det svært at måle på sværhedsgraden direkte, da det afhænger af, hvornår under migræneanfaldet patienten bliver bedt om at gradere sit migræneanfald. Det har derfor været traditionen at anvende forbrug af smertestillende medicin som et surrogatmål, der indikerer, at et migræneanfald har mindst en moderat intensitet. Det skal her også nævnes, at forbrug af smertebehandling er meget relevant i forhold til, at selve de smertestillende lægemidler indebærer en risiko for bivirkninger, herunder overforbrugshovedpine. Derfor er en reduktion af forbrug af smertestillende behandling ønskværdig. Patienter med kronisk migræne har ofte et væsentligt forbrug af anfaldsmedicin i kraft af deres anfaldsfrekvens. I studierne med erenumab og fremanezumab er antallet af dage med anfaldsbehandling hos patienter med kronisk migræne ved baseline i gennemsnit 9-13 dage afhængig af hvilken type medicin, som inkluderes i opgørelserne. Reduktionen efter 12 ugers behandling er i størrelsesordenen 3-4, svarende til en reduktion på ca. 30-35 % [5,6]. Fagudvalget vurderer, at en forskel på 10 %-point i antallet af dage med behov for anfaldsbehandling pr. måned er klinisk relevant og dermed indikerer, at der er en klinisk relevant forskel i effekt på de to lægemidler.

Bivirkninger (vigtig)
Forebyggende behandling af migræne med de traditionelt anvendte lægemidler afbrydes ofte på grund af bivirkninger. Den kliniske erfaring med erenumab og fremanezumab er begrænset, men data fra de kontrollerede kliniske undersøgelser tyder på, at patienterne sjældent oplever bivirkninger som giver anledning til behandlingsophør. Hos patienter med kronisk migræne er det således rapporteret, at andelen af patienter, der oplever behandlingsophør på grund af uønskede hændelser, er ca. 1 %. Fagudvalget vurderer, at en 5 %-pointforskel i andelen af patienter, der oplever bivirkninger, der medfører behandlingsophør, er relevant.

Herudover ønsker fagudvalget en kvalitativ beskrivelse af de hyppigst forekommende bivirkninger ved behandling med galcanezumab.

6 Litteratursøgning

Vurderingen af klinisk merværdi baseres som udgangspunkt på data fra peer-reviewede publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor galcanezumab er sammenlignet direkte med erenumab eller fremanezumab. Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af galcanezumab og erenumab eller fremanezumab.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af galcanezumab og erenumab eller fremanezumab. Det betyder, at der både skal søges efter primærstudier af galcanezumabs effekt og efter primærstudier af effekten af erenumab og fremanezumab. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes nedenfor.

Søgestreng MEDLINE (via PubMed)

#	Søgestreng	Kommentar
#1	"Migraine Disorders"[Mesh] OR migrain*[tiab]	
#2	prophyl*[tiab] OR prevent*[tiab]	
#3	chronic*[tiab]	
#4	#1 and #2 and #3	Populationen
#5	galcanezumab[nm] OR galcanezumab[tiab] OR LY2951742[tiab] OR LY-2951742[tiab] OR Emgality[tiab]	Intervention
#6	erenumab[nm] OR erenumab*[tiab] OR Aimovig[tiab] OR AMG-334[tiab] OR fremanezumab[nm] OR fremanezumab[tiab] OR TEV-48125[tiab] OR Ajovy[tiab]	Komparator
#7	#4 AND (#5 OR #6)	Indirekte sammenligning
#8	randomized controlled trial[pt]	Cochrane RCT-filter
#9	controlled clinical trial[pt]	
#10	randomized[tiab] OR randomised[tiab]	
#11	placebo[tiab]	
#12	clinical trials as topic[mesh:noexp]	
#13	randomly[tiab]	
#14	trial[ti]	
#15	#8 or #9 or #10 or #11 or #12 or #13 or #14	
#16	animals[mh] NOT humans [mh]	
#17	#15 not #16	
#18	#7 and #17	Samlet søgning

Søgestreng CENTRAL (via Cochrane Library)

#	Søgestreng	Kommentar
#1	[mh "Migraine Disorders"]	
#2	migrain*:ti,ab,kw	
#3	(prophyl* or prevent*):ti,ab or prophylaxis:kw	
#4	chronic*:ti,ab,kw	
#5	(#1 or #2) and #3 and #4	Populationen
#6	(galcanezumab or LY2951742 or LY-2951742 or Emgality):ti,ab,kw	Intervention
#7	(erenumab or Aimovig or AMG-334 or fremanezumab or TEV-48125 or Ajovy):ti,ab,kw	Komparator
#8	#5 and (#6 or #7)	Indirekte sammenligning
#9	("conference abstract" or review):pt OR NCT*:au	
#10	("clinicaltrials gov" or trialsearch):so	
#11	#9 OR #10	
#12	#8 not #11	Samlet søgning

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

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Eksklusionskriterier:

- *Andre studiedesign end RCT*
- *Studier med andre populationer end de valgte*
- *Studier der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.*

7 Databehandling og analyse

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

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention to treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

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

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (f.eks. 50 % responder rate, behandlingsstop pga. bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet som angivet i appendiks 3 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser - version 2.0.

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

Der ønskes en indirekte sammenligning af galcanezumab og erenumab eller fremanezumab ved brug af placebo kontrollerede studier.

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

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

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

8 Referencer

1. Flachs E, Eriksen L, Koch M, Ryd J, Dibba E, Skov-Ettrup L, et al. Sygdomsbyrden i Danmark. København; 2015 dec.
2. Bendtsen L, Møller Hansen J, Maargaard R. Migræne [internet]. Pro.medicin. 2018 [citeret 16. august 2018]. Tilgængelig fra: https://pro.medicin.dk/Sygdomme/Sygdom/318362
3. Dansk Hovedpine Selskab. Diagnostik og behandling af hovedpinesygdomme og ansigtssmerter. 2010.
4. Tfelt-Hansen P, Pascual J, Ramadan N, Dahlöf C, D'Amico D, Diener H-C, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia. 2012;32(1):6–38.
5. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet (London, England). 2019;
6. Ashina M, Tepper S, Brandes JL, Reuter U, Boudreau G, Dolezil D, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia. 2018;38(10):1611–21.
7. Bagley CL, Rendas-Baum R, Maglinte GA, Yang M, Varon SF, Lee J, et al. Validating Migraine-Specific Quality of Life Questionnaire v2.1 in episodic and chronic migraine. Headache. 2012;52(3):409–21.
8. Cole JC, Lin P, Rupnow MFT. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version. Cephalalgia. 2009;29(11):1180–7.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende migræne

Formand	**Indstillet af**
Thue Hjortkær Nielsen Overlæge	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Medlemmer	**Udpeget af**
Ana Maria Nan Afdelingslæge	Region Nordjylland
Kan ikke udpege en kandidat	Region Midtjylland
Unni Jeppesen Praktiserende speciallæge	Region Syddanmark
Kan ikke udpege en kandidat	Region Sjælland
Gine Stobberup Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
Jon Andersen Overlæge	Dansk Selskab for Klinisk Farmakologi
Anne Bülow-Olsen Patient/patientrepræsentant	Danske Patienter
Christian Hansen Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Jesper Skov Neergaard (projekt- og metodeansvarlig) Jane Skov (sundhedsvidenskabelig konsulent) Jan Odgaard-Jensen (biostatistiker) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder) Bettina Fabricius Christensen (informationsspecialist)

10 Versionslog

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