Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende fremanezumab som mulig standardbehandling til forebyggende behandling af migræne

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om anbefalingen

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

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

Dokumentoplysninger	
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Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
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Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Ajovy
Generisk navn	Fremanezumab
Firma	Teva
ATC-kode	N02CX07
Virkningsmekanisme	Humant monoklonalt antistof som selektivt binder til CGRP-peptid, som er en del af patofysiologien for migræne. Fremanezumab binder til både α- og β-isoformerne af CGRP-liganden, men ikke til receptoren.
Administration/dosis	225 mg én gang om måneden (månedlig dosering) 675 mg hver tredje måned (kvartalsvis dosering)
EMA-indikation	Forebyggende behandling af migræne hos voksne som har mindst fire migrænedage om måneden.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** fremanezumab som mulig standardbehandling til forebyggelse af migræne hos patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger med mindst ét antihypertensivum og ét antiepileptikum, som et alternativ til behandling med botulinum type A toxin.

Medicinrådet finder, at der er et rimeligt forhold mellem meromkostningerne og den værdi, som lægemidlet tilbyder for denne population. Medicinrådet har desuden lagt vægt på den enklere administration i form af subkutane injektioner med fremanezumab sammenlignet med de intramuskulære injektioner ved behandling med botulinum type A toxin.

Medicinrådet **anbefaler ikke** fremanezumab som mulig standardbehandling til forebyggelse af migræne hos patienter med episodisk migræne med mindst fire migrænedage pr. måned uanset eventuelle tidligere behandlingssvigt med andre forebyggende behandlinger.

Medicinrådet finder ikke, at der er et rimeligt forhold mellem meromkostningerne og den værdi, som lægemidlet tilbyder for denne population.

Medicinrådet **anbefaler ikke** fremanezumab som mulig standardbehandling til forebyggelse af migræne hos patienter med kronisk migræne, og som ikke har oplevet behandlingssvigt på tidligere forebyggende behandlinger med mindst ét antihypertensivum og ét antiepileptikum.

Medicinrådet finder ikke, at der er et rimeligt forhold mellem meromkostningerne og den værdi, som lægemidlet tilbyder for denne population.

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

Hvad er den kliniske merværdi af fremanezumab til patienter med migræne, der har mindst fire migrænedage pr. måned sammenlignet med eksisterende standardbehandling?

Hvad er den kliniske merværdi af fremanezumab til patienter med migræne, der har mindst fire migrænedage pr. måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med eksisterende standardbehandling?

Hvad er den kliniske merværdi af fremanezumab til forebyggelse af migræne hos 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 indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med botulinum type A toxin?*

3 Formål

Formålet med *Baggrund for Medicinrådets anbefaling vedrørende fremanezumab som mulig standardbehandling til forebyggende behandling af migræne* er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Migrænehovedpine kendetegnes ved anfaldsvis hovedpine. Lidelsen er sandsynligvis en genetisk disponeret sygdom, der involverer både nerver og blodkar i hovedet. Calcitonin genrelateret protein (CGRP) menes at spille en væsentlig rolle og er muligvis en forårsagende faktor for sygdommen. De egentlige årsager til migræne kendes ikke med sikkerhed.

Migræne inddeles i "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 hovedpinetype, f.eks. spændingshovedpine.

Der findes ingen øvre grænse for antal migrænedage i indikationen for fremanezumab, som således har indikation for både episodisk og kronisk migræne.

Yderligere baggrundsinformation findes i " Medicinrådets vurdering af fremanezumab til forebyggende behandling af migræne" (bilag 4).

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den endelige ansøgning vedrørende fremanezumab fra Teva den 9. august 2019 (bilag 5). Vurdering af klinisk merværdi blev præsenteret og godkendt på rådsmødet den 23. oktober 2019. Der har været udvidet clock-stop fra den 20. til den 27. november 2019. Medicinrådet har gennemført vurderingen af fremanezumab til forebyggende behandling af migræne på 14 uger og 5 dage.

5 Medicinrådets vurdering af samlet værdi

Fremanezumab til forebyggelse af migræne hos patienter, der har mindst fire migrænedage pr. måned (klinisk spørgsmål 1):

- Medicinrådet finder, at den samlede værdi af fremanezumab sammenlignet med gruppen af antihypertensiva (propranolol, candesartancilexetil og lisinopril) **ikke kan kategoriseres**.

Evidensens kvalitet vurderes at være lav til meget lav. Fremanezumab vurderes samlet set ikke at have dårligere effekt eller sikkerhedsprofil end gruppen af antihypertensiva.
- Medicinrådet vurderer, at fremanezumab giver en **lille merværdi** sammenlignet med topiramat. Evidensens kvalitet vurderes at være lav.

Fremanezumab til forebyggelse af migræne hos patienter, der har mindst fire migrænedage pr. måned, og som har oplevet behandlingssvigt på mindst to migræneforebyggende lægemidler (et antihypertensivum og et antiepileptikum) (klinisk spørgsmål 2):

- Medicinrådet finder, at den samlede værdi af fremanezumab sammenlignet med amitriptylin og valproat **ikke kan kategoriseres**. Evidensens kvalitet vurderes at være meget lav. Fremanezumab vurderes samlet set ikke at have dårligere effekt eller sikkerhedsprofil end de to komparatorer.

Fremanezumab hos patienter med **kronisk migræne**, der har oplevet behandlingssvigt på mindst to migræneforebyggende lægemidler (et antihypertensivum og et antiepileptikum) (klinisk spørgsmål 3):

- Medicinrådet vurderer, at fremanezumab til patienter med kronisk migræne giver en **lille merværdi** sammenlignet med botulinum type A toxin. Evidensens kvalitet vurderes at være meget lav.

6 Høring

Ansøger har den 29. oktober 2019 indsendt et høringssvar, som ikke opponerede mod kategoriseringen og derfor ikke gav anledning til at revurdere Medicinrådets vurdering af lægemidlets værdi. Høringssvaret er vedlagt som bilag 3.

7 Resumé af økonomisk beslutningsgrundlag

De økonomiske analyser er forbundet med betydelige usikkerheder. Antagelserne om hvor mange patienter som frafalder behandlingen, har stor indflydelse på de estimerede omkostninger på en femårig tidshorisont. Budgetkonsekvenserne er også forbundet med betydelig usikkerhed, idet det relevante patientantal er vanskeligt at estimere.

Amgros vurderer, at der ikke er et rimeligt forhold mellem meromkostningerne og lægemidlets værdi for fremanezumab som mulig standardbehandling til patienter med episodisk og kronisk migræne sammenlignet med behandling med propranolol, lisinopril, candesartan, amitriptylin og valproat

Amgros vurderer, at der er et rimeligt forhold mellem meromkostningerne og lægemidlets værdi for fremanezumab som mulig standardbehandling til patienter med episodisk eller kronisk migræne, sammenlignet med behandling med topiramat

Amgros vurderer, at der er et rimeligt forhold mellem meromkostningerne og lægemidlets værdi for fremanezumab som mulig standardbehandling til patienter med kronisk migræne, sammenlignet med behandling med botulinum type A toxin.

8 Overvejelser omkring alvorlighed/forsigtighed

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

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 opfylde Medicinrådets habilitetskrav	Region Midtjylland
Unni Jeppesen Praktiserende speciallæge	Region Syddanmark
Kan ikke udpege en kandidat	Region Sjælland
Gine Stobberup Klinisk farmaceut	Dansk Selskab for Sygehusapoteksledelse
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 (projektdeltager) Jan Odgaard-Jensen (biostatistiker) Anette Pultera Nielsen (fagudvalgskoordinator) Annemette Anker Nielsen (teamleder) Bettina Fabricius Christensen (informationsspecialist) *Tidligere medarbejdere, der har bidraget til arbejdet:* Nour Al-Hussainy (projektdeltager) Diana Odrobináková (biostatistiker)

10 Versionslog

Version	Dato	Ændring
1.0	27. november 2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

1. Amgros' beslutningsgrundlag
2. Amgros' sundhedsøkonomiske analyse
3. Høringssvar fra ansøger
4. Medicinrådets vurdering af fremanezumab til forebyggende behandling af migræne
5. Ansøgers endelige ansøgning
6. Medicinrådets protokol for vurdering af klinisk merværdi for fremanezumab til forebyggende behandling af migræne

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af fremanezumab (Ajovy) som mulig standardbehandling til forebyggende behandling af migræne blandt voksne med mindst fire månedlige migrænedage. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	20-11-2019
Firma	Teva Danmark A/S (ansøger)
Lægemiddel	Fremanezumab (Ajovy)
Indikation	Forebyggende behandling af migræne blandt voksne med mindst fire månedlige migrænedage

Amgros' vurdering

- Amgros vurderer, at der **ikke** er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for fremanezumab (Ajovy) som mulig standardbehandling til patienter med episodisk og kronisk migræne sammenlignet med behandling med propranolol, lisinopril, candesartan, amitriptylin og valproat
- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for fremanezumab (Ajovy) som mulig standardbehandling til patienter med episodisk og kronisk migræne, sammenlignet med behandling med topiramat
- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for fremanezumab (Ajovy) som mulig standardbehandling til patienter med kronisk migræne, sammenlignet med behandling med Botox

Overordnet konklusion

Medicinrådet har vurderet, at fremanezumab (Ajovy) sammenlignet med propranolol, lisinopril, candesartan, amitriptylin og valproat giver en merværdi, der **ikke kan kategoriseres.** Sammenlignet med topiramat og Botox har fremanezumab (Ajovy) en **lille klinisk merværdi** ifølge Medicinrådets vurdering.

Behandling med fremanezumab (Ajovy) er forbundet med betydelige meromkostninger sammenlignet med propranolol, topiramat, lisinopril, candesartan, amitriptylin og valproat til nævnte indikation. Sammenlignet med Botox er fremanezumab (Ajovy) forbundet med begrænsede meromkostninger til nævnte indikation.

Amgros vurderer, at der **ikke** er rimeligt forhold mellem den kliniske merværdi for fremanezumab (Ajovy), sammenlignet med behandling med propranolol, lisinopril, candesartan, amitriptylin og valproat.

Amgros vurderer, at der **er** rimeligt forhold mellem den kliniske merværdi for fremanezumab (Ajovy), sammenlignet med behandling med topiramat og Botox.

Meromkostninger drives af prisen på fremanezumab (Ajovy) samt antagelserne om, hvor mange patienter der fortsætter på behandlingen.

Andre overvejelser

Amgros har indgået en aftale med Teva Danmark A/S om indkøb af fremanezumab (Ajovy) til en SAIP, som er lavere end AIP. Konklusionen er baseret på SAIP. Aftalen er gældende indtil 15. november 2020 med mulighed for forlængelse.

Konklusion for populationen

Tabel 1: Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP).

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
P1: Patienter, der har mindst fire migrænedage per måned.	Propranolol	Ikke kan kategoriseres	Lav evidenskvalitet	Ikke rimeligt
	Topiramat	Lille klinisk merværdi	Lav evidenskvalitet	Rimeligt
	Lisinopril	Ikke kan kategoriseres	Meget lav evidenskvalitet	Ikke rimeligt
	Candesartan	Ikke kan kategoriseres	Meget lav evidenskvalitet	Ikke rimeligt
P2: Patienter, der har mindst fire migrænedage per måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger.	Amitriptylin	Ikke kan kategoriseres	Meget lav evidenskvalitet	Ikke rimeligt
	Valproat	Ikke kan kategoriseres	Meget lav evidenskvalitet	Ikke rimeligt
P3: Patienter, der har kronisk migræne (≥ 15 hovedpinedage per måned hvoraf mindst 8 dage er med migræne), og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger.	Botox	Lille klinisk merværdi	Meget lav evidenskvalitet	Rimeligt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med fremanezumab (Ajovy) er forbundet med betydelige meromkostninger sammenlignet med propranolol, topiramat, lisinopril, candesartan, amitriptylin og valproat. Sammenlignet med Botox er fremanezumab (Ajovy) forbundet med begrænsede meromkostninger.

Amgros' hovedanalyse for episodisk migræne resulterer i betydelige meromkostninger for fremanezumab (Ajovy) sammenlignet med komparatorerne for P1 og P2. Hvis analysen udføres på baggrund af AIP bliver de total inkrementelle omkostninger ca. 41.000 – 49.000 DKK per patient afhængigt af den valgte komparator.

Resultaterne fra Amgros' hovedanalyse for episodisk migræne præsenteres i Tabel 2 og Tabel 3 for hhv. P1 og P2.

Tabel 2: Resultatet af Amgros' hovedanalyse for episodisk migræne for sammenligningen med P1, DKK, SAIP.

	Fremanezumab (Ajovy)	Propranolol	Topiramat	Lisinopril	Candesartancilexetil
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	10.475	6.703	4.384	6.586	9.793
Patientomkostninger	3.167	1.693	1.127	1.693	2.517
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 3: Resultatet af Amgros' hovedanalyse for episodisk migræne for sammenligningen med P2, DKK, SAIP.

	Fremanezumab (Ajovy)	Amitriptylin	Valproat
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	10.475	5.669	3.351
Patientomkostninger	3.167	1.432	807
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

Amgros' hovedanalyse for kronisk migræne resulterer i betydelige meromkostninger for fremanezumab (Ajovy) sammenlignet med komparatorerne for P1 og P2, og begrænsede meromkostninger sammenlignet med komparatoren for P3. Hvis analysen udføres på baggrund af AIP bliver de total inkrementelle omkostninger ca. 13.000 – 50.000 DKK per patient afhængigt af den valgte komparator.

Resultaterne fra Amgros' hovedanalyse for kronisk migræne præsenteres i Tabel 4, Tabel 5 og Tabel 6 for hhv. P1, P2 og P3.

Tabel 4: Resultatet af Amgros' hovedanalyse for kronisk migræne for sammenligningen med P1, DKK, SAIP.

	Fremanezumab (Ajovy)	Propranolol	Topiramat	Lisinopril	Candesartancilexetil
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	15.195	13.339	8.768	13.172	19.585
Patientomkostninger	3.734	3.386	2.254	3.386	5.035
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 5: Resultatet af Amgros' hovedanalyse for kronisk migræne for sammenligningen med P2, DKK, SAIP.

	Fremanezumab (Ajovy)	Amitriptylin	Valproat
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	15.195	11.338	6.702
Patientomkostninger	3.734	2.864	1.615
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

Tabel 6: Resultatet af ansøgers hovedanalyse for kronisk migræne for sammenligningen med P3, DKK, SAIP.

	Fremanezumab (Ajovy)	Botox
Lægemiddelomkostninger	[redacted]	[redacted]
Hospitalsomkostninger	15.195	29.952
Patientomkostninger	3.734	3.734
Totale omkostninger	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer, at anbefaling af fremanezumab (Ajovy) som mulig standardbehandling, vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 afhængigt af den valgte population. Hvis analysen udføres med AIP, vil budgetkonsekvenserne være på ca. 1,2 mio. – 3,3 mio. DKK per år.

Patientantallet, der ligger til grund for Amgros' budgetkonsekvensanalyse, er baseret på de danske hovedpinecentres nuværende kapacitet, og tæller således 600 patienter per år.

FREMANEZUMAB (AJOVY)

FOREBYGGENDE BEHANDLING AF MIGRÆNE

AMGROS 1. november 2019

AMGROS

OPSUMMERING

Baggrund

Fremanezumab (Ajovy) er indiceret til forebyggende behandling af migræne blandt voksne med mindst fire månedlige migrænedage. Omkring 5.000-6.000 patienter kandiderer årligt til behandling af den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Teva Danmark A/S.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med fremanezumab (Ajovy) sammenlignet med betablokker, lisinopril, candesartancilexetil, topiramat (P1), tricykliske antidepressiva og valproat (P2) og Botulinum type A toxin (Botox) (P3) som forebyggende behandling af patienter med migræne.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de inkrementelle omkostninger per patient ved brug af fremanezumab (Ajovy) sammenlignet med komparatorer. De inkrementelle omkostninger er angivet i SAIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger over 5 år for fremanezumab (Ajovy) følgende:

Episodisk migræne:

- P1: ca. [redacted] DKK
- P2: ca. [redacted] DKK

Kronisk migræne:

- P1: ca. [redacted] DKK
- P2: ca. [redacted] DKK
- P3: ca. [redacted] DKK

Hvis analysen udføres med AIP, bliver de inkrementelle omkostninger til sammenligning ca. 13.000 – 50.000 DKK per patient afhængig af den valgte komparator.

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af fremanezumab (Ajovy) som standardbehandling vil være ca. [redacted] DKK. Hvis analysen udføres med AIP, er budgetkonsekvenser ca. 1,2 mio. – 3,3 mio. DKK om året.

Konklusion

Behandling med fremanezumab (Ajovy) er forbundet med betydelige meromkostninger sammenlignet med betablokker (propranolol), topiramat, lisinopril, candesartancilexetil, tricykliske antidepressiva (amitriptylin) og valproat. Sammenlignet med Botulinum type A toxin (Botox) er behandling med fremanezumab (Ajovy) forbundet med begrænsede meromkostninger.

Meromkostningerne er primært drevet af lægemiddelomkostningerne for fremanezumab (Ajovy), og antagelserne om, hvor mange patienter der fortsætter i behandling efter evaluering og forsøg på behandlingsophør.

Budgetkonsekvenserne er forbundet med store usikkerheder. Disse usikkerheder skyldes særligt antagelserne om det forventede patientantal, samt markedsoptaget af fremanezumab (Ajovy).

Liste over forkortelser

AIP	Apotekernes indkøbspris
Botox	Botulinum type A toxin
CGRP	Calcitonin genrelaterede protein
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspris

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Teva Danmark A/S
Handelsnavn:	Ajovy
Generisk navn:	Fremanezumab
Indikation:	Forebyggende behandling af migræne blandt voksne med mindst fire månedlige migrænedage.
ATC-kode:	N02

Proces	
Ansøgning modtaget hos Amgros:	09-08-2019
Endelig rapport færdig:	01-11-2019
Sagsbehandlingstid fra endelig ansøgning:	84 dage
Arbejdsgruppe:	**Line Brøns Jensen** Camilla Nybo Holmberg Mark Friborg Louise Greve Dal Pernille Winther Johansen Lianna Christensen Emma Munk

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Fremanezumab (Ajovy) er indiceret som forebyggende behandling af migræne blandt voksne med mindst fire månedlige migrænedage. Teva Danmark A/S (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver fremanezumab (Ajovy) og har den 09.08.2019 indsendt en ansøgning til Medicinrådet om anbefaling af fremanezumab (Ajovy) som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet, de økonomiske analyser ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de inkrementelle omkostninger forbundet med forebyggende behandling af migræne blandt voksne med mindst fire månedlige migrænedage, i form af de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af fremanezumab (Ajovy) som standardbehandling på danske hospitaler af den nævnte indikation. I analyserne sammenlignes behandling med fremanezumab (Ajovy) med behandling med betablokkere (metoprolol/propranolol), lisinopril, candesartancilexetil og topiramat (P1), tricykliske antidepressiva (amitriptylin/nortritylin) og valproat (P2) og Botox (P3).

1.2 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, 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). Migrænehovedpine kendetegnes ved anfaldsvis hovedpine typisk hen over 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 hovedpinetype, f.eks. spændingshovedpine. Dette skal opfattes som et kontinuerligt spektrum, hvor den enkelte patient i perioder kan gå fra episodisk til kronisk migræne og omvendt.

Migræne er udbredt i alle aldersgrupper. Den debuterer hyppigst inden 40-årsalderen og ofte allerede i barndom eller ungdom. 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. Langt de fleste migrænepatienter bliver behandlet i primærsektoren, men ved utilfredsstillende behandlingseffekt kan patienten blive henvist til en hovedpineklinik/-center på hospitalet. Fagudvalget vedr. migræne vurderer, at antallet af patienter, der bliver behandlet for migræne på de danske hospitaler, er i omegnen af ca. 5.000-6.000 patienter, men at der ikke findes endelige opgørelser over totalt antal migrænepatienter, der er tilknyttet hovedpineklinikker i Danmark. Fagudvalget vedr. migræne skønner, at flertallet af disse patienter opfylder kriterierne for forebyggende migrænebehandling (1).

1.3 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 (2). 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 forebyggende behandling, og nuværende kliniske anbefalinger tilsiger derfor, at medicinen forsøges stoppet hver 6.-12. måned for at sikre, at der fortsat er behov for og effekt af medicinen (2). 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.

De lægemidler, der på nuværende tidspunkt tilbydes som forebyggende behandling af migræne, blev oprindeligt udviklet til andre formål, f.eks. antihypertensiva (blodtryksmedicin), antiepileptika (medicin mod epilepsi) og antidepressiva (medicin mod depression). Disse lægemidler viste sig også at have effekt på forebyggelse af migræne, og visse blev godkendt til dette formål. 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). Derudover er Botox 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) (1).

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 lægemiddel en patient tilbydes, baseres således på en individuel vurdering af bl.a. den enkelte patients risikoprofil, andre sygdomme og tidligere erfaring (1).

Kortfattet kan man dog konkludere, at der generelt er en stor enighed om, at betablokkere (metoprolol/propranolol) opfattes som 1. valg. Det er i øvrigt fagudvalgets skøn, at topiramat og de to "off-label"-lægemidler candesartancilexetil og lisinopril (pga. den relativt gunstige bivirkningsprofil) anvendes i så stor en udstrækning, at de sammen med betablokkere udgør 1. valg ved forebyggende behandling af migræne. Fagudvalget vedr. migræne skønner således, at de fleste patienter, som tager forebyggende migrænebehandling, behandles med et af disse lægemidler.

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 Botox – som 2. valg. Ved behandlingssvigt/kontraindikationer mod 2. valgslægemidlerne kan patienterne tilbydes behandling med andre lægemidler, som er mindre anvendt pga. mindre gunstig bivirkningsprofil, f.eks. lamotrigin og pizotifen (1).

1.4 Behandling med fremanezumab (Ajovy)

Indikation

Fremanezumab (Ajovy) er indiceret til forebyggende behandling af migræne blandt voksne med mindst fire månedlige migrænedage (3).

Virkningsmekanisme

Fremanezumab (Ajovy) er et humaniseret monoklonalt antistof, der selektivt binder til det vasodilaterende neuropeptid 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.

Dosering

Fremanezumab (Ajovy) administreres subkutant og indgives månedligt eller kvartalsvis. Den månedlige dosering er 225 mg, mens den kvartalsvise dosering er 675 mg (3 x 225 mg).

1.4.1 Komparator

Medicinrådet har defineret komparatorer som en behandling med betablokkere (metoprolol/propranolol), lisinopril, candesartancilexetil og topiramat for patienter med migræne, der har mindst fire migrænedage per måned (P1) og en behandling med tricykliske antidepressiva (amitriptylin/nortriptylin) og valproat til patienter med migræne, der har mindst fire migrænedage per måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) (P2), og Botox som komparator til patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (P3), se tabel 1.

Tabel 1: Definerede populationer og komparator.

Population	Komparator
P1: Patienter, der har mindst fire migrænedage per måned.	Betablokkere Lisinopril Candesartancilexetil Topiramat
P2: Patienter, der har mindst fire migrænedage per måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger.	Tricykliske antidepressiva Valproat
P3: Patienter, der har kronisk migræne (≥ 15 hovedpinedage per måned hvoraf mindst 8 dage er med migræne), og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger.	Botox

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af fremanezumab (Ajovy) som forebyggende behandling for følgende populationer:

- **P1:** Hvad er den kliniske merværdi af fremanezumab (Ajovy) til patienter med migræne, der har mindst fire migrænedage per måned sammenlignet med eksisterende standardbehandling?
- **P2:** Hvad er den kliniske merværdi af fremanezumab (Ajovy) til patienter med migræne, der har mindst fire migrænedage per måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med eksisterende standardbehandling?
- **P3:** Hvad er den kliniske merværdi af fremanezumab (Ajovy) til patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med Botox?

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analyserne af inkrementelle omkostninger per patient sammenlignes behandling med fremanezumab (Ajovy) med behandling med propranolol, lisinopril, candesartancilexetil, topiramat (P1), amitriptylin og valproat (P2) og Botox (P3).

Amgros havde nogle indvendinger mod den initiale model, som ansøger indsendte. Det er kun den seneste indsendte model, som præsenteres herunder.

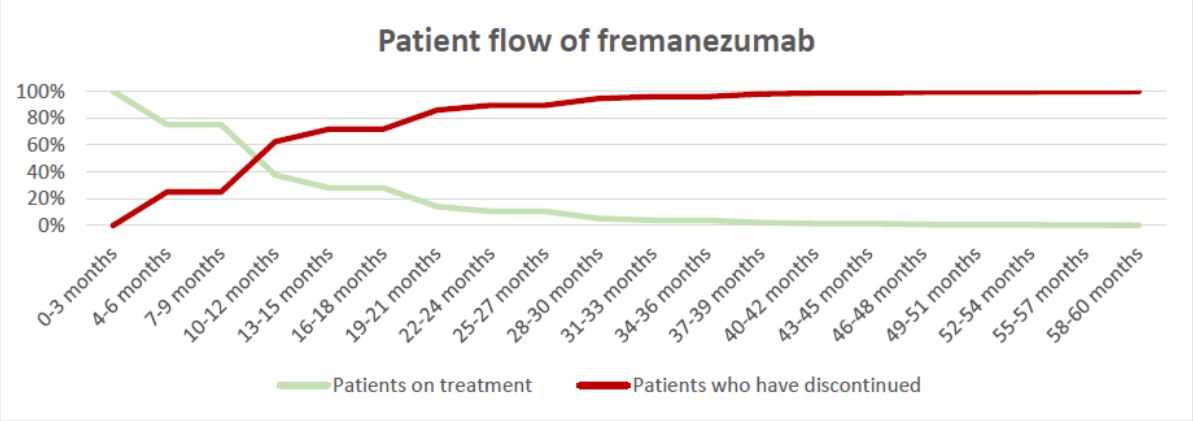
2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse

Ansøger har indsendt en omkostningsanalyse, der inkluderer lægemiddelomkostninger samt hospitalsomkostninger forbundet med kontrolbesøg og udlevering af lægemidler.

Ansøger antager, at alle patienter starter i behandling, hvorefter patienterne enten fortsættes eller stoppes i behandling i forbindelse med et kontrolbesøg efter tre måneders behandling (1 cyklus). Hvis patienten fortsættes i behandling, vil et forsøg på at stoppe behandlingen ske efter ni måneders behandling (3 cyklusser). Efter én måned uden behandling vil patienterne efter et kontrolbesøg enten startes op i behandling igen eller være stoppet. Resten af modellens tidshorisont vil ovenstående behandlingsforløb gentages, så patienterne løbende vil forsøges at stoppe behandling.

Ansøger har fået kliniske eksperter til at estimere andelen af patienter, der fortsætter i behandling efter kontrolbesøg, og andelen af patienter, der stoppes i behandling. Ansøger antager således, at 75% af patienterne fortsætter i behandling med fremanezumab (Ajovy) efter kontrolbesøg, mens 50% fortsætter i behandling med fremanezumab (Ajovy) efter forsøg på at stoppe behandlingen. I Figur 1 ses ansøgers estimater over patientforløb over tid for fremanezumab (Ajovy).



Figur 1: Patientforløb for fremanezumab (Ajovy) over perioder af 3 måneder.

Ansøger antager desuden, at patienter i behandling med én af komparatorerne har et lignende behandlingsforløb, hvor der løbende forsøges at stoppe behandling. I Tabel 2 ses ansøgers estimater på andelen af patienter, der fortsætter i behandling efter evaluering og efter forsøg på behandlingsstop.

Tabel 2: Andel af patienterne, der fortsætter i behandling efter evaluering og andel af patienter, der genopstarter behandling efter forsøg på behandlingsstop.

	Andel af patienter, der fortsætter i behandling efter evaluering	Andel af patienter, der forsætter i behandling efter forsøg på behandlingsstop
Fremanezumab (Ajovy)	75%	50%
Propranolol	50%	50%
Topiramat	25%	50%
Lisinopril	50%	50%
Candesartancilexetil	75%	50%
Amitriptylin	40%	50%
Valproat	10%	50%
Botox	75%	50%

Amgros' vurdering

Modellen drives i høj grad af klinikerestimater. Derfor har Amgros bedt regionerne udpege klinikere med ekspertise indenfor terapiområdet, og bedt de valgte klinikere om at validere ansøgers grundlæggende antagelser og estimater. Regionerne udpegede 3 klinikere, der alle svarede på spørgsmål angående ansøgers modelstruktur og estimater. På baggrund af deres svar finder Amgros ikke anledning til at ændre væsentligt på ansøgers estimater angående, hvor mange patienter, der fortsætter i behandling efter evaluering og ved forsøg på behandlingsstop. Dog udarbejder Amgros følsomhedsanalyser, hvor usikkerhederne ved disse estimater undersøges i forskellige scenarier.

Amgros vurderer, at ansøgers modeltilgang er acceptabel, men vurderer samtidig, at analysens resultat er drevet af, hvor mange patienter, der forsætter på behandlingen efter evaluering og ved forsøg på behandlingsstop. Disse estimater er forbundet med store usikkerheder.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse med et begrænset samfundsperspektiv. Analysen har en tidshorisont på 5 år. Omkostninger, der ligger efter det første år, er diskonteret med en faktor på 4% per år.

Amgros' vurdering

Analysens begrænsede samfundsperspektiv, tidshorisont og diskonteringsrate er i tråd med Amgros' retningslinjer og accepteres.

2.1.3 Omkostninger

Det følgende afsnit om omkostninger redegøres for hvordan og hvilke omkostninger, ansøger har inkluderet i analysen.

Lægemiddelomkostninger

Ansøger har anvendt doser baseret på produktresuméet for fremanezumab (Ajovy) (1). Ansøger har for komparatorer anvendt daglige doser estimeret af en klinisk ekspert. Doseringen af hvert lægemiddel er angivet i Tabel 3.

Tabel 3: Dosering af lægemidler.

Lægemiddel	Titreringsdosis	Vedligeholdelsesdosis
Fremanezumab (Ajovy)	225 mg én gang om måneden	
Propranolol	80 mg dagligt i 7 dage. Derefter 160 mg dagligt i 7 dage.	240 mg per dag.
Lisinopril	5 mg dagligt i 7 dage. Derefter 10 mg dagligt i 7 dage.	20 mg per dag.
Candesartancilexetil	8 mg dagligt i 7 dage. Derefter 16 mg dagligt i 7 dage.	32 mg per dag.
Topiramat	50 mg dagligt i 7 dage. Derefter 100 mg dagligt i 7 dage.	200 mg per dag.
Amitriptylin	10 mg dagligt i 7 dage. Derefter 50 mg dagligt i 7 dage.	100 mg per dag.
Valproat	500 mg dagligt i 7 dage. Derefter 1.000 mg dagligt i 7 dage.	1.500 mg per dag.
Botox	155 enheder i 31-39 injektioner hver 12. uge	

Alle anvendte lægemiddelpriser er i SAIP, se Tabel 4.

Tabel 4: Anvendte lægemiddelpriser, SAIP (oktober 2019).

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Fremanezumab (Ajovy)	225 mg	1 stk.	[redacted]	Teva Danmark A/S
Propranolol	160 mg	100 stk.	[redacted]	Amgros
Lisinopril	20 mg	200 stk.	[redacted]	Amgros
Candesartancilexetil	32 mg	98 stk.	[redacted]	Amgros
Topiramat	50 mg	60 stk.	[redacted]	Amgros
Amitriptylin	50 mg	100 stk.	[redacted]	Amgros
Valproat	300 mg	100 stk.	[redacted]	Amgros
Botox	200 enheder	6 stk.	[redacted]	Amgros

Amgros' vurdering

Ansøger har valgt at benytte den højeste anbefalede dosering for komparatorerne, bortset fra valproat, som dog stadig er højere end standarden. Amgros vurderer, at der er usikkerheder forbundet med denne tilgang, og at det desuden potentielt underestimere de samlede meromkostninger i modellen. Amgros har fået regionernes udpegede klinikere til at validere ansøgers estimater vedrørende dosering af de anvendte lægemidler. På baggrund af deres svar vælger Amgros at nedjustere vedligeholdelsesdoseringen for propranolol, lisinopril, candesartancilexetil, topiramat, amitriptylin og valproat i Amgros' hovedanalyse.

Amgros udarbejder en ny hovedanalyse, hvor vedligeholdelsesdoseringerne for komparatorerne (undtaget Botox) nedjusteres.

Hospitalsomkostninger

Ansøger har inkluderet omkostninger til monitorering af lægemidlerne. Dette inkluderer omkostninger til lægebesøg, indlæggelser, sygeplejersketid i forbindelse med telefonkonsultation, scanninger, blodprøver og medicinudlevering. Ansøger antager, at patienter selv administrerer lægemidlerne, bortset fra Botox, der administreres ved hospitalsbesøg. Derudover skal patienter, der behandles med fremanezumab (Ajovy) oplæres i selvinjektion ved det første ambulante besøg.

Ansøger har estimeret enhedsomkostninger for monitorering ved brug af DRG-takster 2019, ambulante DAGS-takster 2017, Kommunernes og Regionernes Løndatakontor og Rigshospitalets priskatalog fra klinisk biokemisk afdeling. De ambulante DAGS-takster er fremskrevet til 2019.

De anvendte takster ses i Tabel 5.

Tabel 5: Anvendte hospitalsomkostninger, DKK.

Hospitalsomkostning	Enhed	Pris [DKK]	Kilde
Udlevering af medicin	Per udlevering	693,70	Ambulante DAGS-takster 2017
Ambulant besøg	Per besøg	2.230,70	Ambulante DAGS-takster 2017
Ambulant besøg og injektion af Botox	Per besøg	5.979,90	Ambulante DAGS-takster 2017
Sygeplejerske (tid)	Per time	544,50	Kommunernes og Regionernes Løndatakontor
Indlæggelse (1 dag grundet migræne)	Per indlæggelse	3.728,00	DRG-takster 2019
Indlæggelse (>1 dag og <5 dage grundet migræne)	Per indlæggelse	20.264,00	DRG-takster 2019
Blodprøve	Per test	332,00	Rigshospitalets priskatalog fra klinisk biokemisk afdeling
MR-scanning	Per test	2.397,90	Ambulante DAGS-takster 2017
Elektrokardiogram	Per test	412,40	Overenskomst om speciallægehjælp mellem Foreningen af Speciallæger (FAS) og Regionernes Lønnings- og Takstnævn (RLTN)

Ansøger har anvendt estimater for monitoreringsfrekvenserne for patienter med episodisk migræne (P1 og P2) gennem samtale med en kliniker angående behandlingsrutiner. Ansøger antager, at ressourceforbruget for patienter, der behandles med fremanezumab (Ajovy) er 25% mindre end for de patienter, der behandles med komparatorerne, bortset fra udlevering af medicin og elektrokardiogram.

Tabel 6 viser monitoreringsfrekvensen for fremanezumab (Ajovy), propranolol, lisinopril, candesartancilexetil, topiramat, amitriptylin, og valproat for patienter med episodisk migræne.

Tabel 6: Monitoreringsfrekvens for fremanezumab (Ajovy) og komparatorerne for patienter med episodisk migræne, antal pr. år.

	Fremanezumab (Ajovy)	Propranolol, lisinopril, candesartancilexetil, topiramat, amitriptylin og valproat
Udlevering af medicin	4	-
Ambulant besøg	2,25	3
Sygeplejerske (tid)	33,75 min	45 min
Indlæggelse (1 dag grundet migræne)	0,075	0,10
Indlæggelse (>1 dag og <5 dage grundet migræne)	0,075	0,10
Blodprøve	0,75	1 (propranolol, lisinopril, candesartancilexetil, topiramat, amitriptylin) 3 (valproat)
MR-scanning	0,0375	0,05
Elektrokardiogram	-	1 (propranolol) 1 (amitriptylin)

Ansøger har anvendt estimater for monitoreringsfrekvenserne for patienter med kronisk migræne (P1, P2 og P3) gennem samtale med en kliniker angående behandlingsrutiner. Ansøger antager, at ressourceforbruget for patienter, der behandles med fremanezumab (Ajovy) er 25% mindre end for de patienter, der behandles med komparatorerne, bortset fra udlevering af medicin, elektrokardiogram og ambulant besøg.

Tabel 7 viser monitoreringsfrekvensen for fremanezumab (Ajovy), propranolol, lisinopril, candesartancilexetil, topiramat, amitriptylin, valproat og Botox for patienter med kronisk migræne.

Tabel 7: Monitoreringsfrekvens for fremanezumab (Ajovy) og komparatorerne for patienter med kronisk migræne, antal pr. år.

	Fremanezumab (Ajovy)	Propranolol, lisinopril, candesartancilexetil, topiramat, amitriptylin og valproat	Botox
Udlevering af medicin	4	-	-
Ambulant besøg	4	6	-
Ambulant besøg og injektion af Botox	-	-	4
Sygeplejerske (tid)	67,50 min	90 min	90 min
Indlæggelse (1 dag grundet migræne)	0,15	0,20	0,20
Indlæggelse (>1 dag og <5 dage grundet migræne)	0,15	0,20	0,20
Blodprøve	1,5	2 (propranolol, lisinopril, candesar-tancilexetil, topiramat, amitriptylin) 6 (valproat)	2
MR-scanning	0,075	0,10	0,10
Elektrokardiogram	-	2 (propranolol) 2 (amitriptylin)	-

Amgros' vurdering

Amgros har fået regionernes udpegede klinikere til at validere ansøgers estimater vedrørende et 25% lavere ressourceforbrug for fremanezumab (Ajovy) sammenlignet med komparatorerne. Klinikerne vurderer, at der ingen forskel er i monitoreringsfrekvensen for fremanezumab (Ajovy) og komparatorerne for patienter med både kronisk og episodisk migræne. Amgros vælger derfor at justere ressourceforbruget for de anvendte lægemidler, så der ingen forskel er i monitoreringsfrekvensen mellem fremanezumab (Ajovy) og komparatorerne.

Amgros anvender ens estimater for monitoreringsfrekvens i Amgros' hovedanalyse.

Patientomkostninger

Ansøger har valgt at inkludere omkostninger til patienttid. Dette er gjort ud fra monitoreringsbesøg på hospitalet og inkluderer administrationstiden af lægemidlerne på hospitalet, ventetid og transporttid. Ansøger anvender Amgros' enhedsomkostning for patienttid, som er 180 kr. per time, og patienttransportomkostninger på 100 kr. per besøg. Ansøger har justeret disse priser fra 2017, så de svarer til 2019-priser. Ansøgers estimerede patienttid for patienter med episodisk migræne kan ses i Tabel 8, mens ansøgers estimerede patienttid for patienter med kronisk migræne kan ses i Tabel 9.

Tabel 8: Ansøgers estimat af effektiv patienttid for patienter med episodisk migræne.

Lægemiddel	Transporttid (antal besøg)	Patienttid (antal besøg)	Total patientomkostning [DKK]
Fremanezumab (Ajovy)	4,14	14,22	3.026
Propranolol	2,13	7,99	1.693
Lisinopril	2,13	7,99	1.693
Candesartancilexetil	3,19	11,97	2.517
Topiramat	1,42	5,31	1.127
Amitriptylin	1,80	6,74	1.432
Valproat	1,01	3,79	807

Tabel 9: Ansøgers estimat af effektiv patienttid for patienter med kronisk migræne.

Lægemiddel	Transporttid (antal besøg)	Patienttid (antal besøg)	Total patientomkostning [DKK]
Fremanezumab (Ajovy)	4,29	16,46	3.451
Propranolol	4,27	15,98	3.386
Lisinopril	4,27	15,98	3.386
Candesartancilexetil	6,39	23,94	5.035
Topiramat	2,86	10,61	2.254
Amitriptylin	3,60	13,49	2.864
Valproat	2,02	7,57	1.615
Botox	4,39	17,95	3.734

Amgros' vurdering

Ansøgers estimater vedrørende patientomkostninger accepteres, men tilpasses i Amgros' hovedanalyse antallet af monitoreringsbesøg, hvor der ikke er forskel mellem fremanezumab (Ajovy) og komparatorerne.

2.2 Følsomhedsanalyser

Ansøger har udarbejdet en række følsomhedsanalyser, hvor effekten af variation i forskellige parametre undersøges. Følgende sensitivitetsanalyser er udført:

- Andel af patienterne, der fortsætter i behandling efter evaluering og andel af patienter, der genopstarter behandling efter forsøg på behandlingsstop +/- 10%
- Nedjustering af dosis for propranolol, topiramat, candesartancilexetil, amitriptylin og valproat
- Monitoreringsomkostninger +/- 20 %
- Ekskludering af patientfrafald

Amgros' vurdering

Amgros vurderer, at ansøgers følsomhedsanalyser er relevante, men præsenterer dem ikke her, da mange af parametrene justeres i Amgros' hovedanalyse efter samtale med regionernes udpegede klinikere.

Amgros udarbejder følsomhedsanalyser, der belyser usikkerhederne forbundet med antagelserne om andelen af patienter, hvor behandlingen stoppes. Der laves et justeret scenarie baseret på udtalelser fra regionernes udpegede klinikere samt et worst case-scenarie, hvor alle patienter fortsætter i behandling i hele modellens tidshorisont.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Ansøgers hovedanalyse for episodisk migræne resulterer i inkrementelle omkostninger per patient for fremanezumab (Ajovy) sammenlignet med P1:

- Propranolol på ca. [redacted] DKK over 5 år
- Topiramat på ca. [redacted] DKK over 5 år
- Lisinopril på ca. [redacted] DKK over 5 år
- Candesartancilexetil på ca. [redacted] DKK over 5 år

Ansøgers hovedanalyse for episodisk migræne resulterer i inkrementelle omkostninger per patient for fremanezumab (Ajovy) sammenlignet med P2:

- Amitriptylin på ca. [redacted] DKK over 5 år
- Valproat på ca. [redacted] DKK over 5 år

Resultaterne fra ansøgers hovedanalyse for episodisk migræne præsenteres i Tabel 10 og Tabel 11 for hhv. P1 og P2.

Tabel 10: Resultatet af ansøgers hovedanalyse for episodisk migræne for sammenligningen med P1, DKK, SAIP.

	Fremanezumab (Ajovy)	Propranolol	Topiramat	Lisinopril	Candesartancilexetil
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	8.539	6.703	4.384	6.586	9.793
Patientomkostninger	3.026	1.693	1.127	1.693	2.517
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 11: Resultatet af ansøgers hovedanalyse for episodisk migræne for sammenligningen med P2, DKK, SAIP.

	Fremanezumab (Ajovy)	Amitriptylin	Valproat
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	8.539	5.669	3.351
Patientomkostninger	3.026	1.432	807
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

Ansøger estimerer i hovedanalysen de inkrementelle omkostninger per patient for kronisk migræne for fremanezumab (Ajovy) sammenlignet med P1:

- Propranolol på ca. [redacted] DKK over 5 år
- Topiramat på ca. [redacted] DKK over 5 år
- Lisinopril på ca. [redacted] DKK over 5 år
- Candesartancilexetil på ca. [redacted] DKK over 5 år

Ansøger estimerer i hovedanalysen de inkrementelle omkostninger per patient for kronisk migræne for fremanezumab (Ajovy) sammenlignet med P2:

- Valproat på ca. [redacted] DKK over 5 år
- Amitriptylin på ca. [redacted] DKK over 5 år

Ansøger estimerer i hovedanalysen de inkrementelle omkostninger per patient for kronisk migræne for fremanezumab (Ajovy) sammenlignet med P3:

- Botox til at være ca. [redacted] DKK over 5 år

Resultaterne fra ansøgers hovedanalyse for kronisk migræne præsenteres i Tabel 12, Tabel 13 og Tabel 14 for hhv. P1, P2 og P3.

Tabel 12: Resultatet af ansøgers hovedanalyse for kronisk migræne for sammenligningen med P1, DKK, SAIP.

	Fremanezumab (Ajovy)	Propranolol	Topiramat	Lisinopril	Candesartan-cilexetil
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	13.591	13.339	8.768	13.172	19.585
Patientomkostninger	3.451	3.386	2.254	3.386	5.035
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 13: Resultatet af ansøgers hovedanalyse for kronisk migræne for sammenligningen med P2, DKK, SAIP.

	Fremanezumab (Ajovy)	Amitriptylin	Valproat
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	13.591	11.338	6.702
Patientomkostninger	3.451	2.864	1.615
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

Tabel 14: Resultatet af ansøgers hovedanalyse for kronisk migræne for sammenligningen med P3, DKK, SAIP.

	Fremanezumab (Ajovy)	Botox
Lægemiddelomkostninger	[redacted]	[redacted]
Hospitalsomkostninger	13.591	29.952
Patientomkostninger	3.451	3.734
Totale omkostninger	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]

3.2 Amgros' hovedanalyse

3.2.1 Antagelser i Amgros' hovedanalyse

Baseret på Amgros' kritiske vurdering af den tilsendte model, har Amgros udarbejdet sin egen hovedanalyse. Forudsætningerne er som i ansøgers analyse bortset fra følgende:

- Justeret vedligeholdelsesdosis for propranolol (160 mg), lisinopril (20 mg), candesartancilexetil (16 mg), topiramat (100 mg), amitriptylin (60 mg) og valproat (1.000 mg)
- Ingen forskel i monitoreringsfrekvensen for fremanezumab (Ajovy) og komparatorerne for patienter med både kronisk og episodisk migræne
- Patientomkostningerne tilpasses monitoreringsbesøgene

3.2.2 Resultat af Amgros' hovedanalyse

Amgros' hovedanalyse for episodisk migræne resulterer i inkrementelle omkostninger per patient for fremanezumab (Ajovy) sammenlignet med P1:

- Propranolol på ca. [redacted] DKK over 5 år
- Topiramat på ca. [redacted] DKK over 5 år
- Lisinopril på ca. [redacted] DKK over 5 år
- Candesartancilexetil på ca. [redacted] DKK over 5 år

Hvis analysen udføres på baggrund af AIP bliver de total inkrementelle omkostninger ca. 41.000 – 48.000 DKK per patient afhængigt af den valgte komparator.

Amgros' hovedanalyse for episodisk migræne resulterer i inkrementelle omkostninger per patient for fremanezumab (Ajovy) sammenlignet med P2:

- Amitriptylin på ca. [redacted] DKK over 5 år
- Valproat på ca. [redacted] DKK over 5 år

Hvis analysen udføres på baggrund af AIP bliver de total inkrementelle omkostninger ca. 46.000 – 49.000 DKK per patient afhængigt af den valgte komparator.

Resultaterne fra Amgros' hovedanalyse for episodisk migræne præsenteres i Tabel 15 og Tabel 16 for hhv. P1 og P2.

Tabel 15: Resultatet af Amgros' hovedanalyse for episodisk migræne for sammenligningen med P1, DKK, SAIP.

	Fremanezumab (Ajovy)	Propranolol	Topiramat	Lisinopril	Candesartancilexetil
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	10.475	6.703	4.384	6.586	9.793
Patientomkostninger	3.167	1.693	1.127	1.693	2.517
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 16: Resultatet af Amgros' hovedanalyse for episodisk migræne for sammenligningen med P2, DKK, SAIP.

	Fremanezumab (Ajovy)	Amitriptylin	Valproat
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	10.475	5.669	3.351
Patientomkostninger	3.167	1.432	807
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

Amgros estimerer i hovedanalysen de inkrementelle omkostninger per patient for kronisk migræne for fremanezumab (Ajovy) sammenlignet med P1:

- Propranolol på ca. [redacted] DKK over 5 år
- Topiramat på ca. [redacted] DKK over 5 år
- Lisinopril på ca. [redacted] DKK over 5 år
- Candesartancilexetil på ca. [redacted] DKK over 5 år

Hvis analysen udføres på baggrund af AIP bliver de total inkrementelle omkostninger ca. 34.000 – 48.000 DKK per patient afhængigt af den valgte komparator.

Amgros estimerer i hovedanalysen de inkrementelle omkostninger per patient for kronisk migræne for fremanezumab (Ajovy) sammenlignet med P2:

- Valproat på ca. [redacted] DKK over 5 år
- Amitriptylin på ca. [redacted] DKK over 5 år

Hvis analysen udføres på baggrund af AIP bliver de total inkrementelle omkostninger ca. 44.000 – 50.000 DKK per patient afhængigt af den valgte komparator.

Amgros estimerer i hovedanalysen de inkrementelle omkostninger per patient for kronisk migræne for fremanezumab (Ajovy) sammenlignet med P3:

- Botox til at være ca. [redacted] DKK over 5 år

Hvis analysen udføres på baggrund af AIP bliver de total inkrementelle omkostninger ca. 13.000 DKK per patient.

Resultaterne fra Amgros' hovedanalyse for kronisk migræne præsenteres i Tabel 17, Tabel 18 og Tabel 19 for hhv. P1, P2 og P3.

Tabel 17: Resultatet af Amgros' hovedanalyse for kronisk migræne for sammenligningen med P1, DKK, SAIP.

	Fremanezumab (Ajovy)	Propranolol	Topiramat	Lisinopril	Candesartancilexetil
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	15.195	13.339	8.768	13.172	19.585
Patientomkostninger	3.734	3.386	2.254	3.386	5.035
Totale omkostninger	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 18: Resultatet af Amgros' hovedanalyse for kronisk migræne for sammenligningen med P2, DKK, SAIP.

	Fremanezumab (Ajovy)	Amitriptylin	Valproat
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	15.195	11.338	6.702
Patientomkostninger	3.734	2.864	1.615
Totale omkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

Tabel 19: Resultatet af ansøgers hovedanalyse for kronisk migræne for sammenligningen med P3, DKK, SAIP.

	Fremanezumab (Ajovy)	Botox
Lægemiddelomkostninger	[redacted]	[redacted]
Hospitalsomkostninger	15.195	29.952
Patientomkostninger	3.734	3.734
Totale omkostninger	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]

3.2.3 Amgros' følsomhedsanalyser

Amgros udarbejder følsomhedsanalyser, der belyser usikkerhederne forbundet med antagelserne om andelen af patienter, hvor behandlingen stoppes. Der er udarbejdet et justeret scenarie baseret på udtalelser fra regionernes udpegede klinikere samt et worst case-scenarie, hvor alle patienter bliver i behandling i hele modellens tidshorisont.

Antagelserne bag Amgros' følsomhedsanalyser ses i Tabel 20.

Tabel 20: Andel af patienter, der fortsætter i behandling i Amgros' følsomhedsanalyser, i procent.

	Klinikerestimat		Worst case-scenarie	
	Andel af patienter, der fortsætter i behandling efter evaluering	Andel af patienter, der forsætter i behandling efter forsøg på behandlingsstop	Andel af patienter, der fortsætter i behandling efter evaluering	Andel af patienter, der forsætter i behandling efter forsøg på behandlingsstop
Fremanezumab (Ajovy)	75%	66%	100%	100%
Propranolol	50%	33%	50%	50%
Topiramat	33%	33%	25%	50%
Lisinopril	50%	33%	50%	50%
Candesartancile-xetil	75%	33%	75%	50%
Amitriptylin	40%	33%	40%	50%
Valproat	33%	33%	10%	50%
Botox	75%	66%	75%	50%

Benyttes estimaterne baseret på udtalelserne fra regionernes udpegede klinikere øges de inkrementelle omkostninger for alle populationer. Resultaterne af Amgros' følsomhedsanalyser kan ses i Tabel 21.

Tabel 21: Resultat af Amgros' følsomhedsanalyser, DKK, SAIP

	Klinikerestimat	Worst case-scenarie	Amgros' hovedanalyse
Patienter med episodisk migræne			
P1	ca. [redacted]	ca. [redacted]	ca. [redacted]
P2	ca. [redacted]	ca. [redacted]	ca. [redacted]
Patienter med kronisk migræne			
P1	ca. [redacted]	ca. [redacted]	ca. [redacted]
P2	ca. [redacted]	ca. [redacted]	ca. [redacted]
P3	ca. [redacted]	ca. [redacted]	ca. [redacted]

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at fremanezumab (Ajovy) vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- Fremanezumab (Ajovy) bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- Fremanezumab (Ajovy) bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Fagudvalget vedr. migræne under Medicinrådet har i protokollen for denne ansøgning antaget, at der er 5.000-6.000 patienter i behandling for migræne på de danske hospitaler. Fagudvalget skønner desuden at flertallet af disse opfylder kriterierne for forebyggende migrænebehandling (1).

Ansøger har antaget, at patienter ikke skifter mellem episodisk og kronisk migræne. Derudover antages det, at patienter, hvor behandlingen stoppes, ikke kommer tilbage i modellen på en anden behandling.

Ansøger har udarbejdet 4 budgetkonsekvensanalyser for at besvare de 3 kliniske spørgsmål, der er defineret i Medicinrådets protokol for vurdering af den kliniske merværdi (1):

1. Ubehandlede patienter med episodisk migræne (P1)
2. Patienter med episodisk migræne, som har oplevet behandlingssvigt på to eller flere tidligere forebyggende behandlinger (P1 + P2)
3. Ubehandlede patienter med kronisk migræne (P1)
4. Patienter med kronisk migræne, som har oplevet behandlingssvigt på to eller flere tidligere forebyggende behandlinger (P2 + P3)

Ansøger antager, at fremanezumab (Ajovy) får 10% og 15% markedsoptag i hhv. år 1 og år 2, og derfra peaker på et markedsoptag på 20% i år 3, år 4 og år 5 i alle 4 budgetkonsekvensanalyser.

Ansøgers estimerede patientantal for tidligere ubehandlede patienter med episodisk migræne (P1) ses i Tabel 22.

Tabel 22: Ansøgers estimat af antal nye patienter per år med tidligere ubehandlet episodisk migræne (P1).

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovi) anbefales som standardbehandling					
Fremanezumab	125	188	250	250	250
Propranolol	438	425	400	400	400
Topiramat	125	113	100	100	100
Lisinopril	125	113	100	100	100
Candesartancile-xetil	438	413	400	400	400
Fremanezumab (Ajovi) anbefales ikke som standardbehandling					
Fremanezumab	0	0	0	0	0
Propranolol	500	500	500	500	500
Topiramat	125	125	125	125	125
Lisinopril	125	125	125	125	125
Candesartancile-xetil	500	500	500	500	500

Ansøgers estimerede patientantal for patienter med episodisk migræne, der har oplevet behandlingssvigt på mindst to tidligere forebyggende behandlinger (P1 + P2) ses i Tabel 23.

Tabel 23: Ansøgers estimat af antal nye patienter per år med episodisk migræne, der har oplevet behandlingssvigt på mindst to tidligere forebyggende behandlinger (P1 + P2).

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovi) anbefales som standardbehandling					
Fremanezumab	125	188	250	250	250
Topiramate	625	600	600	600	600
Lisinopril	188	175	150	150	150
Amitriptyline	188	175	150	150	150
Valproate	125	113	100	100	100
Fremanezumab (Ajovi) anbefales ikke som standardbehandling					
Fremanezumab	0	0	0	0	0
Topiramate	750	750	750	750	750
Lisinopril	188	188	188	188	188
Amitriptyline	188	188	188	188	188
Valproate	125	125	125	125	125

Ansøgers estimerede patientantal for tidligere ubehandlede patienter med kronisk migræne (P1) ses i Tabel 24.

Tabel 24: Ansøgers estimat af antal nye patienter per år med tidligere ubehandlet kronisk migræne (P1).

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovi) anbefales som standardbehandling					
Fremanezumab	125	188	250	250	250
Propranolol	438	425	400	400	400
Topiramate	125	113	100	100	100
Lisinopril	125	113	100	100	100
Candesartancile-xetil	438	413	400	400	400
Fremanezumab (Ajovi) anbefales ikke som standardbehandling					
Fremanezumab	0	0	0	0	0
Propranolol	500	500	500	500	500
Topiramate	125	125	125	125	125
Lisinopril	125	125	125	125	125
Candesartancile-xetil	500	500	500	500	500

Ansøgers estimerede patientantal for patienter med kronisk migræne, der har oplevet behandlingssvigt på mindst to tidligere forebyggende behandlinger (P2 + P3) ses i Tabel 25.

Tabel 25: Ansøgers estimat af antal nye patienter per år med kronisk migræne, der har oplevet behandlingssvigt på mindst to tidligere forebyggende behandlinger (P2 + P3).

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovi) anbefales som standardbehandling					
Fremanezumab	125	188	250	250	250
Topiramat	375	363	350	350	350
Lisinopril	125	113	100	100	100
Amitriptylin	125	113	100	100	100
Valproat	63	50	50	50	50
Botox	438	425	400	400	400
Fremanezumab (Ajovi) anbefales ikke som standardbehandling					
Fremanezumab	0	0	0	0	0
Topiramat	438	438	438	438	438
Lisinopril	125	125	125	125	125
Amitriptylin	125	125	125	125	125
Valproat	63	63	63	63	63
Botox	500	500	500	500	500

Amgros' vurdering af estimeret antal patienter

Amgros har talt med regionernes udpegede klinikere og bedt dem validere antallet af patienter i hver population. Vurderingen er, at patientantallet for dette område er særdeles svært at estimere. Amgros har derfor yderligere konsulteret de regionale lægemiddelkomitéer og sygehusapotekerne angående dette. Grunden til, at antallet kan være svært at estimere er, at rigtig mange patienter (muligvis titusindvis) med episodisk migræne behandles hos egen læge eller med håndkøbsmedicin og dermed ikke ses af specialister. Derudover er der store kapacitetsproblemer på hovedpinecentrene, der forårsager lange ventelister. Amgros vurderer derfor, at man kan beregne budgetkonsekvenserne ud fra to tilgange; 1) prævalens og incidens af migrænepatienter for hver population eller 2) antal patienter svarende til hovedpinecentrenes kapacitet.

Amgros vurderer, at det mest retvisende billede af budgetkonsekvenserne vil ses ved at benytte det antal patienter, som hovedpinecentrene på nuværende tidspunkt har kapacitet til at behandle. Dette antal svarer til knapt 600 patienter på landsplan ifølge regionernes udpegede klinikere, de regionale lægemiddelkomitéer og sygehusapotekernes estimater.

Amgros vurderer, at markedsoptaget virker rimeligt for de populationer, der omfatter tidligere ubehandlede patienter, da disse først vil blive forsøgt behandlet med de konventionelle terapier, fx antihypertensiva eller antiepileptika.

Amgros vurderer, baseret på estimater fra regionernes udpegede klinikere, at markedsoptaget for populationerne, der omfatter patienter, der har oplevet behandlingssvigt, dog kan være underestimeret, særligt for patienter med kronisk migræne. Amgros øger markedsoptaget for disse populationer, så dette gradvist øges og peaker på 50% i år 3.

Det skal understreges, at estimaterne er forbundet med store usikkerheder, og resultaterne af budgetkonsekvensanalyserne bør derfor tolkes med forsigtighed. Amgros tilføjer derfor også en analyse, der belyser budgetkonsekvenserne, hvis alle 5.000-6.000 patienter, der i dag behandles forebyggende for migræne på de danske hospitaler, vil modtage behandling med fremanezumab (Ajovy). Dette kan ses som et worst case-scenarie.

4.1.2 Estimat af budgetkonsekvenser

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

Med de indlagte antagelser estimerer ansøger, at anvendelse af fremanezumab (Ajovy) vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5, alt efter hvilken population man kigger på.

Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 26, Tabel 27, Tabel 28 og Tabel 29.

Tabel 26: Ansøgers hovedanalyse for totale budgetkonsekvenser for ubehandlede patienter med episodisk migræne (P1), DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovy) anbefales som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Candesartancile-xetil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab (Ajovy) anbefales ikke som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Candesartancile-xetil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budget-konsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 27: Ansøgers hovedanalyse for totale budgetkonsekvenser for patienter med episodisk migræne, der har oplevet behandlingssvigt på to eller flere tidligere forebyggende behandlinger (P1 + P2), DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovy) anbefales som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amitriptyline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab (Ajovy) anbefales ikke som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amitriptyline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budget-konsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 28: Ansøgers hovedanalyse for totale budgetkonsekvenser for patienter med tidligere ubehandlet kronisk migræne (P1), DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovy) anbefales som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Candesartancile-xetil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab (Ajovy) anbefales ikke som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Candesartancile-xetil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budget-konsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 29: Ansøgers hovedanalyse for totale budgetkonsekvenser for patienter med kronisk migræne, der har oplevet behandlingssvigt på mindst to tidligere forebyggende behandlinger (P2 + P3), DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovy) anbefales som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amitriptylin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botox	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab (Ajovy) anbefales ikke som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amitriptylin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botox	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budget-konsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros' vurdering

Amgros vurderer, at ansøgers budgetestimater er forbundet med store usikkerheder, når det kommer til patientantal og markedsoptag.

Amgros udarbejder egen budgetkonsekvensanalyse med udgangspunkt i Amgros' hovedanalyse af meromkostningerne. Amgros justerer desuden på det estimerede antal patienter samt markedsoptaget baseret på samtale med regionernes udpegede klinikere, de regionale lægemiddelkomitéer og sygehusapotekerne. Amgros understreger igen, at estimaterne omhandlende patientantal og markedsoptag er forbundet med store usikkerheder, hvorfor budgetkonsekvensanalyserne bør fortolkes med forsigtighed.

4.2 Amgros' estimater af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Amgros har benyttet omkostninger og antagelser benyttet i Amgros' hovedanalyse
- Amgros benytter justerede patientantal samt markedsoptag, så dette afspejler det antal patienter, som hovedpinecentrene har ressourcer til at behandle i dag

4.2.1 Amgros' estimat af patientantal

Amgros justerer patientantallet fra totalt 5.000 patienter til totalt 600 patienter, hvilket afspejler det antal patienter, som hovedpinecentrene har ressourcer til at behandle i dag. De 600 patienter fordeler sig ligeligt mellem de 4 populationer, som ansøger har benyttet i deres analyse af budgetkonsekvenserne.

Amgros justerer desuden markedsoptaget, så dette øges til 50% ved år 3 og frem for patienter, der har oplevet behandlingssvigt på to eller flere tidligere forebyggende behandlinger.

Med de indlagte antagelser estimerer Amgros, at anvendelse af fremanezumab (Ajovy) vil resultere i budgetkonsekvenser på ca. [redacted] DKK per år per population afhængigt af den valgte population.

Hvis analysen udføres med AIP bliver budgetkonsekvenserne ca. 1,2 mio. – 3,3 mio. DKK per år.

Estimat af budgetkonsekvenserne fremgår af Tabel 30, Tabel 31, Tabel 32 og Tabel 33.

Tabel 30: Amgros' hovedanalyse for totale budgetkonsekvenser for ubehandlede patienter med episodisk migræne (P1), DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovy) anbefales som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Candesartancile-xetil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab (Ajovy) anbefales ikke som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Candesartancile-xetil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budget-konsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 31: Amgros' hovedanalyse for totale budgetkonsekvenser for patienter med episodisk migræne, der har oplevet behandlingssvigt på to eller flere tidligere forebyggende behandlinger (P1 + P2), DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovy) anbefales som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amitriptyline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab (Ajovy) anbefales ikke som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amitriptyline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budget-konsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 32: Amgros' hovedanalyse for totale budgetkonsekvenser for patienter med tidligere ubehandlet kronisk migræne (P1), DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovy) anbefales som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Candesartancile-xetil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab (Ajovy) anbefales ikke som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propranolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Candesartancile-xetil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budget-konsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 33: Amgros' hovedanalyse for totale budgetkonsekvenser for patienter med kronisk migræne, der har oplevet behandlingssvigt på mindst to tidligere forebyggende behandlinger (P2 + P3), DKK, ikke-diskonterede tal, SAIP.

	År 1	År 2	År 3	År 4	År 5
Fremanezumab (Ajovy) anbefales som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amitriptylin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botox	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fremanezumab (Ajovy) anbefales ikke som standardbehandling					
Fremanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lisinopril	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amitriptylin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botox	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budget-konsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.2.2 Amgros' følsomhedsanalyser af budgetkonsekvenser

Amgros har udarbejdet en følsomhedsanalyse af budgetkonsekvenserne, der belyser usikkerheden i patientantallet. Her antages det, at 5.000 patienter (fremfor 600 patienter i hovedanalysen) er kandidater til forebyggende behandling med fremanezumab (Ajovy). Markedsoptaget er uændret ift. Amgros' hovedanalyse af budgetkonsekvenserne.

Resultatet af Amgros' følsomhedsanalyse af budgetkonsekvenserne kan ses i Tabel 34.

Tabel 34: Amgros' følsomhedsanalyse af budgetkonsekvenserne ved år 5, DKK, SAIP.

	Ubehandlet episodisk migræne	Episodisk migræne efter behandlingssvigt	Ubehandlet kronisk migræne	Kronisk migræne efter behandlingssvigt
Amgros' hovedanalyse	[redacted]	[redacted]	[redacted]	[redacted]
Worst-case	[redacted]	[redacted]	[redacted]	[redacted]

5 DISKUSSION

Behandling med fremanezumab (Ajovy) er forbundet med betydelige meromkostninger sammenlignet med propranolol, topiramat, lisinopril, candesartancilexetil, amitriptylin og valproat. Sammenlignet med Botox er behandling med fremanezumab (Ajovy) forbundet med begrænsede meromkostninger.

Meromkostningerne er primært drevet af lægemiddelomkostningerne for fremanezumab (Ajovy), og antagelserne om, hvor mange patienter der fortsætter i behandling efter evaluering og forsøg på behandlingsophør.

Amgros' følsomhedsanalyser belyser usikkerhederne ved antagelserne om behandlingsophør, hvor det ses, at meromkostningerne forbundet med behandling med fremanezumab (Ajovy) øges markant, hvis alle patienterne fortsætter med behandling ved evaluering og efter forsøg på behandlingsstop.

Budgetkonsekvenserne er forbundet med store usikkerheder. Disse usikkerheder skyldes særligt antagelserne og det forventede patientantal, samt markedsoptaget af fremanezumab (Ajovy). Amgros har spurgt regionernes udpegede klinikere, de regionale lægemiddelkomitéer og sygehusapotekerne til råds om mere plausible estimater og må konstatere, at det også for klinikerne er svært at udtale sig om det forventede potentiale hvad angår patientantal og markedsoptag. Budgetkonsekvenserne bør derfor tolkes med stor forsigtighed, da ændringer i disse estimater kan have stor betydning for det endelige resultat. Amgros' worst case-scenarie viser, at regionernes budgetter kan blive påvirket med flere millioner kroner, hvis et uventet stort antal patienter startes i behandling med fremanezumab (Ajovy).

6 REFERENCER

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Søborg. 29. Oktober 2019

Høringssvar til vurdering af fremanezumab i Medicinrådet

Teva kvitterer hermed for at modtage Medicinrådets beslutning om klinisk merværdi for fremanezumab og takker samtidig for muligheden for at komme med et høringssvar til beslutningen.

Teva tager Medicinrådets konklusioner til efterretning og noterer samtidig, som forventet, at det er svært at vurdere værdien af fremanezumab overfor de valgte komparatorer, når der kun findes meget lav evidenskvalitet for komparatorerne.

Teva noterer sig også, at Medicinrådet af egen drift har foretaget en indirekte sammenligning af erenumab og fremanezumab, selvom dette ikke var nævnt i protokollen, men også at fremanezumab står stærkere end erenumab i langt hovedparten af de valgte effektparametre.

Indirekte sammenligning af erenumab til fremanezumab

Konklusionen på baggrund af denne indirekte sammenligning foretaget af Medicinrådet er, at fremanezumab har en numerisk bedre effekt end erenumab på langt hovedparten af effektparametrene (Bilag 5, side 100). Denne numerisk bedre effekt af fremanezumab bør anerkendes af Medicinrådet i Medicinrådets beslutning.

Klinisk spørgsmål 2 (patienter med episodisk og kronisk migræne, som har har oplevet behandlingssvigt på to tidligere forebyggende behandlinger)

Teva undrer sig over, at der for det vigtige effektmål 'Bivirkninger' er givet kategorien 'Kan ikke kategoriseres' for fremanezumab sammenlignet med amitriptylin og valproat i klinisk spørgsmål 2.

De aggregerede kategorier 'Kan ikke kategoriseres' er baseret på de relative og absolutte effektforskelle i sammenligningen af fremanezumab med amitriptylin og valproat. Medicinrådet påpeger i vurderingsrapporten; "*Behandling med amitriptylin/valproat er behæftet med mange bivirkninger, jævnfør beskrivelsen af bivirkningsprofilen. Disse bivirkninger kan være til stor gene for patienten, selvom de ikke nødvendigvis medfører behandlingsophør*" (side 31).

I april i år vurderede Medicinrådet erenumab til at have en 'lille klinisk merværdi' på effektmålet 'Bivirkninger'. Dette med begrundelsen; *"Behandling med amitriptylin/valproat er behæftet med mange bivirkninger, jævnfør beskrivelsen af bivirkningsprofilen. Disse bivirkninger kan være til stor gene for patienten, selvom de ikke nødvendigvis medfører*

behandlingsophør. Derfor vurderer fagudvalget samlet set, til trods for at de relative og absolutte effektforskellig ikke viste nogen merværdi, at erenumab har lille klinisk merværdi på effektmålet "bivirkninger" sammenlignet med amitriptylin/valproat" (side 37). Teva bemærker, at den samme beskrivelse af bivirkningerne for amitriptylin og valproat også er gældende i vurderingen af fremanezumab, hvorfor fremanezumab som minimum bør have en tilsvarende vurdering som erenumab.

Noter også at i den indirekte sammenligning af erenumab og fremanezumab foretaget af Medicinrådet er fremanezumab numerisk bedre end erenumab på effektmålet 'Bivirkninger' for de episodiske og kroniske patienter som tidligere har oplevet behandlingssvigt.

Så derfor bør fremanezumab som minimum anerkendes til at have en lille klinisk merværdi sammenlignet med amitriptylin og valproat, også selvom erenumab er vurderet ud fra en anden metodehåndbog.

Teva tager således den samlede kategorisering af 'Bivirkninger' til efterretning, men stiller sig kritisk angående den manglende merværdi af bivirkningerne baseret på den narrative beskrivelse.

Med venlig hilsen

Jesper Bjerggren

Senior Manager, Market Access Denmark, Norway & Iceland

Medicinrådet

Medicinrådets vurdering af fremanezumab til forebyggende behandling af migræne

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

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

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

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

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

Om vurderingen

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

Vurderingen indgår, når Medicinrådet skal beslutte, om det vil anbefale lægemidlet som mulig standardbehandling.

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

Dokumentoplysninger	
Godkendelsesdato	23. oktober 2019
Ikrafttrædelsesdato	23. oktober 2019
Dokumentnummer	59193
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 23. oktober 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Ajovy
Generisk navn	Fremanezumab
Firma	Teva
ATC-kode	N02CX07
Virkningsmekanisme	Humant monoklonalt antistof som selektivt binder til CGRP-peptid, som er en del af patofysiologien for migræne. Fremanezumab binder til både α- og β-isoformerne af CGRP-liganden, men ikke til receptoren.
Administration/dosis	225 mg én gang om måneden (månedlig dosering) 675 mg hver tredje måned (kvartalsvis dosering)
EMA-indikation	Forebyggende behandling af migræne hos voksne som har mindst fire migrænedage om måneden.

2 Medicinrådets konklusion

Fremanezumab til forebyggelse af migræne hos patienter, der har mindst fire migrænedage pr. måned (klinisk spørgsmål 1):

- Medicinrådet finder, at den samlede værdi af fremanezumab sammenlignet med gruppen af antihypertensiva (propranolol, candesartancilexetil og lisinopril) **ikke kan kategoriseres**. Evidensens kvalitet vurderes at være lav til meget lav. Fremanezumab vurderes samlet set ikke at have dårligere effekt eller sikkerhedsprofil end gruppen af antihypertensiva.
- Medicinrådet vurderer, at fremanezumab giver en **lille merværdi** sammenlignet med topiramat. Evidensens kvalitet vurderes at være lav.

Fremanezumab til forebyggelse af migræne hos patienter, der har mindst fire migrænedage pr. måned og som har oplevet behandlingssvigt på mindst to migræneforebyggende lægemidler (et antihypertensivum og et antiepileptikum) (klinisk spørgsmål 2):

- Medicinrådet finder, at den samlede værdi af fremanezumab sammenlignet med amitriptylin og valproat **ikke kan kategoriseres**. Evidensens kvalitet vurderes at være meget lav. Fremanezumab vurderes samlet set ikke at have dårligere effekt eller sikkerhedsprofil end de to komparatorer.

Fremanezumab hos patienter med **kronisk migræne**, der har oplevet behandlingssvigt på mindst to migræneforebyggende lægemidler (et antihypertensivum og et antiepileptikum) (klinisk spørgsmål 3):

- Medicinrådet vurderer, at fremanezumab til patienter med kronisk migræne giver en **lille merværdi** sammenlignet med botulinum type A toxin. Evidensens kvalitet vurderes at være meget 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.

3 Forkortelser

ACR:	Antaget hændelsesrate i komparatorgruppe
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
EPAR:	*European Public Assessment Report*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
HIT-6:	*Headache Impact Test* (livskvalitetsskala)
HR:	*Hazard ratio*
IHS:	*International Headache Society*
MKRF:	Mindste klinisk relevante forskel
OR:	*Odds ratio*
RR:	Relativ risiko
CGRP:	*Calcitonin gene-related peptide* (calcitonin genrelateret protein)

4 Formål

Formålet med Medicinrådets vurdering af fremanezumab til forebyggende behandling af migræne er at vurdere den værdi, lægemidlet har i forhold til et eller flere lægemidler til samme patientgruppe.

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

5 Baggrund

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 hovedpinetype, f.eks. spændingshovedpine. Dette skal opfattes som et kontinuerligt spektrum, hvor den enkelte patient i perioder kan gå fra episodisk til kronisk migræne og omvendt.

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. Der findes ikke opgørelser over det samlede antal migrænepatienter, der er tilknyttet hovedpineklinikker i Danmark. Fagudvalget skønner, at flertallet af disse patienter opfylder kriterierne for forebyggende migrænebehandling. Foruden de patienter, som behandles på hovedpineklinikker, findes der en større antal af patienter, som er afsluttet, da behandlingsmulighederne er opbrugt uden et tilfredsstillende resultat. Fagudvalget har ikke noget grundlag for at estimere størrelsen på denne gruppe, men anslår at der er tale om flere tusinde patienter (episodisk såvel som kronisk migræne). Fagudvalget skønner, at der også blandt disse patienter er en stor andel, som opfylder kriterierne for forebyggende migrænebehandling.

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 længe en patient har brug for forebyggende behandling, og nuværende kliniske anbefalinger tilsiger 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.

De lægemidler, der på nuværende tidspunkt 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 senere vist sig at have effekt på forebyggelse af migræne, og visse er siden blevet godkendt til dette formål. Lægemidler, der er godkendt til forebyggende behandling af migræne i Danmark, er: metoprolol/propranolol (betablokkere), flunarizin (calciumantagonist), topiramat (antiepileptika), pizotifen (aminantagonist), clonidin (alfa-2-receptor- og imidazolinreceptoragonist) samt amitriptylin (tricyklisk antidepressivum). Derudover er botulinum type A toxin godkendt til patienter med kronisk migræne. Ikke alle lægemidler, der fremgår af de eksisterende danske behandlingsvejledninger, er 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 lægemidlernes indbyrdes placering i behandlingsalgoritmen – se tabel 1 i bilag 2. For den enkelte patient er der i øvrigt stor variation i de enkelte lægemidlers effekt og bivirkninger. Valget af præparat baseres derfor på en individuel vurdering, hvor der blandt andet tages hensyn til patientens risikoprofil, andre sygdomme og tidligere erfaring.

Der er generelt 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 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 andetvalgspræparater. Ved behandlingssvigt/kontraindikationer mod andetvalgspræparaterne kan patienterne tilbydes behandling med andre lægemidler, som er mindre anvendt, f.eks. lamotrigin og pizotifen. Valg af komparator til de enkelte kliniske spørgsmål beror således på ovenstående beskrivelse af, hvad der anvendes i dansk klinisk praksis.

Anvendelse af det nye lægemiddel

Fremanezumab 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. Fremanezumab administreres subkutant og indgives månedligt eller kvartalsvist. Den månedlige dosering er 225 mg, mens den kvartalsvise dosering er 675 mg (3 x 225 mg).

Ligesom øvrige lægemidler til forebyggelse af migræne skal fremanezumab forsøges seponeret hver 6.-12. måned for at vurdere effekt af og evt. fortsat behov for lægemidlet til forebyggelse af migræne. Ved fortsat behov genoptages behandlingen med fremanezumab. Hvor længe en patient har brug for forebyggende behandling er som nævnt ovenfor meget individuelt.

I Danmark er ordinationsretten af fremanezumab begrænset til speciallæger i neurologi, som er ansat på et sygehus.

6 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådet.

Medicinrådet modtog den endelige ansøgning fra Teva den 9. august 2019. Teva har anvendt og fulgt den præspecificerede metode, jf. protokol som blev godkendt i Medicinrådet den 28. februar 2019.

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

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

7 Litteratursøgning

Ansøger har foretaget en systematisk søgning efter publicerede kliniske studier, der muliggør en indirekte sammenligning af fremanezumab og gældende standardbehandling (metoprolol, propranolol, lisinopril, candesartancilexetil, topiramat, amitriptylin, nortriptylin, valproat og botulinum type A toxin) via placebo som fælleskomparator, jf. protokollen. Ansøgers PRISMA-diagrammer og litteraturgennemgang fremgår af ansøgningen.

Alle søgninger er udført den 10. april 2019 i både MEDLINE via PubMed og CENTRAL via Cochrane Library. Ud over de fundne artikler blev European Public Assessment Report (EPAR) for fremanezumab anvendt. Der findes ingen EPAR for de anvendte komparatorer, og derfor er de danske produktresuméer i stedet benyttet.

Ansøger har identificeret 17 relevante studier til besvarelse af klinisk spørgsmål 1, 7 studier til besvarelse af klinisk spørgsmål 2 samt 3 studier til besvarelse af klinisk spørgsmål 3, hvoraf det ene er det samme som et af studierne til klinisk spørgsmål 2. Det samlede antal studier er 26 studier.

Der blev ikke fundet relevante studier for metoprolol eller nortriptylin, som opfylder kriterierne beskrevet i protokollen, og som indeholder de relevante effektmål, hvorfor disse lægemidler ikke indgår i sammenligningen med fremanezumab.

De kliniske studier, som vurderingen baseres på, er følgende:

Fremanezumab

Titel	**Forfatter og publikationsår**	**Studie-navn**	**NCT-nummer**
Effect of fremanezumab compared with placebo for prevention of episodic migraine.	Dodick et al., JAMA, 2018 [4]	HALO EM	NCT02629861
Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study.	Bigal et al., Lancet Neurol., 2015 [5]	-	NCT02025556
Fremanezumab for the preventive treatment of chronic migraine.	Silberstein et al., NEJM, 2017 [6]	HALO CM	NCT02621931
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 Neurol., 2015 [7]	-	NCT02021773
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 [8]	FOCUS	NCT03308968

Propranolol

Titel	**Forfatter og publikationsår**	**Studie-navn**	**NCT-nummer**
Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol.	Diener et al., Cephalalgia, 1996 [9]	-	-
Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control.	Diener et al., J Neurol., 2004 [10]	MIGR-003	-
A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study.	Stovner et al., Cephalalgia, 2014 [11]	-	NCT00884663

Candesartancilexetil

Titel	**Forfatter og publikationsår**	**Studie-navn**	**NCT-nummer**
Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial.	Tronvik et al., JAMA, 2003 [12]	-	-
A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study.	Stovner et al., Cephalalgia, 2014 [11]	-	NCT00884663

Lisinopril

Titel	Forfatter og publikationsår	Studie-navn	NCT-nummer
Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study.	Schrader et al., BMJ, 2001 [13]	-	-

Topiramat

Titel	Forfatter og publikationsår	Studie-navn	NCT-nummer
Topiramate in migraine prevention: a double-blind, placebo-controlled study.	Storey et al., Headache, 2001 [14]	-	-
Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study.	Mei et al., Neurol Sci., 2004 [15]	-	-
Topiramate in migraine prophylaxis - results from a placebo-controlled trial with propranolol as an active control.	Diener et al., J Neurol., 2004 [10]	MIGR-003	-
Topiramate for migraine prevention: a randomized controlled trial. *Assessing the ability of topiramate to improve the daily activities of patients with migraine.*	Brandes et al., JAMA, 2004 [16] Brandes et al., Mayo Clin Proc., 2006 [17]	MIGR-002	-
Topiramate in migraine prevention: results of a large controlled trial. *The impact of migraine on daily activities: effect of topiramate compared with placebo.*	Silberstein et al., Arch Neurol., 2004 [18] Silberstein et al., Curr Med Res Opin., 2006 [19]	MIGR-001	-
Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study.	Silberstein et al., Clin Ther., 2006 [20]	-	-
Efficacy and Safety of Topiramate for the Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. *Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures.*	Silberstein et al., Headache, 2007 [21] Silberstein et al., Headache, 2009 [22]	-	NCT00210912

Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study.	Diener et al., Cephalalgia, 2007 [23]	TOPMAT-MIG-201	-
Topiramate intervention to prevent transformation of episodic migraine: The topiramate INTREPID study.	Lipton et al., Cephalalgia, 2011 [24]	INTREPID	NCT00212810

Valproat

Titel	**Forfatter og publikationsår**	**Studie-navn**	**NCT-nummer**
Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study.	Jensen et al., Neurology, 1994 [25]	-	-
Migraine Prophylaxis with Divalproex.	Mathew et al., Arch Neurol., 1995. [26]	-	-
Divalproex sodium in migraine prophylaxis: a dose-controlled study.	Klapper J., Cephalalgia, 1997. [27]	-	-
A randomised trial of divalproex sodium extended-release tablets in migraine prophylaxis.	Freitag et al., Neurology, 2002 [28]	-	-

Amitriptylin

Titel	**Forfatter og publikationsår**	**Studie-navn**	**NCT-nummer**
Amitriptyline in the prophylactic treatment of migraine and chronic daily headache.	Couch et al., Headache, 2011 [29]	-	-
Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention.	Goncalves et al., J Neurol Neurosurg Psychiatry., 2016 [30]	EDUMAP	NCT01357031

Botox

Titel	Forfatter og publikationsår	Studie-navn	NCT-nummer
OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial.	Aurora et al., Cephalalgia, 2010 [31]	PREEMPT I	NCT00156910
OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial.	Diener et al., Cephalalgia, 2010 [32]	PREEMPT II	NCT00168428

En beskrivelse af studiekarakteristika og population for hvert studie findes i bilag 3 og appendiks 1. Fagudvalget vurderer, at baselinekarakteristika for studiepopulationerne i de inkluderede studier stemmer godt overens med den danske migrænepopulation.

8 Databehandling

Ansøgers fremgangsmåde

Fremanezumab og komparatorerne blev sammenlignet parvist via en indirekte sammenligning med placebo som fælles komparator. For hvert præparat er der, i tilfælde hvor der har været data tilgængelig fra flere studier, foretaget en metaanalyse af studieresultaterne pr. effektmål forud for den indirekte sammenligning. Derefter er resultatet fra metaanalyserne for hver komparator sammenlignet med resultatet fra metaanalysen for fremanezumab ved brug af Buchers metode. I tilfælde, hvor der kun har været data tilgængelig fra ét studie, er effektestimatet herfra anvendt direkte i den indirekte sammenligning.

Alle inkluderede studier har en opfølgningstid på minimum 12 uger. Hovedparten af studierne rapporterer data efter en 12 ugers behandlingsperiode. Enkelte studier rapporterer data baseret på 24 ugers opfølgning.

For effektmålet "Andel patienter som oplever bivirkninger, der medfører behandlingsophør" er analyserne baseret på data for uønskede hændelser. Fagudvalget vurderer, at data for uønskede hændelser kan anvendes som alternativ til de i protokollen ønskede data.

Supplerende beregninger foretaget af Medicinrådets sekretariat

Medicinrådets sekretariat har suppleret ansøgers estimater af antagede hændelsesrater (ACR) for enkelte effektmål og komparatorer. Sekretariatets beregninger fremgår af bilag 4.

Sammenligning mellem erenumab og fremanezumab

Medicinrådet har ønsket at se en sammenligning mellem erenumab og fremanezumab som supplement til vurderingen af fremanezumab, idet erenumab er vurderet i henhold til Medicinrådets tidligere metode for kategorisering af lægemidlers værdi. Rationalet bag sammenligningen er at sikre, at skiftet af metode i sig selv ikke medfører forskellige vurderinger for de to lægemidler. Sekretariatets beregninger fremgår af bilag 5.

Samlet vurdering af de to doser, fremanezumab 225 mg (månedlig dosering) og 675 mg (kvartalsvis dosering)

I den endelige ansøgning har Teva indsendt separate resultater for hver af de to doseringer. Fagudvalget har valgt at vurdere resultaterne for de to doser samlet uden at differentiere fremanezumabs samlede værdi. Resultaterne for hvert effektmål er præsenteret for hver af de to doseringer. Den foreløbige kategorisering er foretaget på baggrund af effektestimater fra ansøgningen, og der fremgår dermed foreløbige kategorier for både den månedlige og den kvartalsvise dosering. Det er fagudvalgets opfattelse, at hovedparten af patienterne vil blive opstartet i behandlingen med den månedlige dosering. Dette sker af hensyn til bekymring for toksicitet. Fagudvalget vurderer, at den kvartalsvise dosering kan blive relevant for nogle patienter senere i et behandlingsforløb. Derfor er de aggregerede værdier og den samlede kliniske værdi af fremanezumab baseret på en samlet vurdering af resultaterne for begge doseringsregimer, med hovedvægt på den månedlige dosering.

9 Lægemidlets værdi

9.1 Konklusion klinisk spørgsmål 1

Hvad er den kliniske merværdi af fremanezumab til patienter med migræne, der har mindst fire migrænedage pr. måned sammenlignet med eksisterende standardbehandling?

Fagudvalget finder, at den samlede værdi for fremanezumab til forebyggende behandling af patienter med migræne sammenlignet med gruppen af antihypertensiva (propranolol, candesartancilexetil og lisinopril) **ikke kan kategoriseres**. Evidensens kvalitet vurderes at være lav til meget lav. Fagudvalget vurderer dog, at fremanezumab samlet set ikke har dårligere effekt eller sikkerhedsprofil end propranolol, candesartancilexetil og lisinopril.

Fagudvalget vurderer, at fremanezumab til forebyggende behandling af patienter med migræne giver en **lille merværdi** sammenlignet med topiramat. Evidensens kvalitet vurderes at være lav.

Tabellen herunder viser den samlede kategori for lægemidlet og kvaliteten af en samlede evidens. I tabellen indgår absolutte og relative effektforskelle samt foreløbige og aggregerede værdier.

Tabel 1: Kategorier og resultater

Effektmål	Måleenhed	Vigtighed	Komparator	Forskel i absolutte tal[†]		Forskel i relative tal[†]		Aggregeret værdi pr. effektmål
				Forskel (95 % CI)[*]	Foreløbig værdi	Forskel RR (95 % CI)	Foreløbig værdi	
Frekvens af migrænedage	Procentuel ændring af månedlige migrænedage Justeret mindste klinisk relevante forskel (MKRF): 5 %-point	Kritisk	Propranolol	M -28,69 (-50,08; -7,31) Q -18,93 (-39,59; 1,74)	M Mærværdi af ukendt størrelse Q Ingen dokumenteret mærværdi	-	-	Mærværdi af ukendt størrelse
			Candesartan	M -34,93 (-74,15; 4,29) Q -23,26 (-61,93; 15,41)	M Ingen dokumenteret Q Kan ikke kategoriseres	-	-	Ingen dokumenteret mærværdi
			Topiramat	M -12,25 (-27,32; 2,82) Q -4,91 (-19,40; 9,58)	M Ingen dokumenteret mærværdi Q Kan ikke kategoriseres	-	-	Ingen dokumenteret mærværdi
			Lisinopril	M -7,85 (-44,94; 29,24) Q -0,62 (-37,48; 36,25)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
	≥ 50 % reduktion af månedlige migrænedage Justeret MKRF: 2,5 %-point	Vigtig	Propranolol	M 0,80 (-17,20; 33,60) Q -2,80 (-19,70; 27,60)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	M 1,02 (0,57; 1,84) Q 0,93 (0,51; 1,69)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
			Candesartan	M -24,13 (-39,11; 82,79) Q -25,79 (-39,52; 71,56)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	M 0,42 (0,06; 2,99) Q 0,38 (0,05; 2,72)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
			Topiramat	M -10,27 (-28,10; 152,30) Q -12,09 (-28,10; 135,98)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	M 0,66 (0,07; 6,04) Q 0,60 (0,07; 5,50)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
			Lisinopril	M -18,47 (-26,51; 7,15) Q -19,66 (-26,81; 3,87)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	M 0,38 (0,11; 1,24) Q 0,34 (0,10; 1,13)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	Gennemsnitlig ændring fra baseline på HIT-6 Justeret MKRF: -0,75 point (EM) -1,15 point (CM)	Kritisk	Propranolol	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
			Candesartan	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
			Topiramat	M -0,21 point (-2,60; 2,17) Q 0,46 point (-2,20; 3,13)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
			Lisinopril	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
Anfalds-sværhedsgrad	Procentuel ændring af antal dage med anfaldsbehandling pr. måned Justeret MKRF: 5 %-point	Vigtig	Propranolol	M -20,47 (-38,10; -2,85) Q -25,64 (-55,42; 4,14)	M Ingen dokumenteret mærværdi Q Ingen dokumenteret mærværdi	-	-	Ingen dokumenteret mærværdi
			Candesartan	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
			Topiramat	M -19,88 (-31,63; -8,13) Q -24,72 (-50,08; 0,65)	M Mærværdi af ukendt størrelse Q Ingen dokumenteret mærværdi	-	-	Mærværdi af ukendt størrelse

			Lisinopril	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
Bivirkninger	Andel patienter som oplever uønskede hændelser, der medfører behandlingsophør Justeret MKRF: 2,5 %-point	Vigtig	Propranolol	M -8,66 (-12,84; 2,47) Q -9,74 (-13,30; 0,15)	M Ingen dokumenteret Q Ingen dokumenteret	M 0,44 (0,17; 1,16) Q 0,37 (0,14; 1,01)	M Kan ikke kategoriseres Q Ingen dokumenteret	Ingen dokumenteret merværdi
			Candesartan	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
			Topiramat	M -12,19 (-15,94; -2,81) Q -13,13 (-16,50; -4,88)	M Merværdi af ukendt størrelse Q Merværdi af ukendt størrelse	M 0,35 (0,15; 0,85) Q 0,30 (0,12; 0,74)	M Moderat merværdi Q Stor merværdi	Moderat merværdi
			Lisinopril	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
Frekvens af hovedpinedage	Procentuel ændring af månedlige hovedpinedage (non-migræne) Justeret MKRF: 5 %-point	Vigtig	Propranolol	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
			Candesartan	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
			Topiramat	M -6,58 (-16,14; 2,98) Q -4,79 (-14,46; 4,88)	M Ingen dokumenteret merværdi Q Ingen dokumenteret merværdi	-	-	Ingen dokumenteret merværdi
			Lisinopril	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi (kvalitet af den samlede evidens)			Propranolol	**Kan ikke kategoriseres (lav evidenskvalitet)**				
			Candesartan	**Kan ikke kategoriseres (meget lav evidenskvalitet)**				
			Topiramat	**Lille merværdi (lav evidenskvalitet)**				
			Lisinopril	**Kan ikke kategoriseres (meget lav evidenskvalitet)**				

*Hvis andet ikke er angivet, er alle absolutte forskelle angivet i %-point.
† Estimater for den månedlige dosering er angivet ved M. Estimater for den kvartalsvise dosering er angivet ved Q.

9.1.1 Gennemgang af studier

Til besvarelse af dette spørgsmål blev der identificeret 17 studier af patienter med migræne, hvor studiepopulationen gennemsnitligt har mindst fire migrænedage pr. måned: 4 studier med fremanezumab, 3 studier med propranolol, 2 studier med candesartancilexetil, 1 studie med lisinopril og 9 studier med topiramat.

Populationen og de væsentligste studiekarakteristika med betydning for vurderingen fremgår af bilag 3 og appendiks 1.

Population

For fremanezumabstudierne indgår en gruppe af patienter (ca. 30 %), som fortsætter deres eksisterende migræneforebyggende behandling ved inklusion i studierne. Fremanezumab tilføjes som supplerende behandling for denne gruppe af patienter. Studiernes randomisering er stratificeret i forhold til brug af anden forebyggende behandling, og andelen af patienter, som får fremanezumab som supplerende behandling, er dermed ligeligt fordelt mellem de aktive behandlingsarme og placebo. Fagudvalget kan ikke vurdere, om de patienter, som behandles med to lægemidler, vil påvirke effektestimaterne, og i givet fald i hvilken retning estimaterne vil påvirkes. I komparatorstudierne er supplerende behandling (forebyggende behandling med to lægemidler) ikke en mulighed. Forskellen mellem de sammenlignede studier giver en øget usikkerhed i forhold til tolkningen de indirekte sammenligninger.

Patientpopulationerne i de fremanezumabstudier, som inkluderer patienter med episodisk migræne, har generelt en højere frekvens af migrænedage ved baseline, end tilfældet er for komparatorstudierne. Ikke alle studier indgår i analyserne for de enkelte effektmål. Derfor kan det på nogle effektmål for visse komparatorer betyde, at der er forskel, hvad angår patienternes sygdomssværhedsgrad ved baseline i de indirekte sammenligninger. Fagudvalget har ikke noget grundlag for at vurdere, om disse forhold vil påvirke effektestimaterne og i hvilken retning. Fagudvalget bemærker, at der på tværs af de fremanezumabstudier, som indgår i besvarelsen af dette kliniske spørgsmål, generelt er sammenlignelig effekt i patienter med episodisk og kronisk migræne. Der er således ikke noget, der antyder, at effektstørrelsen (relative såvel som absolutte effektestimater) af behandlingen afhænger af sygdomssværhedsgraden ved baseline. Opdelingen mellem episodisk og kronisk migræne er i øvrigt baseret på en arbitrær grænse, og sygdommen opfattes som et kontinuerligt spektrum. Begge disse forhold taler for, at forskelle i sygdomssværhedsgrad ved baseline ikke har væsentlig betydning for validiteten af de indirekte analyser. Fagudvalget har derfor vurderet, at studierne kan danne grundlag for en sammenlignende kvantitativ analyse.

Fagudvalget vurderer, at baselinekarakteristika for studiepopulationerne i de inkluderede studier i øvrigt stemmer godt overens med den danske migrænepopulation.

9.1.2 Resultater og vurdering

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

Frekvens af migrænedage – procentuel reduktion af månedlige migrænedage (kritisk)

Effektmålet beskriver reduktionen i antal migrænedage pr. måned og er et kritisk effektmål. Idet effektmålet ”frekvens af migrænedage – procentuel ændring af månedlige migrænedage” er et kontinuert effektmål, er det ikke muligt at beregne et relativt effektestimat, og effektmålet vurderes derfor udelukkende på baggrund af de absolutte effektestimater.

Da der er stor variation blandt migrænepatienter i antal migrænedage pr. måned, blev den mindste klinisk relevante forskel fastsat som en procentuel forskel i stedet for et antal dage. De indirekte estimater er omregnet til procentuel ændring ved hjælp af antagede hændelsesrater for patienter behandlet med hver af komparatorerne. De antagede hændelsesrater er beregnet på baggrund af effekten fra studierne og er 3,6; 3,0; 4,7 og 4,8 migrænedage pr. måned for henholdsvis propranolol, candesartancilexetil, topiramat og lisinopril. Den beregnede procentuelle ændring og tilhørende konfidensintervaller af migrænedage fremgår af tabel 1.

Grundlaget for beregningerne er effektestimaterne fra de placebokontrollerede studier, hvor fremanezumab 225 mg, på tværs af de fire inkluderede studier, gav en ændring af månedlige migrænedage på -1,78 dage [-2,25; -1,30] sammenlignet med placebo. Den kvartalsvise dosering på 675 mg var anvendt i to studier og gav en samlet ændring på -1,43 dage [-1,86; -0,99] sammenlignet med placebo. Behandling med propranolol medførte en ændring på -0,76 dage [-1,35; -0,16] (2 studier), candesartancilexetil en ændring på -0,74 dage [-1,80; 0,33] (2 studier), topiramat en ændring på -1,20 dage [-1,73; -0,67] (6 studier) og lisinopril en ændring på -1,40 dage [-2,61; -0,19] (1 studie) sammenlignet med placebo. De indirekte effektestimater viser, at behandling med fremanezumab reducerer frekvensen af månedlige migrænedage med gennemsnitligt 1,02 dage (månedlig dosering) og 0,67 dage (kvartalsvis dosering) yderligere i forhold til propranolol, 1,04 dage og 0,69 dage yderligere i forhold til candesartancilexetil, 0,58 dage og 0,23 dage yderligere i forhold til topiramat og mellem 0,03-0,58 dage yderligere i forhold til lisinopril.

For propranolol:

Punktestimaterne for både månedlig og kvartalsvis dosering af fremanezumab viser en større procentuel reduktion sammenlignet med propranolol. For den månedlige dosering ses en statistisk signifikant og klinisk betydende forskel til fordel for fremanezumab, idet den øvre grænse i konfidensintervallet på -7,31 %-point er mindre end den justerede mindste klinisk relevante forskel på -5 %-point. Dette svarer til en foreløbig kategori i merværdi af ukendt størrelse for denne dosering. Den øvre grænse i konfidensintervallet for den kvartalsvise dosering er 1,74 %-point, og der er således ingen dokumenteret merværdi af denne dosering. Den procentuelle reduktion er baseret på en reduktion på op til ca. 1 migrænedag sammenlignet med propranolol. Baseret på de absolutte effektforskelle vurderer fagudvalget, at fremanezumab på tværs af de to doser har en **merværdi af ukendt størrelse** for effektmålet "Frekvens af migrænedage" (moderat evidenskvalitet).

For candesartancilexetil:

For begge doseringer viser punktestimaterne en større procentuel reduktion for fremanezumab sammenlignet med candesartancilexetil. Der er en betydelig usikkerhed omkring begge estimater, hvilket indplacerer fremanezumab i henholdsvis ingen dokumenteret og en værdi, som ikke kan kategoriseres for henholdsvis den månedlige og den kvartalsvise dosering. Den procentuelle ændring svarer til en reduktion på op til ca. 1 migrænedag sammenlignet med candesartancilexetil. Baseret på de absolutte effektforskelle vurderer fagudvalget, at fremanezumab på tværs af de to doseringer har **ingen dokumenteret merværdi** på effektmålet "Frekvens af migrænedage" (meget lav evidenskvalitet).

For topiramat:

Punktestimaterne viser, for begge doseringer, en større procentuel reduktion for fremanezumab sammenlignet med topiramat. Numerisk er forskellen noget lavere, end tilfældet var for propranolol og candesartancilexetil. Den øvre grænse i konfidensintervallet på 2,82 for sammenligningen med den månedlige dosering resulterer i en foreløbig kategorisering i ingen dokumenteret merværdi. Usikkerheden for den kvartalsvise dosering betyder, at den foreløbige værdi ikke kan kategoriseres. Baseret på de absolutte effektforskelle vurderer fagudvalget, at fremanezumab på tværs af de to doseringer har **ingen dokumenteret merværdi** på effektmålet "Frekvens af migrænedage" (moderat evidenskvalitet). Den procentuelle ændring svarede til en reduktion på op til ca. 0,6 migrænedag sammenlignet med topiramat.

For lisinopril:

Baseret på de absolutte effektforskelle vurderer fagudvalget, at værdien af fremanezumab **ikke kan kategoriseres** for effektmålet "Frekvens af migrænedage" (meget lav evidenskvalitet). Dette baseres på den betydelige usikkerhed, der ses omkring effektestimaterne. Punktestimaterne antyder, at behandling med fremanezumab ikke umiddelbart giver en yderligere reduktion i patientens migrænedage, men da konfidensintervallerne er brede, er der ikke grundlag for at fastsætte foreløbige kategorier og en aggregeret kategori for dette effektmål.

Frekvens af migrænedage – andel af patientpopulationen, som opnår ≥ 50 % reduktion af månedlige migrænedage (vigtig)

Effektmålet beskriver andelen af patienter, der opnår forbedring (minimum halvering) af migrænedage uden nødvendigvis at opnå fuldstændig sygdomsfrihed. Dette benævnes i resten af dokumentet "50 % responderrate".

De absolutte effektforskelle er beregnet ud fra de relative effektestimater fra de indirekte sammenligninger. De absolutte effektforskelle er angivet som en procentuel forskel og blev beregnet ved hjælp af antagede hændelsesrater. De antagede hændelsesrater er beregnet på baggrund af effekterne fra studierne. Her ses, at en andel på henholdsvis 40 %, 42 %, 30 % og 30 % af patientpopulationen opnår mindst 50 % reduktion af månedlige migrænedage ved behandling med henholdsvis propranolol, candesartancilexetil, lisinopril og topiramat. De absolutte og de relative effektforskelle fremgår af tabel 1.

Grundlaget for beregning af indirekte effektestimater er effektestimaterne fra de placebokontrollerede studier. Den månedlige dosering af fremanezumab gav på tværs af de to inkluderede studier en relativ øgning i 50 % responderrate på RR 1,75 [1,45; 2,12] sammenlignet med placebo. Den kvartalsvise dosering gav en samlet relativ øgning på RR 1,59 [1,27; 1,99] sammenlignet med placebo (1 studie). Behandling med propranolol medførte en øgning på RR 1,71 [0,99;2,89] (1 studie), candesartancilexetil en øgning på RR 4,16 [0,59;29,26] (2 studier), topiramat en øgning på RR 2,65 [0,29; 24,03] (2 studier) og lisinopril en øgning på 4,67 [1,43; 15,18] (1 studie) sammenlignet med placebo. De indirekte sammenligninger er baseret på disse estimater.

De beregnede absolutte og relative effektestimater fra de indirekte sammenligninger er alle behæftet med stor usikkerhed. Baseret på de absolutte og relative effektforskelle er der ikke fundet tilstrækkeligt grundlag for at kategorisere fremanezumabs værdi i forhold til de fire komparatorer. De foreløbige og de aggregerede værdier **kan ikke kategoriseres** (lav – meget lav evidenskvalitet).

Livskvalitet (kritisk)

Livskvalitet er et centralt effektmål for migrænepatienter og er af fagudvalget vurderet som et kritisk effektmål. HIT-6 er et af de mest kendte spørgeskemaer til vurdering af livskvalitet blandt danske patienter med migræne.En reduktion af patientens score på spørgeskemaet er udtryk for forbedring i patientens livskvalitet.

I litteraturen er der angivet en mindste klinisk relevant forskel på -1,5 point for patienter med episodisk migræne og -2,3 point for patienter med kronisk migræne i forhold til at vise en forbedret effekt af behandlingen for HIT-6-værktøjet [33,34].

Dette effektmål er ikke undersøgt for komparatorerne: propranolol, candesartancilexetil og lisinopril. Der er dermed ikke grundlag for formelt at kategorisere fremanezumabs værdi i forhold til disse tre komparatorer. For topiramat er der udført indirekte analyser, hvor estimaterne er behæftet med stor usikkerhed.

Usikkerheden gør, at effektestimaterne for sammenligningen med topiramat falder i kategorien ”kan ikke kategoriseres”.

Fagudvalget vurderer, at værdien af fremanezumab **ikke kan kategoriseres** i forhold til propranolol, candesartancilexetil, topiramat og lisinopril for patienter med migræne, hvad angår livskvalitet. Evidensen kvalitet for sammenligningen med topiramat er lav.

Anfaldssværhedsgrad (vigtig)

Ud over reduktion af migræneanfaldsfrekvens bliver effekten af forebyggende behandling ved reduktion af sværhedsgraden af migræne målt. Forbrug af smertestillende medicin anvendes som et surrogatmål, der indikerer, om et migræneanfald har mindst moderat intensitet. Idet effektmålet ”Anfaldssværhedsgrad – procentuelle ændring i antal dage med anfaldsbehandling pr. måned” er et kontinuert effektmål, er det ikke muligt at beregne relative effektestimater. Effektmålet bliver derfor udelukkende vurderet på baggrund af de absolutte effektforskelle.

De absolutte effektforskelle er omregnet til en procentuel ændring ved hjælp af antagede hændelsesrater for hver af komparatorerne. Disse hændelsesrater er bestemt til 3,8 og 4,1 dage med anfaldsbehandling for henholdsvis propranolol og topiramat. Den beregnede procentuelle ændring fremgår af tabel 1.

Grundlaget for beregning af indirekte effektestimater er effektestimaterne fra de placebokontrollerede studier. Månedlig dosering af fremanezumab medførte en ændring af dage med anfaldsbehandling på -1,58 dage [-1,93; -1,22] sammenlignet med placebo (4 studier). Den kvartalsvise dosering viste på tværs af 2 studier en ændring på -1,77 dage [-2,75; -0,80]. Behandling med propranolol medførte en ændring på -0,80 dage [-1,37; -0,23] (1 studie) og topiramat en ændring på -0,77 dage [-1,09; -0,45] (6 studier). Ingen data findes for hverken candesartancilexetil eller lisinopril. De indirekte sammenligninger er baseret på disse estimater.

Behandling med fremanezumab reducerer således frekvensen af dage med anfaldsbehandling med op til yderligere en dag sammenlignet med propranolol og topiramat.

<u>For propranolol:</u>

Punktestimaterne for både månedlig og kvartalsvis dosering viser en større procentuel reduktion i størrelsesordenen 20-25 %-point sammenlignet med propranolol. Idet de øvre grænser i konfidensintervallet for begge de indirekte effektestimater er større end -5 %-point og samtidig mindre end 5 %-point, kategoriserer begge estimaterne foreløbig til ingen dokumenteret merværdi. På tværs af de to doseringer vurderer fagudvalget, at fremanezumab har **ingen dokumenteret merværdi** vedr. anfaldssværhedsgrad (lav evidenskvalitet)

<u>For topiramat:</u>

Punktestimaterne for både månedlig og kvartalsvis dosering viser en større procentuel reduktion i størrelsesordenen 20-25 %-point sammenlignet med topiramat. Den månedlige dosering kategoriserer foreløbig til merværdi af ukendt størrelse, idet den øvre grænse i konfidensintervallet på -8,13 %-point er mindre end den justerede mindste klinisk relevante forskel på -5 %-point. Den øvre grænse for den kvartalsvise dosering på 0,65 %-point er større end -5 %-point og samtidig mindre end 5 %-point og kategoriserer dermed foreløbig til ingen dokumenteret merværdi. På tværs af de to doser vurderer fagudvalget, at fremanezumab har **merværdi af ukendt størrelse** vedr. anfaldssværhedsgrad (moderat evidenskvalitet)

For candesartancilexetil og lisinopril:

Fagudvalget vurderer, at værdien af fremanezumab **ikke kan kategoriseres** i forhold til candesartancilexetil og lisinopril for patienter med migræne, hvad angår anfaldssværhedsgrad, idet effektmålet ikke er undersøgt for disse komparatorer.

Bivirkninger (vigtig)

Forebyggende behandling af migræne afbrydes ofte på grund af bivirkninger. Fagudvalget ønskede derfor at vurdere bivirkninger på effektmålet "bivirkninger der medfører behandlingsophør". Kategoriseringen er foretaget på data for uønskede hændelser frem for bivirkninger.

Herudover ønskede fagudvalget at foretage en kvalitativ beskrivelse af de hyppigst forekommende bivirkninger ved forebyggende migrænebehandling, herunder sedation, svimmelhed, vægtøgning og affektive symptomer.

I den samlede vurdering af dette effektmål vil fagudvalget således inddrage både en kvantitativ vurdering i form af andel patienter, som ophører med behandling grundet uønskede hændelser og en kvalitativ gennemgang af bivirkninger ved behandling med henholdsvis fremanezumab og komparatorerne.

De absolutte effektforskelle mellem fremanezumab og komparatorerne er beregnet ud fra de relative forskelle ved hjælp af antagede hændelsesrater for behandling med hver af komparatorerne. Der er i beregningerne taget udgangspunkt i effekten fra studierne. De antagede hændelsesrater er fastsat til en andel på henholdsvis 15,5 % og 18,8 % af patienterne, der ophører med behandling grundet uønskede hændelser ved behandling med henholdsvis propranolol og topiramat. Den absolutte (procentuelle) og relative effektforskel i andel patienter, der ophører med behandlingen på grund af uønskede hændelser, fremgår af tabel 1. Ingen data er tilgængelige for candesartancilexetil og lisinopril.

Grundlaget for beregning af indirekte effektestimater er effektestimaterne fra de placebokontrollerede studier. For andelen af patienter der ophører med behandling pga. uønskede hændelser, viser den månedlige dosering af fremanezumab en RR på 0,92 [0,42; 2,00] sammenlignet med placebo (2 studier). Den kvartalsvise dosering giver en RR på 0,77 [0,34;1,76] sammenlignet med placebo (2 studier). Behandling med komparatorerne medførte en øget andel af patienter, som ophører med behandling grundet uønskede hændelser sammenlignet med placebo. For propranolol var RR på 2,07 [1,19;3,62] (2 studier), mens behandling med topiramat resulterede i en RR på 2,60 [1,76; 3,83] (9 studier). De indirekte sammenligninger er baseret på disse estimater.

For propranolol:

Baseret på den absolutte effektforskel har fremanezumab foreløbigt **ingen dokumenteret** merværdi vedr. uønskede hændelser, der medfører behandlingsophør, idet de øvre grænser for konfidensintervallerne for begge doseringer på hhv. 2,47 %-point og 0,15 %-point er lavere end den justerede mindste klinisk relevante forskel på 2,5 %-point.

Baseret på den relative effektforskel har den månedlige dosering af fremanezumab foreløbig en værdi, som **ikke kan kategoriseres**. Den foreløbige kategori for den kvartalsvise dosering falder i **ingen dokumenteret merværdi**.

På aggregeret niveau vurderer fagudvalget, at fremanezumab har **ingen dokumenteret merværdi** vedr. uønskede hændelser, der medfører behandlingsophør (lav evidenskvalitet).

For topiramat:

Baseret på de absolutte effektforskelle har fremanezumab foreløbig en **merværdi af ukendt størrelse** vedr. uønskede hændelser, der medfører behandlingsophør, idet de øvre grænser for konfidensintervallerne for begge doseringer på hhv. -2,81 %-point og -4,88 %-point er lavere end den justerede mindste klinisk relevante forskel på -2,5 %-point.

Baseret på de relative effektforskelle har fremanezumab foreløbig en **moderat** og en **stor** merværdi, idet de øvre grænser for konfidensintervallerne er hhv. 0,85 og 0,74 for den månedlige og den kvartalsvise dosering.

På aggregeret niveau vurderer fagudvalget, at fremanezumab har en **moderat merværdi** vedr. uønskede hændelser, der medfører behandlingsophør (lav evidenskvalitet).

For candesartancilexetil og lisinopril:

Fagudvalget vurderer, at værdien af fremanezumab **ikke kan kategoriseres** i forhold til candesartancilexetil og lisinopril for patienter med migræne, hvad angår uønskede hændelser, der medfører behandlingsophør, idet der ikke er publiceret data for dette effektmål for disse komparatorer.

Kvalitativ beskrivelse af bivirkninger:

Fagudvalget har desuden bedt om en kvalitativ gennemgang af de hyppigst fremkommende bivirkninger ved behandling med fremanezumab og komparatorerne, herunder bivirkninger i form af sedation, svimmelhed, vægtøgning og affektive symptomer.

For fremanezumab er flere end 2.500 patienter (mere end 1.900 behandlingsår) blevet behandlet med fremanezumab i de kliniske studier. Af disse blev flere end 1.400 patienter eksponeret i mindst 12 måneder. Overordnet er der i de kliniske studier ikke væsentlig forskel på sikkerhedsprofilerne for fremanezumab og placebo.

De hyppigst rapporterede bivirkninger var lokale reaktioner ved injektionsstedet (smerter [24 %], induration [17 %], rødme [16 %] og kløe [2 %]) [35].

Fremanezumab er tilsyneladende forbundet med meget få bivirkninger, men fagudvalget ønsker at fremhæve, at erfaring med længerevarende behandling er begrænset, og at der dermed er usikkerhed om sjældne og mere langsigtede bivirkninger. Grundet den relativt lange halveringstid (ca. 30 dage) for fremanezumab udtrykker fagudvalget også usikkerhed om varigheden og reversibiliteten af eventuelle sjældne bivirkninger.

Komparatorerne propranolol, candesartancilexetil, topiramat og lisinopril er velkendte lægemidler i klinikken og er forbundet med en række bivirkninger. Det er dog fagudvalgets erfaring, at behandlingsophør med propranolol, candesartancilexetil og lisinopril oftest skyldes manglende effekt fremfor generende bivirkninger, mens det modsatte er tilfældet med topiramat.

Vedrørende propranolol:

For propranolol er følgende bivirkninger beskrevet som almindelige bivirkninger: søvnforstyrrelser, mareridt, bradykardi (langsom puls), kolde ekstremiteter, dyspnø, diarré, kvalme og opkast. Dertil kommer en række sjældne bivirkninger, herunder svimmelhed, hypotension/synkope og paræstesier [36]. Fagudvalget vurderer, at især ortostatisk hypotension er en hyppig bivirkning ved behandling af patienter med migræne, mens kvalme og opkast ikke er en kendt bivirkning ved brug af propranolol hos migrænepatienter.

Den kvalitative gennemgang af bivirkninger understøtter kategoriseringerne for de absolutte og relative effekter.

Vedrørende candesartancilexetil:

For candesartancilexetil er de almindelige bivirkninger luftvejsinfektioner, svimmelhed og hovedpine [37]. Desuden bemærker fagudvalget, at tør hoste også er en hyppig bivirkning ved behandling med candesartancilexetil af migrænepatienter.

Der findes ikke komparative data vedrørende effektmålet behandlingsophør grundet uønskede hændelser, og vurderingen er udelukkende baseret på en kvalitativ beskrivelse af bivirkningerne for henholdsvis candesartancilexetil og fremanezumab. Derfor vurderer fagudvalget, at værdien af fremanezumab for effektmålet bivirkninger **ikke kan kategoriseres**.

Vedrørende topiramat:

For topiramat er bl.a. følgende bivirkninger (meget) almindelige: nasopharyngitis, nedsat appetit, depression, søvnløshed, ekspressive taleforstyrrelser, angst, konfusion, desorientering, aggression, humørændringer, uopmærksomhed, nedsat hukommelse, amnesi, kognitiv lidelse, nedsat psykisk funktionsevne, nedsat psykomotorisk evne, kramper, anormal koordinationsevne, tremor, letargi, hypæstesi, nystagmus, balanceforstyrrelser, dysartri, intentionstremor, sedation, paræstesi, døsighed, svimmelhed, unormal adfærd, sløret syn, diplopi, synsforstyrrelser, tinnitus, ørepine, opkastning, obstipation, dyspepsi, abdominalsmerter, mundtørhed, gastritis, kvalme, diarré, alopeci, udslæt, pruritus, artralgi, muskelkramper, myalgi, muskeltrækninger, muskelsvaghed, muskuloskeletale brystsmerter, træthed, vægttab og vægtøgning [38]. Fagudvalget vurderer, at især bivirkningerne nedsat appetit, depression, nedsat hukommelse, paræstesier, døsighed og svimmelhed er særligt hyppige hos patienter med migræne, der behandles med topiramat.

De absolutte og relative effektforskelle for effektmålet "behandlingsophør grundet uønskede hændelser" indikerer en moderat klinisk merværdi for fremanezumab. Desuden er behandling med topiramat behæftet med en del bivirkninger, som ikke nødvendigvis medfører behandlingsophør, men som kan være til stor gene for patienten.

Vedrørende lisinopril:

For lisinopril er nogle af de hyppigst rapporterede bivirkninger hoste, svimmelhed, hypotension og hovedpine. Blandt de almindelige bivirkninger er desuden synkope, diarré, opkastning og dysfunktion af nyrerne. Bivirkningerne er sædvanligvis lette og forbigående, og i de fleste tilfælde er det ikke nødvendigt at afbryde behandlingen [39].

Eftersom der ikke forefindes komparative data vedrørende effektmålet behandlingsophør grundet uønskede hændelser, og vurderingen dermed udelukkende kan baseres på en kvalitativ beskrivelse af bivirkningerne for henholdsvis lisinopril og fremanezumab, vurderer fagudvalget, at værdien af fremanezumab sammenlignet med lisinopril, for effektmålet bivirkninger, **ikke kan kategoriseres**.

Frekvens af hovedpinedage (vigtig)

Patienter med kronisk migræne har ≥ 15 hovedpinedage om måneden, heraf mindst 8 dage som migrænehovedpine, resten som non-migrænehovedpine, oftest spændingshovedpine. Ved monitorering af behandlingseffekt af den forebyggende behandling hos patienter med kronisk migræne er det et centralt element at vurdere effekten af den forebyggende behandling på øvrig non-migrænehovedpine.

Fagudvalget har fastsat en retningsgivende mindste klinisk relevant forskel på 10 %-point på reduktion af månedlige hovedpinedage. Da fagudvalget kun har ønsket dette effektmål belyst for gruppen af patienter med kronisk migræne, indgår der kun effektestimater for sammenligningen mellem fremanezumab og topiramat for dette effektmål, idet der ikke findes studier på kronisk migræne for de øvrige komparatorer.

Månedlig dosering af fremanezumab medførte en ændring af månedlige hovedpinedage på -2,06 dage [-2,67; -1,45] sammenlignet med placebo (2 studier). Den kvartalsvise dosering viste i et studie en ændring på -2,30 dage [-2,97; -1,67]. Behandling med topiramat medførte en ændring på -1,1 dag [-2,35; 0,15] (1 studie). De indirekte sammenligninger er baseret på disse estimater. De absolutte effektforskelle er omregnet til en procentuel ændring af månedlige hovedpinedage ved hjælp af en antaget hændelsesrate for topiramat. Den beregnede procentuelle ændring for den indirekte sammenligning fremgår af tabel 1.

Behandling med fremanezumab reducerer således frekvensen af hovedpinedage med ca. en dag yderligere sammenlignet med topiramat. Værdien for sammenligningen med de øvrige komparatorer: propranolol, candesartancilexetil og lisinopril **kan ikke kategoriseres** for dette effektmål, idet der ikke findes studier på kronisk migræne for disse komparatorer.

For topiramat

Punktestimaterne for både månedlig og kvartalsvis dosering viser en mindre reduktion i størrelsesordenen 5-7 %-point sammenlignet med topiramat. De øvre grænser i konfidensintervallerne ligger på hhv. 2,98 %-point og 4,88 %-point, hvilket foreløbigt indplacerer begge doseringer i ingen dokumenteret merværdi. På tværs af de to doseringer vurderer fagudvalget, at fremanezumab har **ingen dokumenteret merværdi** vedr. månedlige hovedpinedage sammenlignet med topiramat (meget lav evidenskvalitet)

9.1.3 Evidensens kvalitet

1. Propranolol

Evidensens kvalitet for sammenligningen mellem fremanezumab og propranolol er samlet set vurderet som værende **lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Den lave evidenskvalitet skyldes, at effektestimaterne for nogle effektmål udelukkende er baseret på ét studie, og at der for visse effektestimater er brede konfidensintervaller. Derudover er der tale om en indirekte sammenligning, så evidensens kvalitet nedgraderes yderligere for ”indirectness”.

2. Candesartancilexetil

Evidensens kvalitet for sammenligningen mellem fremanezumab og candesartancilexetil er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

3. Topiramat

Evidensens kvalitet for sammenligningen mellem fremanezumab og topiramat er samlet set vurderet som værende **lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Den lave evidenskvalitet skyldes, at der for visse effektestimater ses brede konfidensintervaller. Derudover er der tale om en indirekte sammenligning, og derfor nedgraderes evidensens kvalitet til en lav evidenskvalitet.

4. Lisinopril

Evidensens kvalitet for sammenligningen mellem fremanezumab og lisinopril er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Den meget lave evidenskvalitet skyldes, at effektestimaterne for lisinopril udelukkende er baseret på ét studie, og at kun få effektmål i øvrigt er rapporteret i studiet. Derudover er der tale om en indirekte sammenligning og derfor nedgraderes yderligere til en samlet meget lav evidenskvalitet.

9.1.4 Konklusion for klinisk spørgsmål 1

1. Propranolol

Fagudvalget vurderer, at den samlede værdi af fremanezumab sammenlignet med propranolol **ikke kan kategoriseres** (lav evidenskvalitet). Hvad angår behandlingseffekt og bivirkninger, vurderer fagudvalget samlet set, at fremanezumab ikke er underlegent i forhold til propranolol. Fagudvalget bemærker i øvrigt, at der er en mulig gevinst på patientens frekvens af migrænedage ved anvendelse af fremanezumab.

Fagudvalget vurderer, at en yderligere reduktion i antal månedlige migrænedage med op til en dag (svarende til en reduktion på ca. 30 %-point) for den månedlige dosering af fremanezumab i forhold til propranolol giver en merværdi af ukendt størrelse. Størrelsen af merværdien kan ikke kvantificeres yderligere, idet kategoriseringen for dette effektmål udelukkende er baseret på absolutte effektestimater. Fagudvalget vurderer, at en reduktion på yderligere en migrænedag pr. måned er af væsentlig betydning for patienter. Vedrørende effektmålene "bivirkninger" og "anfaldssværhedsgrad" ses ingen dokumenteret merværdi af fremanezumab i forhold til propranolol. For effektmålene "50 % responderrate", "livskvalitet" og "frekvens af hovedpinedage" kunne værdien af fremanezumab ikke kategoriseres. For de to sidstnævnte effektmål skyldtes den manglende mulighed for kategorisering, at der ikke er data, mens der var betydelig usikkerhed på effektestimatet, hvad angår "50 % responderrate". Fagudvalget bemærker, at der ud fra data ikke er noget der tyder på, at fremanezumab øger andelen af patienter, som opnår 50 % reduktion i månedlige migrænedage sammenlignet med propranolol.

Den samlede indplacering i "kan ikke kategoriseres" skyldes, at det udelukkende er effektmålet "frekvens af migrænedage", som viser en fordel ved fremanezumab. Værdien på flere af de øvrige effektmål, herunder det andet kritiske effektmål "Livskvalitet", kunne ikke kategoriseres.

2. Candesartancilexetil

Fagudvalget vurderer, at den samlede værdi af fremanezumab sammenlignet med candesartancilexetil **ikke kan kategoriseres** (meget lav evidenskvalitet). Hvad angår behandlingseffekt og bivirkninger, vurderer fagudvalget samlet set, at fremanezumab ikke er underlegent i forhold til candesartancilexetil.

Datagrundlaget for vurderingen af fremanezumab i forhold til candesartancilexetil var begrænset, idet der for effektmålene "livskvalitet", "anfaldssværhedsgrad", "bivirkninger" og "frekvens af hovedpinedage" ikke foreligger evidens, som muliggør en formel sammenligning. Effektmålet "50 % responderrate" var forbundet med betydelig usikkerhed, og data viste her ingen umiddelbar fordel ved fremanezumab. Det kritiske effektmål "frekvens af migrænedage" viste ingen dokumenteret merværdi.

Den samlede indplacering i "kan ikke kategoriseres" skyldes, at det udelukkende er effektmålet "frekvens af migrænedage", som kunne kategoriseres. Værdien på de øvrige effektmål, herunder det andet kritiske effektmål "Livskvalitet", kunne ikke kategoriseres.

3. Topiramat:

Fagudvalget vurderer, at fremanezumab til forebyggelse af migræne giver en **lille merværdi** for patienter med migræne sammenlignet med topiramat (lav evidenskvalitet).

For de to kritiske effektmål "frekvens af månedlige migrænedage" og "livskvalitet" viser kategoriseringen ingen forskel på fremanezumab og topiramat. For effektmålet "anfaldssværhedsgrad" ses en merværdi af ukendt størrelse svarende til en reduktion i antallet af dage med anfaldsbehandling på op til en 1 dag. Dette understøttes af effektmålet frekvens af månedlige migrænedage, hvor fagudvalget vurderer, at punktestimaterne kan antyde en lille tendens til fordel for fremanezumab. Det er dog behæftet med betydelig usikkerhed, da kategoriseringen for dette effektmål viste ingen dokumenteret merværdi, idet forskellene ikke

var statistisk signifikante. For effektmålet ”bivirkninger” opnår fremanezumab en moderat merværdi – dels på baggrund af de absolutte effektforskelle, hvor fremanezumab opnår den mindste klinisk relevante forskel for begge doseringer og også på baggrund af de relative effektforskelle, som kategoriserede til henholdsvis moderat og stor merværdi. Desuden er der lagt vægt på den kvalitative gennemgang af de samlede bivirkninger ved behandling med topiramat.

Hvad angår livskvalitet, var usikkerheden for effektestimaterne så stor, at værdien ikke kunne kategoriseres. Umiddelbart synes de to behandlinger at have samme effekt, hvad angår livskvalitet, idet punktestimaterne for begge doseringer ligger tæt på nul. Der var også betydelig usikkerhed, hvad angår ”50 % responderrate”. Fagudvalget bemærker her, at der ud fra data ikke er noget, der tyder på, at fremanezumab øger andelen af patienter, som opnår 50 % reduktion af månedlige migrænedage sammenlignet med topiramat. For ”frekvens af hovedpinedage” ses ingen dokumenteret merværdi i forhold til topiramat.

Fagudvalget påpeger samtidig, at behandling med topiramat er en relativ tidskrævende proces for sundhedspersonale og patienten, idet der som regel er behov for dosisjustering for at opnå en optimal dosis. Fagudvalget vurderer samlet set, at fremanezumab har en **lille merværdi** i forhold til topiramat.

4. Lisinopril:

Fagudvalget vurderer, at den samlede værdi for fremanezumab sammenlignet med lisinopril **ikke kan kategoriseres** (meget lav evidenskvalitet). Hvad angår behandlingseffekt og bivirkninger, vurderer fagudvalget samlet set, at fremanezumab ikke er underlegent i forhold til lisinopril.

Datagrundlaget for vurderingen af fremanezumab i forhold til lisinopril er begrænset, idet der for effektmålene ”livskvalitet”, ”anfaldssværhedsgrad”, ”bivirkninger” og ”frekvens af hovedpinedage” ikke foreligger evidens, som muliggør en sammenligning. Effektmålet ”50 % responderrate” er forbundet med betydelig usikkerhed, og data viser her ingen umiddelbar fordel ved fremanezumab. Det kritiske effektmål ”frekvens af migrænedage” er ligeledes forbundet med stor usikkerhed.

Den samlede indplacering i **kan ikke kategoriseres** skyldes, at værdien på alle de valgte effektmål ikke kunne kategoriseres.

9.2 Konklusion klinisk spørgsmål 2

Hvad er den kliniske merværdi af fremanezumab til patienter med migræne, der har mindst fire migrænedage pr. måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med eksisterende standardbehandling?

Fagudvalget finder, at den samlede værdi for fremanezumab til forebyggende behandling af patienter med migræne sammenlignet med amitriptylin og valproat **ikke kan kategoriseres**. Evidensens kvalitet vurderes at være meget lav. Fagudvalget vurderer dog, at fremanezumab samlet set ikke har dårligere effekt eller sikkerhedsprofil end de to komparatorer. Hvad angår bivirkninger, skønner fagudvalget, at fremanezumab kan være bedre, idet behandling med amitriptylin og valproat er forbundet med en række meget generende bivirkninger.

Tabel 2: Kategorier og resultater

Effektmål	Måleenhed	Vigtighed	Komparator	Forskel i absolutte tal†		Forskel i relative tal†		Aggregeret værdi pr. effektmål
				Forskel (95 % CI)*	Foreløbig værdi	Forskel RR (95 % CI)	Foreløbig værdi	
Frekvens af migrænedage	Procentuel ændring af månedlige migrænedage Justeret mindste klinisk relevante forskel (MKRF): 5 %-point	Kritisk	Amitriptylin	M -48,00 (-78,62; -17,38) Q -40,00 (-70,62; -9,38)	M Merværdi af ukendt størrelse Q Merværdi af ukendt størrelse	-	-	Merværdi af ukendt størrelse
			Valproat	Intet estimat	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
	≥ 50 % reduktion af månedlige migrænedage Justeret MKRF: 2,5 %-point	Vigtig	Amitriptylin	M 41,71 (0,03; 128,25) Q 42,10 (0,18; 129,03)	M Ingen dokumenteret merværdi Q Ingen dokumenteret merværdi	M 2,07 (1,00; 4,29) Q 2,08 (1,00; 4,31)	M Merværdi af ukendt størrelse Q Merværdi af ukendt størrelse	Kan ikke kategoriseres
			Valproat	M 7,17 (-26,30; 94,22) Q 7,65 (-26,30; 94,70)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	M 1,15 (0,45; 2,97) Q 1,16 (0,45; 2,98)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
Livskvalitet	Gennemsnitlig ændring fra baseline på HIT-6 Justeret MKRF: -0,75 point (EM) -1,15 point (CM)	Kritisk	Amitriptylin	Intet estimat	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
			Valproat	Intet estimat	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
Anfalds-sværhedsgrad	Procentuel ændring af antal dage med anfaldsbehandling pr. måned Justeret MKRF: 5 %-point	Vigtig	Amitriptylin	Intet estimat	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
			Valproat	Intet estimat	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Kan ikke kategoriseres
Bivirkninger	Andel patienter som oplever uønskede hændelser, der medfører behandlingsophør Justeret MKRF: 5 %-point	Vigtig	Amitriptylin	M -3,32 (-10,20; 31,54) Q -9,60 (-11,62; 11,62)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	M 0,72 (0,14; 3,66) Q 0,19 (0,02; 1,95)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
			Valproat	M -3,08 (-10,59; 35,46) Q -9,97 (-12,06; 12,93)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	M 0,75 (0,14; 3,88) Q 0,19 (0,02; 2,05)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Kan ikke kategoriseres
Frekvens af hovedpinedage	Procentuel ændring af månedlige hovedpinedage (non-migræne) Justeret MKRF: 5 %-point	Vigtig	Amitriptylin	Intet estimat	M Kan ikke kategoriseres Q Kan ikke kategoriseres			Kan ikke kategoriseres
			Valproat	Intet estimat	M Kan ikke kategoriseres Q Kan ikke kategoriseres			Kan ikke kategoriseres
Samlet kategori for lægemidlets værdi (Kvalitet af den samlede evidens)			Amitriptylin	**Samlet værdi kan ikke kategoriseres (meget lav evidenskvalitet)**				
			Valproat	**Samlet værdi kan ikke kategoriseres (meget lav evidenskvalitet)**				

*Hvis ikke andet er angivet, er alle absolutte forskelle angivet i %-point.

† Estimater for den månedlige dosering er angivet ved M. Estimater for den kvartalsvise dosering er angivet ved Q.

9.2.1 Gennemgang af studier

Til besvarelse af dette spørgsmål blev der identificeret 7 studier af patienter med migræne, hvor studiepopulationen gennemsnitligt har mindst fire migrænedage pr. måned: 1 studie med fremanezumab, 2 studier med amitriptylin og 4 studier med valproat.

Populationen og de væsentligste studiekarakteristika med betydning for vurderingen fremgår af bilag 3 og appendiks 1.

Population

Fagudvalget vurderer, at baselinekarakteristika for studiepopulationerne i de inkluderede studier stemmer godt overens med den danske migrænepopulation.

Fremanezumabstudiet inkluderede kun patienter med tidligere behandlingssvigt på andre migræneforebyggende lægemidler. For amitriptylinstudierne fremgår det ikke, om de inkluderede patienter tidligere har oplevet behandlingssvigt med andre præparater inden inklusion i studiet. For valproatstudierne er det nævnt, at patienter kunne have behandlingssvigt på op til to tidligere præparater, dog uden angivelse af hvor mange patienter, der havde oplevet behandlingssvigt på tidligere behandling(er). Det er fagudvalgets vurdering, at både amitriptylin og valproat normalt ikke gives som førstevalgspræparater. Derfor er det sandsynligt, at patienterne i studierne har oplevet behandlingssvigt på tidligere lægemidler inden opstart i behandling med et af disse to lægemidler. Under denne antagelse vurderer fagudvalget, at de inkluderede patienter både i fremanezumab- og komparatorstudierne generelt kan opfattes som patienter med mere svært behandlelig migræne. Studierne er således sammenlignelige og relevante til besvarelse af dette kliniske spørgsmål, som vedrører patienter med tidligere behandlingssvigt.

En del af patienterne i fremanezumabstudiet har et overforbrug af smertestillende lægemidler. Et overforbrug medfører ofte såkaldt ”medicinoverforbrugshovedpine”, hvor behandlingen i dansk klinisk praksis 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 med migræneforebyggende medicin, så længe patienterne er stratificerede ift. deres medicinoverforbrug. Ikke alle komparatorstudier angiver, om patienter med medicinoverforbrug kan indgå. I de komparatorstudier, hvor der fremgår information om overforbrug af smertestillende lægemidler, er overforbrug ikke tilladt. Forskellen mellem de sammenlignede studier giver en øget usikkerhed i forhold til tolkningen af de indirekte sammenligninger.

Fagudvalget bemærker i øvrigt, at der er betydelig forskel i de sammenlignede populationer, hvad angår gennemsnitlig sygdomssværhedsgrad, idet ca. 60 % af patienterne i fremanezumabstudiet har kronisk migræne. I komparatorstudierne indgår udelukkende patienter, som må karakteriseres som patienter med episodisk migræne. Fagudvalget bemærker dog, at der på tværs af de fremanezumabstudier, som indgår i besvarelsen af dette kliniske spørgsmål, generelt er sammenlignelig effekt i patienter med episodisk og kronisk migræne. Der er således ikke noget, der antyder, at effektstørrelsen afhænger af sygdomssværhedsgraden ved baseline. Opdelingen mellem episodisk og kronisk migræne er i øvrigt baseret på en arbitrær grænse, og sygdommen opfattes som et kontinuerligt spektrum. Begge disse forhold taler for, at forskelle i sygdomssværhedsgrad ved baseline har mindre betydning i forhold til validiteten af de indirekte analyser.

9.2.2 Resultater og vurdering

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

Frekvens af migrænedage – procentuel reduktion af månedlige migrænedage (kritisk)

Grundlaget for beregningerne er effektestimaterne fra de placebokontrollerede studier. Den månedlige dosering af fremanezumab gav en ændring i månedlige migrænedage på -3,5 dage [-4,19; -2,78] sammenlignet med placebo i FOCUS-studiet. Den kvartalsvise dosering på 675 mg gav, i samme studie, en ændring på -3,1 dage [-3,84; -2,42] sammenlignet med placebo. Behandling med amitriptylin medførte en ændring på -1,1 dage [-2,46; 0,26] (1 studie). De indirekte sammenligninger er baseret på disse estimater. Behandling med fremanezumab reducerer frekvensen af månedlige migrænedage med gennemsnitligt 2,4 dage (månedlig dosering) og 2,0 dage (kvartalsvis dosering) yderligere i forhold til amitriptylin.

De inkluderede studier for valproat rapporterer ikke entydigt estimater for usikkerhed på forskellen i månedlige migrænedage, derfor indgår data ikke i vurderingen. Tre studier rapporterer forskellen i månedlige migrænedage sammenlignet med placebo i størrelsesordenen 1,0-2,6 dage.

For amitriptylin

Punktestimaterne for både månedlig og kvartalsvis dosering viser en større procentuel reduktion i månedlige migrænedage ved behandling med fremanezumab sammenlignet med amitriptylin. Der ses en statistisk signifikant og klinisk betydende forskel til fordel for fremanezumab, idet de øvre grænser i konfidensintervallerne på henholdsvis -17,38 og -9,38 %-point er mindre end den justerede mindste klinisk relevante forskel på -5 %-point. Dette svarer til en foreløbig kategori i merværdi af ukendt størrelse. Baseret på de absolutte effektforskelle vurderer fagudvalget, at fremanezumab på tværs af de to doseringer har en **merværdi af ukendt størrelse** for effektmålet "Frekvens af migrænedage" (meget lav evidenskvalitet). Den procentuelle reduktion vurderes at være en væsentlig gevinst for patienterne, idet det i analysen svarer til en reduktion på op til ca. 2,4 migrænedage sammenlignet med amitriptylin.

For valproat

Fagudvalget vurderer, at værdien af fremanezumab **ikke kan kategoriseres** i forhold til valproat for patienter med migræne, hvad angår reduktion af månedlige migrænedage, idet der ikke findes komparativ evidens.

Frekvens af migrænedage – andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage (vigtig)

De absolutte effektforskelle er angivet som en procentuel forskel og blev beregnet ved hjælp af antagede hændelsesrater. De antagede hændelsesrater er beregnet på baggrund af effekterne fra studierne. Her ses, at en andel på henholdsvis 39 % og 48 % af patientpopulationen opnår mindst 50 % reduktion af månedlige migrænedage ved behandling med henholdsvis amitriptylin og valproat. De absolutte og relative effektforskelle fremgår af tabel 2.

Grundlaget for beregning af indirekte effektestimater er effektestimaterne fra de placebokontrollerede studier. Den månedlige dosering af fremanezumab gav en relativ øgning i 50 % responderrate på RR 3,97 [2,62; 6,01] sammenlignet med placebo. Den kvartalsvise dosering gav en relativ øgning på RR 3,99 [2,63; 6,04] sammenlignet med placebo. Behandling med amitriptylin medførte en øgning på RR 1,92 [1,05; 3,48]

(1 studie) og valproat en øgning på RR 3,44 [1,47; 8,06] (1 studie) sammenlignet med placebo. De indirekte sammenligninger er baseret på disse estimater.

For amitriptylin

Baseret på den absolutte effektforskel har fremanezumab foreløbig **ingen dokumenteret merværdi** vedr. 50 % responderrate, idet de nedre grænser for konfidensintervallerne for begge doseringer på hhv. 0,03 %-point og 0,18 %-point er lavere end den justerede mindste klinisk relevante forskel på 2,5 %-point.

Baseret på de relative effektforskelle har begge doseringer af fremanezumab foreløbig en **merværdi af ukendt størrelse**, idet de nedre grænser akkurat er større end 1,00. Fagudvalget bemærker at konfidensintervallerne er meget brede.

På aggregeret niveau vurderer fagudvalget, at fremanezumabs værdi ikke kan kategoriseres vedr. andel af patienter, som opnår ≥ 50 % reduktion af månedlige migrænedage, idet usikkerheden omkring effektestimaterne, særligt de absolutte effektforskelle, er stor (meget lav evidenskvalitet).

For valproat

Baseret på de absolutte og relative effektforskelle er der ikke fundet tilstrækkeligt grundlag for at kategorisere fremanezumabs værdi i forhold til valproat, idet alle effektestimater er behæftet med stor usikkerhed. De foreløbige og de aggregerede værdier **kan ikke kategoriseres** (meget lav evidenskvalitet). Usikkerheden taget i betragtning bemærker fagudvalget, at punktestimaterne indikerer, at der ikke er forskel i responsraterne ved behandling med fremanezumab og valproat.

Livskvalitet (kritisk)

Eftersom der ikke findes komparative data vedrørende effektmålet livskvalitet, vurderer fagudvalget, at værdien af fremanezumab **ikke kan kategoriseres**.

Anfaldssværhedsgrad (vigtig)

Eftersom der ikke findes komparative data vedrørende effektmålet anfaldssværhedsgrad, vurderer fagudvalget, at værdien af fremanezumab **ikke kan kategoriseres**.

Bivirkninger (vigtig)

De absolutte effektforskelle mellem fremanezumab og komparatorerne er beregnet ud fra de relative forskelle ved hjælp af antagede hændelsesrater for behandling med hver af komparatorerne. Der er i beregningerne taget udgangspunkt i effekten fra studierne. De antagede hændelsesrater er fastsat til en andel på henholdsvis 12 % og 12 % af patienterne, der ophører med behandling grundet uønskede hændelser ved behandling med henholdsvis amitriptylin og valproat. Den absolutte (procentuelle) og relative effektforskel i andel patienter, der ophører med behandlingen på grund af uønskede hændelser, fremgår af tabel 2.

Grundlaget for beregning af indirekte effektestimater er effektestimaterne fra de placebokontrollerede studier. For andelen af patienter, der ophører med behandling pga. uønskede hændelser, viser den månedlige dosering af fremanezumab en RR på 1,30 [0,29; 5,74] sammenlignet med placebo. Den kvartalsvise dosering giver en RR på 0,33 [0,04; 3,20] sammenlignet med placebo. For amitriptylin var RR på 1,80 [0,94; 3,44] (1 studie), mens behandling med valproat resulterede i en RR på 1,74 [0,85; 3,54] (4 studier). De indirekte sammenligninger er baseret på disse estimater.

Baseret på de absolutte og relative effektforskelle er der ikke fundet tilstrækkeligt grundlag for at kategorisere fremanezumabs værdi for effektmålet "uønskede hændelser der medfører behandlingsophør" i forhold til amitriptylin og valproat, idet alle effektestimater er behæftet med stor usikkerhed. De foreløbige og de aggregerede værdier **kan ikke kategoriseres** (meget lav evidenskvalitet).

Kvalitativ beskrivelse af bivirkninger:

For fremanezumab er flere end 2.500 patienter (mere end 1.900 behandlingsår) blevet behandlet med fremanezumab i de kliniske studier. Af disse blev flere end 1.400 patienter eksponeret i mindst 12 måneder. Overordnet er der i de kliniske studier ikke væsentlig forskel på sikkerhedsprofilerne for fremanezumab og placebo.

De hyppigst rapporterede bivirkninger var lokale reaktioner ved injektionsstedet (smerter [24 %], induration [17 %], rødme [16 %] og kløe [2 %]) [35].

Fremanezumab er tilsyneladende forbundet med meget få bivirkninger, men fagudvalget ønsker at fremhæve, at erfaring med længerevarende behandling er begrænset, og at der dermed er usikkerhed om sjældne og mere langsigtede bivirkninger. Grundet den relativt lange halveringstid (ca. 30 dage) for fremanezumab udtrykker fagudvalget også usikkerhed om varigheden og reversibiliteten af eventuelle sjældne bivirkninger.

Vedrørende amitriptylin:

Amitriptylin har en del (meget) almindelige bivirkninger, herunder aggression, konfusion, søvnighed, tremor, svimmelhed, hovedpine, døsighed, taleforstyrrelser, opmærksomhedsforstyrrelser, smagsforstyrrelser, paræstesi, ataksi, akkommodationsforstyrrelser, mydriasis, hjertebanken, hjerterytmeforstyrrelser, ortostatisk hypotension, mundtørhed, forstoppelse, kvalme, hyperhidrose, vandladningsforstyrrelser og træthed [40]. Fagudvalget vurderer, at især bivirkninger i form af vægtøgning, mundtørhed med deraf følgende cariesdannelse samt træthed og påvirkning af korttidshukommelsen er de hyppigst forekommende bivirkninger hos migrænepatienter, der behandles med amitriptylin. Fagudvalget mener i øvrigt ikke, at konfusion er en særlig hyppig bivirkning hos migrænepatienter, der behandles med amitriptylin.

Behandling med amitriptylin er behæftet med mange bivirkninger, jævnfør beskrivelsen af bivirkningsprofilen. Disse bivirkninger kan være til stor gene for patienten, selvom de ikke nødvendigvis medfører behandlingsophør.

Vedrørende valproat:

Valproat har en del (meget) almindelige bivirkninger herunder anæmi, trombocytopeni, tremor, kramper, somnolens, hukommelsessvækkelse, hovedpine, nystagmus, svimmelhed, døvhed, opkastning, mavesmerter, hyponatriæmi, vægtøgning/vægttab, forøget/nedsat appetit, forvirring, hallucinationer og aggression [41]. Fagudvalget vurderer, at vægtøgning, tremor og træthed er de vigtigste bivirkninger, der ses hos migrænepatienter, der behandles med valproat, og for kvinder i den fødedygtig alder er især udvikling af polycystisk ovariesyndrom en særlig vigtig bivirkning.

Behandling med valproat er behæftet med mange bivirkninger, jævnfør beskrivelsen af bivirkningsprofilen. Disse bivirkninger kan være til stor gene for patienten, selvom de ikke nødvendigvis medfører behandlingsophør.

Frekvens af hovedpinedage (vigtig)

Eftersom der ikke findes komparative data vedrørende effektmålet "frekvens af hovedpinedage", vurderer fagudvalget, at værdien af fremanezumab **ikke kan kategoriseres**.

9.2.3 Evidensens kvalitet

Evidensens kvalitet for sammenligningen mellem fremanezumab og amitriptylin eller valproat er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Den meget lave evidenskvalitet skyldes hovedsageligt en række forbehold vedrørende sammenligneligheden af studiepopulationerne fra henholdsvis fremanezumabstudiet og amitriptylin- og valproatstudierne, og at der i øvrigt er tale om en indirekte sammenligning. Samlet er dette medvirkende til flere nedgraderinger på GRADE-domænet *"indirectness"*.

9.2.4 Konklusion for klinisk spørgsmål 2

1. Amitriptylin

Fagudvalget vurderer, at den samlede værdi for fremanezumab sammenlignet med amitriptylin **ikke kan kategoriseres** (meget lav evidenskvalitet). Hvad angår behandlingseffekt og bivirkninger, vurderer fagudvalget samlet set, at fremanezumab ikke er underlegent i forhold til amitriptylin og bemærker i øvrigt, at der ser ud til at være en gevinst på patientens frekvens af migrænedage og andelen af patienter, som opnår en 50 % reduktion i antallet af migrænedage. Fagudvalget finder derfor belæg for at antage, at fremanezumab har en bedre effekt og sikkerhed, men har vanskeligt ved at kvantificere det, idet en række forhold vedrørende sammenligneligheden af studiepopulationerne påvirker validiteten af de indirekte analyser.

Fagudvalget vurderer, at en yderligere reduktion af månedlige migrænedage med op til 2,4 dage (svarende til en reduktion på ca. 40-50 %-point) for fremanezumab i forhold til amitriptylin giver en merværdi af ukendt størrelse. Effektestimatets størrelsesorden vurderes at være af væsentlig betydning for patienterne.

Vedrørende effektmålene "livskvalitet", "anfaldssværhedsgrad" og "frekvens af hovedpinedage" er der ikke data fra komparatorstudierne, og en formel sammenligning er derfor ikke mulig. For effektmålet "bivirkninger" kunne værdien af fremanezumab ikke kategoriseres, idet der var brede konfidensintervaller omkring de indirekte effektestimater.

2. Valproat

Fagudvalget vurderer, at den samlede værdi for fremanezumab sammenlignet med valproat **ikke kan kategoriseres** (meget lav evidenskvalitet). Fagudvalget vurderer samlet set, at fremanezumab ikke er underlegent i forhold til valproat, hvad angår behandlingseffekt. Hvad angår bivirkninger, synes fremanezumab at have en fordel, idet behandling med valproat, foruden en række kontraindikationer, også er forbundet med flere generende bivirkninger.

Datagrundlaget for vurderingen af fremanezumab i forhold til valproat er begrænset, idet der for effektmålene "frekvens af migrænedage", "livskvalitet", "anfaldssværhedsgrad" og "frekvens af hovedpinedage" ikke foreligger data, som muliggør en sammenligning. Effektmålet "50 % responderrate" var forbundet med betydelig usikkerhed, og data viste her ingen umiddelbar fordel ved fremanezumab. Effektmålet "bivirkninger" var ligeledes forbundet med stor usikkerhed.

Den samlede indplacering i **kan ikke kategoriseres** skyldes, at værdien på alle de valgte effektmål ikke kunne kategoriseres.

9.3 Konklusion klinisk spørgsmål 3

*Hvad er den kliniske merværdi af fremanezumab til forebyggelse af migræne hos 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 indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med botulinum type A toxin?*

Fagudvalget vurderer, at fremanezumab til patienter med kronisk migræne giver en **lille merværdi** sammenlignet med botulinum type A toxin. Evidensens kvalitet vurderes at være meget lav.

Tabel 3: Kategorier og resultater

Effektmål	Måleenhed	Vigtighed	Komparator	Forskel i absolutte tal[†]		Forskel i relative tal[†]		Aggregeret værdi pr. effektmål
				Forskel (95 % CI)[*]	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Frekvens af migrænedage	Procentuel ændring af månedlige migrænedage Justeret mindste klinisk relevante forskel: 5 %-point	Kritisk	botulinum type A toxin	M -13,76 (-22,93; -4,60) Q – 10,09 (-19,26; -0,93)	M Ingen dokumenteret merværdi Q Ingen dokumenteret merværdi	-	-	Ingen dokumenteret merværdi
	≥ 50 % reduktion af månedlige migrænedage Justeret MKRF: 2,5 %-point	Vigtig	botulinum type A toxin	M 95,52 (45,12; 173,28) Q 96,00 (45,60; 174,72)	M Merværdi af ukendt størrelse Q Merværdi af ukendt størrelse	M 2,99 (1,94; 4,61) Q 3,00 (1,95; 4,64)	M Stor merværdi Q Stor merværdi	Moderat merværdi
Livskvalitet	Gennemsnitlig ændring fra baseline på HIT-6 Justeret MKRF: -1,15 point (CM)	Kritisk	botulinum type A toxin	M -1,50 (-3,15; 0,15) Q -0,60 (-2,26; 1,06)	M Ingen dokumenteret merværdi Q Ingen dokumenteret merværdi	-	-	Ingen dokumenteret merværdi
Anfalds-sværhedsgrad	Procentuel ændring af antal dage med anfaldsbehandling pr. måned Justeret MKRF: 5 %-point	Vigtig	botulinum type A toxin	M -30,59 (-42,20; -18,97) Q -27,06 (-38,67; -15,44)	M Merværdi af ukendt størrelse Q Merværdi af ukendt størrelse	-	-	Merværdi af ukendt størrelse
Bivirkninger	Andel patienter som oplever uønskede hændelser, der medfører behandlingsophør Justeret MKRF: 5 %-point	Vigtig	botulinum type A toxin	M -2,27 (-3,52; 4,28) Q -3,41 (-3,75; 0,45)	M Kan ikke kategoriseres Q Ingen dokumenteret merværdi	M 0,40 (0,07; 2,13) Q 0,10 (0,01; 1,12)	M Kan ikke kategoriseres Q Kan ikke kategoriseres	Merværdi kan ikke kategoriseres
Frekvens af hovedpinedage	Procentuel ændring af månedlige hovedpinedage (non-migræne) Justeret MKRF: 5 %-point	Vigtig	botulinum type A toxin	*Intet estimat*	M Kan ikke kategoriseres Q Kan ikke kategoriseres	-	-	Merværdi kan ikke kategoriseres
Samlet kategori for lægemidlets værdi (kvalitet af den samlede evidens)			botulinum type A toxin	**Lille merværdi (meget lav evidenskvalitet)**				

*Hvis ikke andet er angivet, er alle absolutte forskelle angivet i %-point.

[†] Estimater for den månedlige dosering er angivet ved M. Estimater for den kvartalsvise dosering er angivet ved Q

9.3.1 Gennemgang af studier

Til besvarelse af dette spørgsmål blev der identificeret 3 studier: et studie med fremanezumab og 2 studier med botulinum type A toxin.

Population
Populationskarakteristika og de væsentligste studiekarakteristika med betydning for vurderingen fremgår af bilag 3 og appendiks 1.

Fagudvalget vurderer, at baselinekarakteristika på studiepopulation i de inkluderede studier stemmer godt overens med den danske migrænepopulation. En del patienter har såkaldt "medicinoverforbrugshovedpine" (migræne/hovedpine pga. overforbrug af smertestillende lægemidler), hvor behandlingen først og fremmest består af udtrapning af deres medicin fremfor yderligere tillæg af forebyggende behandling. Fagudvalget bemærker, at alle inkluderede studier i dette kliniske spørgsmål har inkluderet patienter med medicinoverforbrug. Jævnfør retningslinjerne fra International Headache Society (IHS) er det acceptabelt at inkludere disse patienter i kliniske studier, som undersøger effekten af et migræneforebyggende lægemiddel. Dette er dog under forudsætning af, at patienterne er stratificerede ift. deres medicinforbrug [42]. Alle inkluderede studier i dette kliniske spørgsmål har stratificeret patienterne ift. deres medicinforbrug, og dermed anser fagudvalget det rimeligt at anvende studierne til besvarelse af dette kliniske spørgsmål.

De inkluderede patienter i fremanezumabstudiet har alle oplevet behandlingssvigt på tidligere migræneforebyggende behandlinger. For botulinum type A toxin-studierne fremgår antallet af tidligere behandlingssvigt ikke eksplicit. I studiet indgår en andel af behandlingsnaive patienter (ca. 1/3). For andelen af patienter, som tidligere har anvendt forebyggende behandling, vurderer fagudvalget, at det er rimeligt at antage, at disse patienter har oplevet behandlingssvigt på flere tidligere behandlinger, idet man i dansk klinisk praksis aldrig vil tilbyde patienter behandling med botulinum type A toxin, hvis ikke de har testet og oplevet behandlingssvigt på mindre invasive behandlinger først. Da placeboresponset kan variere med antallet af tidligere behandlingssvigt og formentlig er lavere hos patienter, som tidligere har oplevet flere behandlingssvigt, kan effektestimaterne fra botulinum type A toxin-studierne muligvis være underestimeret.

Fagudvalget bemærker i øvrigt, at opfølgningstiden i botulinum type A toxin-studierne er 24 uger mod 12 uger i fremanezumabstudierne. I forlængelsesfasestudiet med fremanezumab hos patienter med både episodisk og kronisk migræne tyder data på, at effekten af fremanezumab kan akkumulere over tid [43]. Dette betyder, at de effektestimater, som for fremanezumab ligger til grund for vurderingen, muligvis kan være underestimeret, idet effekten efter 24 ugers behandling muligvis er større.

9.3.2 Resultater og vurdering

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

Frekvens af migrænedage – procentuel reduktion af månedlige migrænedage (kritisk)

Grundlaget for beregningerne er effektestimaterne fra de placebokontrollerede studier. Den månedlige dosering af fremanezumab gav en ændring af månedlige migrænedage på -3,5 dage [-4,19; -2,78] sammenlignet med placebo i FOCUS-studiet. Den kvartalsvise dosering på 675 mg gav, i samme studie, en ændring på -3,1 dage [-3,84; -2,42] sammenlignet med placebo. Behandling med botulinum type A toxin medførte en ændring på -2,0 dage [-2,71; -1,29], baseret på de to PREEMPT-studier. De indirekte sammenligninger er baseret på disse estimater. Behandling med fremanezumab reducerer frekvensen af

månedlige migrænedage med gennemsnitligt 1,5 dag (månedlig dosering) og 1,1 dag (kvartalsvis dosering) yderligere i forhold til botulinum type A toxin.

De øvre grænser i konfidensintervallerne ligger på hhv. -4,60 %-point og -0,93 %-point, hvilket foreløbigt indplacerer begge doseringer i "ingen dokumenteret merværdi", da den justerede mindste klinisk relevante forskel er -5 %-point. På tværs af de to doseringer vurderer fagudvalget, at fremanezumab har **ingen dokumenteret merværdi** vedr. reduktion af månedlige migrænedage sammenlignet med botulinum type A toxin (meget lav evidenskvalitet)

Frekvens af migrænedage – andel af patientpopulationen, som opnår ≥ 50 reduktion af månedlige migrænedage (vigtig)

De absolutte effektforskelle er beregnet ud fra de relative effektestimater fra de indirekte sammenligninger. De absolutte effektforskelle er angivet som en procentuel forskel og blev beregnet ved hjælp af antagede hændelsesrater. Den antagede hændelsesrate er beregnet på baggrund af effekterne fra studierne. Her ses, at en andel på 48 % af patientpopulationen opnår mindst 50 % reduktion af månedlige migrænedage ved behandling med botulinum type A toxin. De absolutte og relative effektforskelle fremgår af tabel 3.

Grundlaget for beregningerne er effektestimaterne fra de placebokontrollerede studier, hvor den månedlige dosering af fremanezumab gav en relativ øgning i 50 % responderrate på RR 3,97 [2,62; 6,01] sammenlignet med placebo. Den kvartalsvise dosering gav en relativ øgning på RR 3,99 [2,63; 6,04] sammenlignet med placebo. Behandling med botulinum type A toxin medførte en øgning på RR 1,33 [1,17; 1,50] sammenlignet med placebo. De indirekte sammenligninger er baseret på disse estimater.

Baseret på den absolutte effektforskel har fremanezumab foreløbig en **merværdi af ukendt størrelse** vedr. andel af patienter, som opnår ≥ 50 % reduktion af månedlige migrænedage. Fagudvalget bemærker, at der her er tale om urealistisk høje absolutte forskelle mellem fremanezumab og botulinum type A toxin. Dette skyldes sandsynligvis forskelle i placeboresponset, da det varierer med antallet af tidligere behandlingssvigt og er observeret lavere hos patienter, som tidligere har oplevet flere behandlingssvigt. Det sande estimat er derfor muligvis lavere. Ser man isoleret på fremanezumabs effekt i FOCUS-studiet er 50 % responderrate på 34 %, mens responderraten for botulinum type A toxin i PREEMPT ligger på 48 %. De respektive responsrater for placebogrupperne er henholdsvis 9 % og 36 %.

Baseret på den relative effektforskel har fremanezumab foreløbig en **stor merværdi** vedr. andel af patienter, som opnår ≥ 50 % reduktion af månedlige migrænedage.

På aggregeret niveau vurderer fagudvalget, at fremanezumab har en **moderat merværdi** vedr. andel af patienter, som opnår ≥ 50 % reduktion af månedlige migrænedage (meget lav evidenskvalitet), idet både de absolutte og relative effektforskelle viser en betydelig fordel ved fremanezumab. De relative effektforskelle kategoriserede til en stor merværdi, men usikkerhed om den sande effektstørrelse gør, at fagudvalget fastsætter den aggregerede kategori til moderat.

Livskvalitet (kritisk)

Den månedlige dosering af fremanezumab giver i FOCUS-studiet en ændring på -3,90 point [-5,40; -2,40], mens den kvartalsvise dosering giver en ændring på -3,00 [-4,51; -1,49] sammenlignet med placebo. I PREEMPT-studierne giver behandling med botulinum type A toxin en ændring på -2,40 point [-3,09; -1,71]. Som angivet i tabel 3 svarer dette til en yderligere reduktion ved behandling med fremanezumab på 0,6-1,5 point sammenlignet med botulinum type A toxin.

De øvre grænser i konfidensintervallerne ligger på hhv. 0,15 point og 1,06 point, hvilket foreløbig indplacerer begge doseringer i "ingen dokumenteret merværdi", da den justerede mindste klinisk relevante forskel er -1,15 point. På tværs af de to doseringer vurderer fagudvalget, at fremanezumab har **ingen dokumenteret merværdi** vedr. livskvalitet sammenlignet med botulinum type A toxin (lav evidenskvalitet)

Anfaldssværhedsgrad (vigtig)

De absolutte effektforskelle er omregnet til en procentuel ændring ved hjælp af antagede hændelsesrater for komparator. Hændelsesraten er bestemt til 8,5 dage med anfaldsbehandling for botulinum type A toxin. Den beregnede procentuelle ændring fremgår af tabel 3.

Grundlaget for beregning af indirekte effektestimater er effektestimaterne fra de placebokontrollerede studier. Den månedlige dosering af fremanezumab giver i FOCUS-studiet en ændring på -3,40 dage [-4,03; -2,69], mens den kvartalsvise dosering giver en ændring på -3,10 dage [-3,75; -2,41] sammenlignet med placebo. I PREEMPT-studierne giver behandling med botulinum type A toxin en ændring på -0,80 dag [-1,53; -0,07]. Dette svarer til en yderligere reduktion i antal dage med anfaldsbehandling pr. måned ved behandling med fremanezumab på 2,3-2,6 dage sammenlignet med botulinum type A toxin.

Baseret på de absolutte effektforskelle har fremanezumab foreløbig en merværdi af ukendt størrelse vedr. anfaldssværhedsgrad. På tværs af de to doseringer vurderer fagudvalget, at fremanezumab har en **merværdi af ukendt størrelse** vedr. anfaldssværhedsgrad (meget lav evidenskvalitet), idet der ses en betydelig reduktion i antal dage med anfaldsbehandling pr. måned ved behandling med fremanezumab sammenlignet med botulinum type A toxin.

Bivirkninger (vigtig)

De absolutte effektforskelle mellem fremanezumab og komparatorerne er beregnet ud fra de relative forskelle ved hjælp af antagede hændelsesrater for behandling med hver af komparatorerne. Der er i beregningerne taget udgangspunkt i effekten fra studierne. Den antagede hændelsesrate er fastsat til en andel på 3,8 % af patienterne, der ophører med behandling grundet uønskede hændelser ved behandling med botulinum type A toxin. Den absolutte (procentuelle) og relative effektforskel i andel patienter, der ophører med behandlingen på grund af uønskede hændelser, fremgår af tabel 3.

Grundlaget for beregning af indirekte effektestimater er effektestimaterne fra de placebokontrollerede studier. For andelen af patienter, der ophører med behandling pga. uønskede hændelser, viser den månedlige dosering af fremanezumab en RR på 1,30 [0,29; 5,74] sammenlignet med placebo. Den kvartalsvise dosering giver en RR på 0,33 [0,04; 3,20] sammenlignet med placebo. For botulinum type A toxin var RR på 3,27 [1,49; 7,18] (2 studier). De indirekte sammenligninger er baseret på disse estimater.

Baseret på de absolutte effektforskelle er det, grundet stor usikkerhed, ikke muligt at kategorisere værdien af den månedlige dosering af fremanezumab i forhold til botulinum type A toxin for uønskede hændelser, der medfører behandlingsophør. Den kvartalsvise dosering kategoriserer foreløbigt til ingen dokumenteret merværdi.

Baseret på de relative effektforskelle er det ikke muligt at kategorisere fremanezumabs værdi vedr. uønskede hændelser, der medfører behandlingsophør, idet konfidensintervallerne er brede.

På aggregeret niveau vurderer fagudvalget, at værdien af fremanezumab **ikke kan kategoriseres** vedr. uønskede hændelser, der medfører behandlingsophør (lav evidenskvalitet), idet effektestimaterne er forbundet med stor usikkerhed.

Kvalitativ beskrivelse af bivirkninger:

For fremanezumab er flere end 2.500 patienter (mere end 1.900 behandlingsår) blevet behandlet med fremanezumab i de kliniske studier. Af disse blev flere end 1.400 patienter eksponeret i mindst 12 måneder. Overordnet er der i de kliniske studier ikke væsentlig forskel på sikkerhedsprofilerne for fremanezumab og placebo.

De hyppigst rapporterede bivirkninger var lokale reaktioner ved injektionsstedet (smerter [24 %], induration [17 %], rødme [16 %] og kløe [2 %]) [35].

Fremanezumab er tilsyneladende forbundet med meget få bivirkninger, men fagudvalget ønsker at fremhæve, at erfaring med længerevarende behandling er begrænset, og at der dermed er usikkerhed om sjældne og mere langsigtede bivirkninger. Grundet den relativt lange halveringstid (ca. 30 dage) for fremanezumab udtrykker fagudvalget også usikkerhed om varigheden og reversibiliteten af eventuelle sjældne bivirkninger.

Vedrørende botulinum type A toxin

Botulinum type A toxin er et relativt velkendt lægemiddel i dansk klinisk praksis (blev godkendt til behandling af kronisk migræne af Lægemiddelstyrelsen den 29. februar 2012 og er anvendt på hovedpineklinikker i Danmark siden 2012). I kliniske studier af patienter med kronisk migræne var incidensen af bivirkninger 26 % efter første behandling, hvorefter incidensen faldt til 11 % efter anden behandling. I reglen optræder uønskede hændelser inden for de første få dage efter injektionen, og selv om de generelt er kortvarige, kan nogle vare ved i flere måneder og i sjældne tilfælde endnu længere. For patienter med kronisk migræne, som behandles med botulinum type A toxin, er følgende bivirkninger almindelige: hovedpine, migræne, facialisparese, ptose, pruritus, udslæt, nakkesmerter, myalgi, muskuloskeletale smerter, muskuloskelatal stivhed, muskelspasmer, muskelstramhed, muskelsvaghed og smerter på injektionsstedet [44]. Fagudvalget vurderer, at især muskelsvaghed med påvirkning af tygge- og synkefunktionen samt ptose er de bivirkninger som patienter med kronisk migræne oplever i forbindelse med behandling med botulinum type A toxin, og som ofte er til særlig gene for patienterne.

Frekvens af hovedpinedage (vigtig)

Eftersom der ikke findes komparative data vedrørende effektmålet frekvens af hovedpinedage, vurderer fagudvalget, at værdien af fremanezumab **ikke kan kategoriseres**.

9.3.3 Evidensens kvalitet

Evidensens kvalitet for sammenligningen af forebyggende behandling til patienter med kronisk migræne med fremanezumab og botulinum type A toxin er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 1.

Den meget lave evidenskvalitet skyldes hovedsageligt en række forbehold vedrørende sammenligneligheden af studiepopulationerne fra henholdsvis fremanezumabstudiet og botulinum type A toxin-studierne, og at der i øvrigt er tale om en indirekte sammenligning. Samlet er dette medvirkende til flere nedgraderinger på GRADE-domænet *"indirectness"*.

9.3.4 Konklusion for klinisk spørgsmål 3

Fagudvalget vurderer, at fremanezumab til forebyggelse af migræne giver en **lille merværdi** for patienter med **kronisk migræne** sammenlignet med behandling med botulinum type A toxin (meget lav

evidenskvalitet). Vurderingen baseres på, at behandling med fremanezumab medførte en øgning af "50 % responderraten", der overgik den fastsatte mindste klinisk relevante forskel betydeligt. Den indirekte analyse gav et urealistisk højt estimat, og der er derfor tvivl om den reelle effektstørrelse. Effektmålet "anfaldssværhedsgrad" medførte en reduktion på op til ca. 2,5 dage i antallet af dage med behov for anfaldsmedicin i forhold til botulinum type A toxin, hvilket viste en merværdi af ukendt størrelse.

For de kritiske effektmål "frekvens af migrænedage" og "livskvalitet" ses ingen dokumenteret merværdi af fremanezumab i forhold til botulinum type A toxin, men her bemærker fagudvalget en tendens til fordel for fremanezumab, hvad angår frekvens af migrænedage. Værdien for de to resterende effektmål "bivirkninger" og "frekvens af hovedpinedage" kunne ikke kategoriseres. Samlet set vurderer fagudvalget, med baggrund i den moderate merværdi for effektmålet "50 % responderrate" og en merværdi af ukendt størrelse for effektmålet "anfaldssværhedsgrad", at fremanezumab har en **lille merværdi** i forhold til botulinum type A toxin. Fagudvalget har i den samlede kategorisering lagt vægt på en mere gunstig bivirkningsprofil og en enklere administration af fremanezumab, hvilket, fagudvalget vurderer, vil medføre færre gener for patienten.

10 Andre overvejelser

Fagudvalget vil gøre opmærksom på, at halveringstiden for fremanezumab på ca. 30 dage er betydeligt længere, end tilfældet er for de fleste andre migræneforebyggende lægemidler. Da der normalt anbefales pausering af migræneforebyggende lægemidler hver 6.-12. måned for at vurdere, om der fortsat findes behov for behandling, skal den behandlende neurolog således være opmærksom på behovet for en længere pause ved behandling med fremanezumab pga. den længere halveringstid.

Fagudvalget vil endnu engang understrege, at migrænepatienter med medicinoverbrug af akut anfaldsbehandling først skal være ude af deres medicinoverforbrug, inden de kan komme i betragtning til forebyggende migrænebehandling. Dette skyldes, at medicinoverforbrug af akut anfaldsmedicin i sig selv kan medføre forværring af migræne/hovedpine.

Fagudvalget anbefaler, at ordinationen af fremanezumab begrænses til specialiserede kliniske enheder med særlig erfaring i behandling af hovedpine. Dette skyldes, at fremanezumab er et nyt lægemiddel, hvor langtidsbivirkninger ikke er kendte. Ved at ordinationen af fremanezumab begrænses til specialiserede kliniske enheder med særlig erfaring i behandling af hovedpine, sikrer man, at der sker en mere systematisk registrering af eventuelle langtidsbivirkninger.

Fagudvalget bemærker, at der, ud fra sammenligningen mellem erenumab og fremanezumab, ikke er dokumenteret forskelle i effekt eller sikkerhed (se bilag 5). Fagudvalget vurderer, at effekten af erenumab og fremanezumab i forhold til de valgte komparatorer er ens. Det er derfor rimeligt at betragte de to lægemidler som klinisk ligestillede.

11 Fagudvalgets vurdering af samlet værdi og samlet evidensniveau

Fagudvalget vurderer samlet, at værdien af fremanezumab til forebyggelse af migræne hos patienter, der har mindst fire migrænedage pr. måned **ikke kan kategoriseres** sammenlignet med gruppen af antihypertensiva (**propranolol, candesartancilexetil og lisinopril**). Fagudvalget vurderer, at fremanezumab samlet set ikke har dårligere effekt eller sikkerhedsprofil end gruppen af antihypertensiva. Evidensens kvalitet vurderes at være lav til meget lav. I sammenligningen med topiramat mener fagudvalget, at fremanezumab har **en lille merværdi**. Fagudvalget har særligt vægtet den moderate merværdi, hvad angår bivirkninger og en merværdi

på antallet af dage med anfaldsbehandling, hvor der ses en reduktion ved behandling med fremanezumab. Evidensens kvalitet vurderes her at være lav.

Fagudvalget vurderer, at værdien af fremanezumab sammenlignet med **amitriptylin og valproat** til forebyggelse af migræne hos patienter, der har mindst fire migrænedage pr. måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger, **ikke kan kategoriseres**. Evidensens kvalitet vurderes at være meget lav. Fagudvalget vurderer samlet, på tværs af de to komparatorer, at fremanezumab ikke er dårligere, hvad angår effekt. Hvad angår bivirkninger, synes fremanezumab at have en fordel, idet både amitriptylin og valproat ofte er forbundet med generende bivirkninger.

Fagudvalget vurderer, at fremanezumab til forebyggelse af migræne hos 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, giver en **lille merværdi** sammenlignet med botulinum type A toxin. Evidensens kvalitet vurderes at være meget lav. Denne del af migrænepopulationen er kendetegnet ved at være svært ramt af migræne. Fremanezumab medførte en relevant reduktion i antallet af dage med behov for anfaldsbehandling samt en øgning af "50 % responderraten" i forhold til botulinum type A toxin. Fagudvalget har i den samlede kategorisering for sammenligningen med botulinum type A toxin lagt vægt på en mere gunstig bivirkningsprofil og en enklere administration af fremanezumab, hvilket, fagudvalget vurderer, vil medføre færre gener for patienten.

12 Rådets vurdering af samlet værdi og samlet evidensniveau

Fremanezumab til forebyggelse af migræne hos patienter, der har mindst fire migrænedage pr. måned (klinisk spørgsmål 1):

- Medicinrådet finder, at den samlede værdi af fremanezumab sammenlignet med gruppen af antihypertensiva (propranolol, candesartancilexetil og lisinopril) **ikke kan kategoriseres**. Evidensens kvalitet vurderes at være lav til meget lav. Fremanezumab vurderes samlet set ikke at have dårligere effekt eller sikkerhedsprofil end gruppen af antihypertensiva.
- Medicinrådet vurderer, at fremanezumab giver en **lille merværdi** sammenlignet med topiramat. Evidensens kvalitet vurderes at være lav.

Fremanezumab til forebyggelse af migræne hos patienter, der har mindst fire migrænedage pr. måned og som har oplevet behandlingssvigt på mindst to migræneforebyggende lægemidler (et antihypertensivum og et antiepileptikum) (klinisk spørgsmål 2):

- Medicinrådet finder, at den samlede værdi af fremanezumab sammenlignet med amitriptylin og valproat **ikke kan kategoriseres**. Evidensens kvalitet vurderes at være meget lav. Fremanezumab vurderes samlet set ikke at have dårligere effekt eller sikkerhedsprofil end de to komparatorer.

Fremanezumab hos patienter med **kronisk migræne**, der har oplevet behandlingssvigt på mindst to migræneforebyggende lægemidler (et antihypertensivum og et antiepileptikum) (klinisk spørgsmål 3):

- Medicinrådet vurderer, at fremanezumab til patienter med kronisk migræne giver en **lille merværdi** sammenlignet med botulinum type A toxin. Evidensens kvalitet vurderes at være meget lav.

13 Relation til eksisterende behandlingsvejledning

Der eksisterer ingen behandlingsvejledning vedrørende forebyggende behandling af migræne. Indtil der foreligger en behandlingsvejledning på området, finder fagudvalget det rimeligt at betragte erenumab og fremanezumab som klinisk ligestillede. Dette er begrundet med, at de to lægemidler har tilsvarende virkningsmekanisme, effekt og sikkerhed.

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende migræne

Formand	**Indstillet af**
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Medlemmer	**Udpeget af**
Ana Maria Nan Afdelingslæge	Region Nordjylland
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16 Versionslog

Version	Dato	Ændring
1.0	23. oktober 2019	Godkendt af Medicinrådet.

17 Bilag 1: GRADE-evidensprofiler

17.1 Cochrane Risk of Bias

Studiets risiko for bias er vurderet ved brug af tjeklisten Cochrane Risk of Bias tool (Cochrane handbook version 5.1 del 2.8, se http://handbook-5-1.cochrane.org/

1. Propranololstudier

Studie: Diener et al., 1996

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	214 patients were randomized in 3:2:3 ratio to cyclandelate, placebo or propranolol.
Allocation concealment	**Unclear**	As the details of the allocation concealment are not revealed in the article, the risk of bias remains unclear.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes (rate of responders, mean "migraine duration" in hours)	**Moderate**	As part of the outcomes were reported by patients (e.g. a weekly diary with migraine attacks, impairment of working ability, intensity of headache etc.), and subsequently transcribed by a (blinded) physician, the risk of bias is here judged as moderate.
Objective outcomes (e.g. some AEs)	**Moderate**	For the secondary end-points, adverse events and intake of acute migraine medication, only posthoc analyses are presented. Even though all patients were stratified based on the intake of analgesics/antimigraine drugs during a defined number of weeks in the course of the trial, the posthoc analyses present a moderate risk of bias by definition.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	As part of the outcomes were reported by patients (e.g. a weekly diary with migraine attacks, impairment of working ability, intensity of headache etc.), and subsequently transcribed by a (blinded) physician, the risk of bias is here judged as moderate.
Objective outcomes	**Moderate**	For the secondary end-points, adverse events and intake of acute migraine medication, only posthoc analyses are presented. Even though all patients were stratified based on the intake of analgesics/antimigraine drugs during a defined number of weeks in the course of the trial, the posthoc analyses present a moderate risk of bias by definition.

Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Moderate**	21/235 of the screened patients did not qualify for randomization. 81 patients (37,9 %) were treated with cyclandelate, 55 (25,7 %) with placebo and 78 (66,4 %) with propranolol. 36/214 patients (16,8 %) dropped out after randomization. 40 patients had to be excluded from the ITT analysis for various reasons, and 174 patients remained for the PP analysis. Due to these relative high percentages of discontinuations, the risk of bias is judged as moderate.
Reporting bias: selective reporting outcome data	**Unclear**	As the article neither includes the study protocol nor links to it, the risk of bias regarding the selective reporting is unclear.
Other bias	**Low**	No other concerns.
Overall bias	**Moderate**	The overall risk of bias is judged moderate due to the performance and detection bias, and due to the high percentage of missing patients in the analyses (attrition bias).

Studie: Diener et al., 2004

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Unclear**	Not described in sufficient detail.
Allocation concealment	**Unclear**	Not described in sufficient detail.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Not described in sufficient detail.
Objective outcomes	**Unclear**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Not described in sufficient detail.
Objective outcomes	**Unclear**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	A total of 575 subjects were randomised; of these, 568 contributed to efficacy data after randomisation and were included in the intent-to-treat cohort for the efficacy Analyses (7 patients excluded as they did not provide post-baseline efficacy data); 570 contributed to the safety analyses.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting.
Other bias	**Unclear**	Industry sponsored.

Overall bias	**Moderate**	As randomization and blinding are not sufficiently explained, the overall risk of bias is judged moderate.

Studie: Stovner et al., 2014

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	72 adult patients were randomized in a triple-blind (to participants, clinicians and statistician), double cross-over study through three 12-week treatment periods on either candesartan 16 mg, propranolol slow-release 160 mg, or placebo. Patients were recruited either from patients referred to the clinic, or among those who contacted the study nurse after advertisements in newspapers or on the Internet, or after information on a national TV channel. The risk of bias is judged as low.
Allocation concealment	**Low**	Participants fulfilling criteria for randomization were consecutively given a randomization number (1–72) assigning them to one of the six treatment sequences according to a computer-generated list, premade by the company producing the drugs, but unknown to participants, clinicians and statistician. Randomization numbers were pre-printed on study medication labels, and on three sealed envelopes containing information about the medication in each period for each participant. Hence, in case of serious AEs (SAEs), it was possible to unblind a single period. These envelopes were kept in a limited-access area. PLA tablets and capsules were identical to those with active medication and packaged in identical bottles. After completion of the study, the data file, together with the unopened envelopes containing randomization codes, were handed over to personnel at the Unit for Applied Clinical Research at the Faculty of Medicine who opened the codes and returned the file with each treatment type having a code (A, B or C). A predetermined statistical protocol had been written for the analysis of the primary and secondary efficacy variables, and the statistician (TS) performed analysis of this file without knowing the actual type of treatment. This was revealed first after tables with efficacy data had been created (triple-blind study). A few data entry errors were detected during the blinded analysis, and these were corrected before the final unblinding. Since the allocation concealment is described in detail and does not seem to introduce bias into the study, the risk of bias is judged as low.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		

Patient-reported outcomes (rate of responders, mean "migraine duration" in hours)	**Moderate**	During the whole study, patients kept a headache diary recording relevant attack variables, as well as AEs or other health-related condition. Moreover, they were asked about the diaries at telephone calls. Due to the possibly subjective nature of the outcomes, the risk of bias is considered moderate.
Objective outcomes	**Low**	No concerns.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	During the whole study, patients kept a headache diary recording relevant attack variables, as well as AEs or other health-related condition. Moreover, they were asked about them at telephone calls. Due to the possibly subjective nature of the outcomes, the risk of bias is considered moderate.
Objective outcomes	**Low**	No concerns.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Moderate**	Of the 72 randomized patients, one woman was later excluded before unblinding because it was detected that she did not fulfil inclusion criteria. In addition, 10 patients dropped out of the study - five on CAN, three on PRO, and two on PLA. Three women dropped out because of pregnancy (two on CAN and one on PRO), and one (on CAN) because she wanted to become pregnant a short time after randomization. 55/72 (76 %) patients completed both CAN and PRO periods of the cross-over study. The relatively low percentage poses a moderate risk of bias due to the incompleteness of the data.
Reporting bias: selective reporting outcome data.	**Low**	All outcome data are reported according the clinicaltrials.gov (NCT00884663).
Other bias	**Moderate**	There are known disadvantages of the crossover design, why the risk of bias is judged moderate.
Overall bias	**Moderate**	Moderate concerns due to the subjective nature of PROs, missing data and crossover study design in Other bias.

2. Candesartancilextilstudier

Studie: Stovner et al., 2014

Allerede gennemgået under (propranololstudier)

Studie: Tronvik et al., 2003

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Randomized, double-blind, placebo-controlled crossover study of 60 patients.
Allocation concealment	**Low**	After a 4-week single-blind placebo run-in period to verify the frequency of attacks, the participants were randomized by a computer-generated randomization scheme to receive either active medication (candesartan cilexetil, one 16-mg tablet daily) or placebo. The tablets (active and placebo) that were used in the study had the same size, weight, taste and appearance to ensure blindness.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	Participants were keeping diaries recording headaches in detail. These are assumed to have moderate risk of bias due to the possible subjectivity in assessment.
Objective outcomes	**Low**	Matching placebos were used to ensure blindness.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	The first part of the study was single-blind, and no details are provided for the second part.
Objective outcomes	**Moderate**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Moderate**	75 participants were screened, and 60 were randomized. Out of those, 46 (76 %) were included in the per-protocol analysis. When patients failed to enter data in their diaries, missing data were imputed from the mean values of that measure for the remaining days of the treatment period. Due to the relatively high percentage of missing data (more than 20 %), and the method for imputation of missing data is the risk of bias judged as moderate.
Reporting bias: selective reporting outcome data.	**Low**	Even though the full study protocol was not linked in the article, the outcome measures prespecified on the beginning match those in the result section. Therefore, there is no concern of selective reporting.
Other bias	**Moderate**	Due to the known disadvantages of the crossover design, the risk of other bias is judged as moderate.

Overall bias	**Moderate**	There are concerns regarding the performance and detection bias, missing data and their handling, and the study design (crossover study). Overall is the risk of bias judged as moderate.

3. Topiramatstudier

Studie: Brandes et al., 2004

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Patients were randomized to 1 of 4 treatment groups: placebo or topiramate at 50 mg/d, 100 mg/d, or 200 mg/d.
Allocation concealment	**Low**	An interactive voice response system was used to assign randomization numbers to patients.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded. Treatment assignments were not revealed to study patients, investigators, clinical staff, or study monitors until all patients had completed therapy and the database had been finalized.
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded. Treatment assignments were not revealed to study patients, investigators, clinical staff, or study monitors until all patients had completed therapy and the database had been finalized.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Efficacy analyses were conducted on the intent-to-treat population, which was defined as randomized patients who had at least 1 postbaseline efficacy assessment.
Reporting bias: selective reporting outcome data.	**Low**	All expected outcomes reported.
Other bias	**Unclear**	Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Diener et al., 2004

Allerede gennemgået under (propranololstudier).

Studie: Diener et al., 2007

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Medications were randomized in blocks of four, two topiramate and two placebos.
Allocation concealment	**Low**	Computer randomization was used.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded. Topiramate and placebo, identical tablets produced by the manufacturer.
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded. Topiramate and placebo, identical tablets produced by the manufacturer.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Efficacy analyses were performed on the intent-to-treat (ITT) population, which consisted of all randomized patients who received at least one postbaseline efficacy evaluation Safety analyses performed on same population as efficacy analysis.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting.
Other bias	**Unclear**	1. Each study center received at least two blocks: one for subjects without medication overuse and one for subjects with medication overuse. The subgroup of patients who were overusing acute medication (n = 46) consisted of 23 patients receiving topiramate and 23 receiving placebos. There were no significant differences in demographics and baseline characteristics between the topiramate-treated and placebo-treated patients. Therefore, no bias concerns regarding medication overuse. 2. Patients taking any migraine prophylactic drug were excluded unless the drug had been used for at least 3 months (at a stable dose for at least 1 month) prior to trial entry and was continued throughout the trial. Ten patients were on a stable dose of a medicine that might have had a concomitant prophylactic effect. Three patients in the topiramate arm were on a b-blocker and five in the placebo arm, while one in each arm took a calcium channel blocker. As the number of patients is well-balanced between the two arms, the risk of bias is judged low. 3. The study was sponsored and the data analysed by the sponsor.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Lipton et al., 2011

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Eligible patients were randomized 1:1 in double-blind fashion to daily treatment with either topiramate or matching placebo.
Allocation concealment	**Low**	Subjects were assigned to either of the two treatment groups based on a computer-generated predetermined randomization schedule.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	The double-blind study medication tablets were identical in appearance and packaged in identically appearing bottles.
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	The double-blind study medication tablets were identical in appearance and packaged in identically appearing bottles.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	The intent-to-treat (ITT) analysis set comprised randomized subjects who received at least one dose of study drug and had at least one post-dose efficacy assessment. The efficacy-evaluable (EE) analysis set comprised ITT subjects who completed at least 28 days of the double-blind phase. The safety analysis set included randomized subjects who took at least one dose of study drug and had at least one post-dose safety assessment.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting,
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Mei et al., 2004

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	In this double-blind study 135 subjects were selected and 115 of them were randomized to treatment with topiramate (TPM) or placebo.
Allocation concealment	**Low**	Patients were allocated to groups in balanced blocks of 2 using a computer-generated random number scheme.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	Patients noted the number, intensity, duration of the crisis, signs or symptoms attributable to side effects of the drug and quantity of symptomatic drugs prescribed, in a diary. Due to the possible

		subjectivity of reporting, the risk of bias regarding the PROs is moderate.
Objective outcomes	**Low**	No concerns.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Patients noted the number, intensity, duration of the crisis, signs or symptoms attributable to side effects of the drug and quantity of symptomatic drugs prescribed, in a diary. As the details of blinding are not described in the article, the risk of detection bias remains unclear.
Objective outcomes	**Low**	No concerns.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**High**	20/57 subjects treated with placebo and 23/58 treated with topiramate withdrew from the study. This means over 37 overall dropout rate, which is judged as having high risk of attrition bias.
Reporting bias: selective reporting outcome data.	**Unclear**	Even though the outcomes specified in the article provide results for these, the study protocol is not available and therefore it is impossible to check those prespecified in the study itself. Therefore, the risk of bias regarding the selective reporting is unclear.
Other bias	**Low**	No other concerns.
Overall bias	**Moderate**	Overall bias is judged as moderate, primarily due to the high discontinuation rate in the study, the moderate risk of performance bias and unclear detection and reporting bias.

Studie: Silberstein et al., 2004

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Patients were randomized (permutation blocks of 4 stratified by center) to placebo or topiramate, 50, 100, or 200 mg/d.
Allocation concealment	**Unclear**	Not described in sufficient detail.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Patients and clinicians were blinded to study medication with preprinted medication code labels. Placebo was identical in appearance and packaging to active drug.
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Patients and clinicians were blinded to study medication with preprinted medication code labels. Placebo was identical in appearance and packaging to active drug.

Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Efficacy analyses were conducted on the intent-to-treat population, which was defined as those randomized patients who had at least 1 postbaseline efficacy assessment.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting.
Other bias	**Unclear**	Industry supported.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Silberstein et al., 2006

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Subjects who met the entrance criteria were randomized in a 2:1 ratio to receive TPM 200 mg/d or Placebo
Allocation concealment	**Unclear**	Not described in sufficient detail.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded. Nothing suggest blinding was unveiled during study.
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded. The investigator, who was blinded to treatment assignment, evaluated the relationship of each AE to study treatment.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Statistical analyses were conducted in the intent-to-treat (ITT) population, which included all randomized subjects who received ≥1 dose of study drug and provided ≥1 postbaseline efficacy evaluation.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting.
Other bias	**Unclear**	Industry supported
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Silberstein et al., 2007 inkl. Silberstein et al., 2009

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Patients were randomized 1:1 to either topiramate 100 mg/day or placebo into the randomized, placebo-controlled, parallel-group, multicenter double-blind study. An initial dose of topiramate 25 mg/day (or placebo) was titrated upward in weekly increments of 25 mg/day to a maximum of 100 mg/day (or to the maximum tolerated dose).
Allocation concealment	**Low**	At visit 1, subjects were assigned a 5-digit number that was retained for the duration of the study. Computer-generated random medication code numbers were prepared and preprinted on the study medication labels. Eligible subjects were randomized and assigned sequentially 1:1 to either topiramate or placebo. The investigators entered the qualified patient's identifier in numerical order. The randomization was performed using permuted blocks.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	The therapeutic response for PGIC and SGIC (Physician's/Subject's Global Impression of Change) was graded by use of a 7-point scale, from 1 = very much improved to 7 = very much worse. Since the grades were not described in detail (which could cause subjectivity in grading), there is a moderate risk of bias. A similar issue could be happening in the measuring of change in the average severity of migraine symptoms: it is evaluated using a 4-point scale from 0 = none to 3 = severe, where similar subjectivity, and therefore risk of bias, could be present.
Objective outcomes	**Low**	Safety measures included assessment of vital signs, physical and brief neurologic examinations, and clinical laboratory parameters. Spontaneously reported adverse events were collected and recorded at each visit. No concern of bias.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	The therapeutic response for PGIC and SGIC (Physician's/Subject's Global Impression of Change) was graded by use of a 7-point scale, from 1 = very much improved to 7 = very much worse.

		Since the grades were not described in detail (which could cause subjectivity in grading), there is a moderate risk of bias. A similar issue could be happening in the measuring of change in the average severity of migraine symptoms: it is evaluated using a 4-point scale from 0 = none to 3 = severe, where similar subjectivity, and therefore risk of bias, could be present.
Objective outcomes	**Low**	Safety measures included assessment of vital signs, physical and brief neurologic examinations, and clinical laboratory parameters. Spontaneously reported adverse events were collected and recorded at each visit. No concern of bias.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**High**	The intent-to-treat population included 306 (topiramate, n = 153; placebo, n = 153) of 328 randomized subjects who provided at least 1 efficacy assessment. 92 subjects in the topiramate group (55.8 %) and 90 subjects of the placebo group (55.2 %) completed the trial. Due to the almost half of all patients not completing the trial, the attrition bias is judged as high.
Reporting bias: selective reporting outcome data.	**Low**	No concerns. Reported based on clinicaltrials.gov (NCT00210912/CR004684).
Other bias	**Low**	No other concerns.
Overall bias	**Moderate**	The overall risk of bias is judged as moderate, due to the high attrition bias (high percentage of discontinuation) and moderate risk of bias regarding the PROs.

Studie: Storey et al., 2001

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Patients were randomly assigned on a 1:1 ratio to receive topiramate or placebo.
Allocation concealment	**Unclear**	Not described in sufficient detail.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded. Matching placebo was used
Objective outcomes	**Low**	Ibid.

Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded. Matching placebo was used
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Statistical analysis based on all patients who were randomly assigned to receive topiramate or placebo and for whom double-blind efficacy data were available.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting.
Other bias	**Unclear**	Concomitant migraine prevention was also allowed if the patient had been on a stable dose for 3 months prior to enrollment. The following concomitant migraine preventive medications were used: propranolol, amitriptyline, nortriptyline, divaloprex, fluoxetine, sertraline, verapamil, imipramine, and cyproheptadine. Two patients in the topiramate group were on more than one concomitant migraine preventive medication. Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

4. Lisinoprilstudie

Studie: Schrader et al., 2001

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Double-blind, placebo controlled, crossover study. The 60 patients who fulfilled the inclusion criteria were allocated to treatment according to a computer-generated randomization procedure with 15 consecutive balanced blocks of four patients (two active, two placebo).
Allocation concealment	**Low**	Participants entered a four-week placebo run-in period to verify the frequency of attacks. They were instructed to take one tablet daily and told that they would continue in the study only if the headache diary in this period showed two to six migraine attacks. All tablets for this study were supplied as round, white tablets containing either 10 mg lisinopril or placebo. Active and inactive tablets were identical in appearance and were packed in identical bottles that were labelled with the patient number and appropriate period of the study. This ensured that both the patient and the investigator were unaware of the treatment that the participant was taking during the double-blind treatment periods; during the run-in and wash out periods the investigator was aware that placebo treatment was being taken.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	The diaries kept by patients as well as the SF-36 questionnaire pose due to its subjective nature a moderate risk of bias.

Objective outcomes	**Low**	Matching placebos were used.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	During the run-in and wash out periods the investigator was aware that placebo treatment was being taken.
Objective outcomes	**Moderate**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Moderate**	Of the 60 patients who were randomized, three withdrew from the study because of adverse events, one declined to continue, and one had an inadequate response on placebo. Eight patients did not comply with treatment but kept a diary for the whole study period. The 47 remaining participants (38 women, 9 men) provided complete data for final evaluation of efficacy. The risk of bias is judged as moderate due to almost 22 of missing/incomplete data.
Reporting bias: selective reporting outcome data.	**Low**	Even though the original study protocol is not available, the reported outcome data matches the outcomes prespecified on the beginning of the article. Therefore, there risk of bias is judged as low.
Other bias	**Moderate**	There are known disadvantages of the crossover design, however, the authors did have these in mind, but they find no period effect and no carry over effect biasing the results. The risk of bias is therefore not judged high (as it could be in some cases of crossover study design), but only moderate.
Overall bias	**Moderate**	The overall risk of bias is judged as moderate, primarily due to the performance and detection bias, incompleteness of the data and the design of the study (crossover).

5. Amitriptylinstudier

Studie: Concalves et al., 2016

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Patients were randomized 1:1:1 to one of the three groups: placebo, melatonin 3 mg or amitriptyline 25 mg. The study was conducted in a double-blind, multi-center, parallel-group, placebo-controlled design. Randomization was performed centrally with the use of randomization lists with randomly permuted block lengths stratified according to center.
Allocation concealment	**Low**	Patients, treating clinicians and the outcome assessor were blinded. Study medications were also blinded and delivered to the investigators by the pharmacy which prepared the three study medications equally in design, shape, and color.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		

Patient-reported outcomes	**Moderate**	Patients recorded information about migraine or non-migraine headache occurrence a paper-based diary. Trained neurologists in headache abstracted the information, which was double-checked by another investigator and uploaded into a spreadsheet. Due to the possible subjectivity, the PROs are judged as having moderate risk of bias.
Objective outcomes	**Low**	Matching placebos were used.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	Patients recorded information about migraine or non-migraine headache occurrence a paper-based diary. Trained neurologists in headache abstracted the information, which was double-checked by another investigator and uploaded into a spreadsheet. Due to the possible subjectivity, the PROs are judged as having moderate risk of bias.
Objective outcomes	**Moderate**	Patients were monitored by adverse events and vital signs to determine tolerability and safety. An adverse event was defined as any medical occurrence reported by a patient or noted by a clinician during the study, regardless of its suspected cause. It was recorded if it was considered to be related to study medication. Due to the system of recording AEs, the risk of bias is judged as moderate.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Moderate**	Missing data were analyzed by three methods. The first method extended the calendar earlier into the treatment period until 28 days of non-missing data contributed to the count of migraine headache days. The second method proportionately adjusted the number of migraine headache days (multiplied by 28 and divided by the number of non-missing days). The third method treated all missing days as non-migraine headache days (used for the primary end point). After a 4-week baseline phase, 196 participants were randomized to placebo, amitriptyline 25 mg or melatonin 3 mg, and 178 took a study medication and were followed for 12 weeks. Between 69 and 75 of patients completed the study in the treatment groups. Due to the handling with missing data and quite high percentage of patients not completing the trial, the risk of bias is judged moderate.
Reporting bias: selective reporting outcome data.	**Low**	No concern. The outcome effects prespecified in the protocol on clinicaltrials.gov (NCT01357031) matches the outcomes provided in the article.
Other bias	**Low**	No other concerns.
Overall bias	**Moderate**	Overall risk of bias is judged as moderate due to the missing data, handling with it and performance and detection bias.

Studie: Couch et al., 2010

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	This study was a double-blind, placebo-controlled study comparing amitriptyline in doses of 25-100 mg/day, depending on the tolerance of the patient, with a matched placebo. Patients were randomized after receiving placebo for 4 weeks (blinded) to either amitriptyline or placebo therapy on a 1:1 basis in blocks of 4 subjects.
Allocation concealment	**Low**	Each investigator received study medication in blocks of 4 subjects and had to dispense all of one block before moving to the next block. Investigators were blind as to the medication dispensed.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Moderate**	The patients were given a data form to fill out for each headache experienced. This was based on a subjective opinion, and therefore could cause bias.
Objective outcomes	**Low**	Medications were supplied by Merck, Sharp, and Dohme Research Laboratories as amitriptyline 25 mg or placebo in identically appearing tablets.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	No information on how the patient diaries were analyzed/blinded, which poses an unclear risk of bias.
Objective outcomes	**Low**	Medications were supplied by Merck, Sharp, and Dohme Research Laboratories as amitriptyline 25 mg or placebo in identically appearing tablets.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**High**	There were 391 subjects who entered the baseline phase of this study, of whom 194 (21 male) were randomized to receive amitriptyline and 197 (17 male) to receive placebo. Overall, 93/194 (48 %) of amitriptyline subjects and 106/197 (54 %) of placebo subjects discontinued the study before 20 weeks. Among those who dropped out, the most common reason given was unwillingness to continue in a clinical research project, which included 34 amitriptyline and 36 placebo subjects. The risk of bias is judged as high due to the high dropout rate, which could bias the results.
Reporting bias: selective reporting outcome data.	**Low**	Even though the original study protocol is not available, the outcome effects reported in the Results section match those predefined at the beginning of the article.
Other bias	**Unclear**	The study was described more than 30 years after its termination. Randomization of medications was carried out by Merck, Sharp, and Dohme Research Laboratories.
Overall bias	**High**	The overall bias is judged as high. This is mostly due to the high percentage of missing data, moderate risk of bias regarding the reporting of PROs, unclear risk regarding the detection bias and other bias – i.e. the length of time between the study realization and writing of the article.

6. Valproatstudier

Studie: Freitag et al., 2002

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Subjects were randomly assigned in a 1:1 ratio at each center to receive either extended-release divalproex sodium or matching placebo tablets.
Allocation concealment	**Low**	Randomization schedule assigned a unique series of randomized subject numbers to each center, was computer generated. Randomization was accomplished by instructing investigators to assign the subject numbers in ascending numerical sequence as subjects qualified for randomization.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes:	**Low**	To maintain the blind, matching placebos were used.
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Nothing suggest blinding was unveiled during study.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	The efficacy data set was an intent-to-treat data set that included all data from randomized subjects who received study drug and provided at least one headache evaluation during the experimental phase. All randomized subjects who received study drug were evaluated for safety.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Jensen et al., 194

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Unclear**	Not described in sufficient detail.
Allocation concealment	**Unclear**	Not described in sufficient detail.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	To maintain the blind, matching placebos were used.
Objective outcomes	**Low**	Ibid.

Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Nothing suggest blinding was unveiled during study.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	Not described in sufficient detail. Patients who dropped out of the trial after randomization were excluded from the statistical analysis.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Moderate**	As method used for randomization was unclear, and the statistical method used was not sufficiently explained, the overall risk of bias is judged moderate.

Studie: Klapper et al., 1997

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Subjects were randomly assigned in a 1:1:1:1 ratio to receive placebo or either 500 mg, 1000 mg or 1500 mg divalproex.
Allocation concealment	**Unclear**	Not described in sufficient detail.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Not described in sufficient detail.
Objective outcomes	**Unclear**	Not described in sufficient detail.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Unclear**	Not described in sufficient detail.
Objective outcomes	**Unclear**	Not described in sufficient detail.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Efficacy analyses were based upon the intent-to-treat dataset of all randomized patients providing headache data during the experimental phase. Five of the 176 randomized patients (two placebo and three in the 1000 mg – group) failed to provide any headache data during the experimental phase, therefore, 171 patients were included in the intent-to-treat efficacy analysis.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Moderate**	As method used for randomization was unclear, and the blinding not sufficiently explained, the overall risk of bias is judged moderate.

Studie: Mathew et al., 2017

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Patients were randomized to groups receiving divalproex or placebo in a 2:1 ratio.
Allocation concealment	**Unclear**	Not described in sufficient detail.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	To maintain the blind, matching placebos were used.
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Nothing suggest blinding was unveiled during study.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Unclear**	Not described in sufficient detail. Analyses were performed using all data from randomized patients.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Low**	No other concern regarding potential risk of bias.
Overall bias	**Moderate**	As method used for randomization was unclear, and the statistical method used was not sufficiently explained, the overall risk of bias is judged moderate.

7. Botulinum type A toxin-studier

Studie: Aurora et al., 2010

Bias	Risk of bias	Elaboration
Selection bias		
Random sequence generation	**Low**	Computer-generated randomization sequence. Eligible patients were randomized in blinded fashion (1:1) to on a botulinum toxin A treatment or placebo.
Allocation concealment	**Low**	Upon randomization subject number was linked to next randomization number grouped within strata for that site, site was then notified of medication kit assigned to that number.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded.

Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	All efficacy analyses used the intent-to-treat population, which included all randomized patients. Safety analysis was performed on all randomized patients who received at least one dose of study medication at day 0. Withdrawals balanced across groups and adjusted LOCF method used.
Reporting bias: selective reporting outcome data.	**Low**	All expected outcomes reported.
Other bias	**Unclear**	Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Diener et al., 2010

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Computer-generated randomization sequence. Qualified subjects were randomized (1:1) in a double-blind fashion to on a botulinum toxin A or placebo.
Allocation concealment	**Low**	Upon randomization subject number was linked to next randomization number grouped within strata for that site, site was then notified of medication kit assigned to that number.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Double-blinded.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Withdrawals balanced across groups and adjusted LOCF method used.
Reporting bias: selective reporting outcome data.	**Low**	All expected outcomes reported.
Other bias	**Unclear**	Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

8. Fremanezumabstudier

Studie: Dodick et al. HALO EM

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Randomization was performed using electronic interactive response technology.
Allocation concealment	**Unclear**	Not described in sufficient detail.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Patients, investigators, the sponsor, and designated personnel were blinded to treatment assignments.
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	Patients, investigators, the sponsor, and designated personnel were blinded to treatment assignments.
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Efficacy analyses were conducted in the full analysis set, which included all randomized patients (intention-to-treat population) who received at least 1 dose of study drug and had at least 10 days of postbaseline efficacy assessments for the primary end point. Analyses of adverse events were performed in all randomized patients who received at least 1 dose of study drug. For withdrawals or patients with missing e-diary days and 10 or more days of data for a month, the monthly number of days of efficacy variables was prorated to 28 days for that month. A multiple imputation method was also conducted as a sensitivity analysis
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Unclear**	Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Bigal et al., EM

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Randomisation (1:1:1) was done by block via an electronic interactive web response system

Allocation concealment	**Low**	Patients were masked to treatment allocation; they received the same number of injections, which were identical in packaging regardless of treatment group from masked study coordinators.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	double-blind
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	double-blind
Objective outcomes	**Low**	Ibid
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	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. Missing entries in electronic diaries were imputed
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Unclear**	Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Silberstein et al. HALO CM

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Randomization was performed by means of electronic interactive-response technology,
Allocation concealment	**Low**	Patients, investigators, the sponsor, and trial staff were unaware of the trial-group assignments.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	double-blind
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	double-blind
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	Efficacy analyses were conducted in the modified intention-to-treat population, which included all randomly assigned patients who received at least one dose of a trial regimen and had at least 10 days of postbaseline efficacy assessments regarding the primary end point. Safety analyses

		included all randomly assigned patients who received at least one dose of a trial regimen. Missing data regarding headache days were imputed.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Unclear**	Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Bigal et al., CM

Bias	**Risk of bias**	**Elaboration**
Selection bias		
Random sequence generation	**Low**	Randomisation (1:1:1) was done by block via an electronic interactive web response system
Allocation concealment	**Low**	Patients were masked to treatment allocation; they received the same number of injections, which were identical in packaging regardless of treatment group from masked study coordinators.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	double-blind
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	double-blind
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	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. Missing entries in electronic diaries were imputed
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Unclear**	Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

Studie: Ferrari et al., FOCUS EM/CM

Bias	**Risk of bias**	**Elaboration**
Selection bias		

Random sequence generation	**Low**	Participants were randomly assigned (1:1:1) to quarterly fremanezumab, monthly fremanezumab, or placebo by electronic interactive response technology.
Allocation concealment	**Low**	The sponsor, investigators, study staff, and participants were masked to treatment assignment during the double-blind period.
Performance bias: blinding of participants and personnel. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	double-blind
Objective outcomes	**Low**	Ibid.
Detection bias: blinding of outcome assessment. Assessment made for class of outcomes.		
Patient-reported outcomes	**Low**	double-blind
Objective outcomes	**Low**	Ibid.
Attrition bias: incomplete outcome data. Assessment made for class of outcomes.	**Low**	The intention-to-treat analysis set comprised all randomly assigned participants. The safety analysis set comprised all randomly assigned participants who received at least one dose of study drug.
Reporting bias: selective reporting outcome data.	**Low**	Nothing suggests reporting bias due to selective outcome reporting
Other bias	**Unclear**	Industry sponsored.
Overall bias	**Low**	Overall risk of bias judged low.

17.2 GRADE-evaluering af evidenskvaliteten

Klinisk spørgsmål 1

Question: Fremanezumab monthly compared to placebo for patients with migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
4	randomised trials	not serious	not serious	not serious	not serious	none	844	854	-	mean **1.78 days fewer** (2.25 fewer to 1.30 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
50 % responderrate												
2	randomised trials	not serious	not serious	not serious	not serious	none	182/372 (49 %)	109/390 (28 %)	**RR 1.75** (1.45 to 2.12)	-	⨁⨁⨁⨁ HIGH	IMPORTANT
Livskvalitet (HIT-6)												
3	randomised trials	not serious	not serious	not serious	not serious	none	757	765	-	SMD **0.27 point lower** (0.37 lower to 0.17 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Anfaldsbehandling												
4	randomised trials	not serious	not serious	not serious	not serious	none	844	854		mean **1.58 days fewer** (1.93 fewer to 1.22 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Bivirkninger der medfører behandlingsophør												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	12/669 (1.8 %)	13/668 (1.9 %)	**RR 0.92** (0.42 to 2.00)	-	⨁⨁⨁◯ MODERATE	IMPORTANT
Månedlige hovedpinedage												
2	randomised trials	not serious	not serious	not serious	not serious	none	462	460	-	mean **2.06 days fewer** (2.67 fewer to 1.45 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Brede konfidensintervaller.

Question: Fremanezumab quarterly compared to placebo for patients with migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
2	randomised trials	not serious	not serious	not serious	not serious	none	663	661	-	mean 1.**43 days fewer** (1.86 fewer to 0.99 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
50 % responderrate												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	127/288 (44 %)	81/290 (28 %)	**RR 1.59** (1.27 to 1.99)	**-**	⨁⨁⨁◯ MODERATE	IMPORTANT
Livskvalitet (HIT-6)												
2	randomised trials	not serious	not serious	not serious	not serious	none	663	661	-	SMD **0.20 point lower** (0.31 lower to 0.09 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Anfaldsbehandling												
2	randomised trials	not serious	not serious	not serious	not serious	none	663	661		mean **1.77 days fewer** (2.75 fewer to 0.80 fewer)	⨁⨁⨁⨁ HIGH	IMPORTANT
Bivirkninger der medfører behandlingsophør												
2	randomised trials	not serious	not serious	serious [b]	not serious	none	10/667 (1.5 %)	13/668 (1.9 %)	**RR 0.77** (0.34 to 1.76)	-	⨁⨁⨁◯ MODERATE	IMPORTANT
Månedlige hovedpinedage												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	375	371	**-**	mean 1.**8 days fewer** (2.46 fewer to 1.15 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Da den estimerede effekt er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

b. Brede konfidensintervaller.

Question: Propranolol compared to placebo for patients with migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
2	randomised trials	not serious	not serious	not serious	not serious	none	210	207	-	mean **0.76 days fewer** (1.35 fewer to 0.16 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
50 % responderrate												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	24/60 (40.0%)	14/60 (23.3%)	**RR 1.71** (0.99 to 2.89)	-	⨁⨁⨁◯ MODERATE	IMPORTANT
Anfaldsbehandling												
1	randomised trials	not serious	serious [a]	not serious	not serious	none	143	143	-	mean **0.8 days fewer** (1.37 fewer to 0.23 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Bivirkninger der medfører behandlingsophør												
2	randomised trials	not serious	not serious	not serious	not serious	none	35/222 (15.8%)	16/201 (8.0%)	**RR 2.07** (1.19 to 3.62)	-	⨁⨁⨁⨁ HIGH	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Da den estimerede effekt af propranolol er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens

Question: Candesartan compared to placebo for patients with migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Candesartan	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
2	randomised trials	serious [a]	not serious	not serious	serious[b]	none	113	117	-	mean **0.74 days fewer** (1.80 fewer to 0.33 more)	⨁⨁◯◯ LOW	CRITICAL
50 % responderrate												
2	randomised trials	serious [a]	serious [c]	not serious	serious[b]	none	47/113 (41.6 %)	16/117 (13.7 %)	**RR 4.16** (0.59 to 29.26)	-	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Cross-over studies. Handling of missing data.

b. Effektestimatets konfidensinterval indeholder 0 og det er dermed uklart om den sande værdi favoriserer interventionen eller komparator.

c. Da den estimerede effekt af candesartancilexetil er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

c. Der er betydelig forskel på de to effektestimater, og dermed er det uklart hvor den sande værdi ligger.

Question: Topiramate compared to placebo for patients with migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
6	randomised trials	not serious	not serious	not serious	not serious	none	1217	723	-	mean **1.20 days fewer** (1.73 fewer to 0.67 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
50 % responderrate												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	66/185 (35.7%)	47/180 (26.1%)	**RR 2.65** (0.29 to 24.03)	-	⊕⊕⊕◯ MODERATE	IMPORTANT
Anfaldsbehandling												
6	randomised trials	not serious	not serious	not serious	not serious	none	1217	723	-	mean **0.77 days fewer** (1.09 fewer to 0.45 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Bivirkninger der medfører behandlingsophør												
9	randomised trials	not serious	not serious	not serious	not serious	none	341/1589 (21.5%)	67/909 (7.4%)	**RR 2.60** (1.76 to 3.83)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
Månedlige hovedpinedage												
1	randomised trials	not serious	serious [b]	not serious	serious[c]	none	153	153	-	mean **1.10 days fewer** (2.35 fewer to 0.15 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Brede konfidensintervaller.

b. Da den estimerede effekt er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

c. Effektestimatets konfidensinterval indeholder 0 og det er dermed uklart om den sande værdi favoriserer interventionen eller komparator.

Question: Lisinopril compared to placebo for patients with migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lisinopril	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
1	randomised trials	serious [a]	serious [b]	not serious	not serious	none	47	47	-	mean **1.4 days fewer** (2.61 fewer to 0.19 fewer)	⨁⨁◯◯ LOW	CRITICAL
50 % responderrate												
1	randomised trials	serious [a]	serious [b]	not serious	not serious	none	47	47	**RR 4.67** (1.43 to 15.18)	-	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Performance and detection bias, incompleteness of the data and the design of the study (crossover).

b. Da den estimerede effekt af lisinopril er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

Klinisk spørgsmål 2

Question: Fremanezumab monthly compared to placebo for patients with episodic and chronic migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	283	279	-	mean **3.5 days fewer** (4.19 fewer to 2.78 fewer)	⨁⨁◯◯ LOW	CRITICAL
50 % responderrate												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	97/283 (34 %)	24/278 (9 %)	**RR 3.97** (2.62 to 6.01)	**-**	⨁⨁◯◯ LOW	IMPORTANT
Livskvalitet (HIT-6)												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	283	279	-	mean **3.9 point lower** (5.40 lower to 2.40 lower)	⨁⨁◯◯ LOW	CRITICAL
Anfaldsbehandling												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	283	279		mean **3.4 days fewer** (4.03 fewer to 2.69 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Bivirkninger der medfører behandlingsophør												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	4/285 (1 %)	3/277 (1 %)	**RR 1.30** (0.29 to 5.74)	-	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Da den estimerede effekt er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

b. Patienter med medicinoverforbrug kunne godt blive inkluderet i studiet.

Question: Fremanezumab quarterly compared to placebo for patients with episodic and chronic migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	276	279	-	mean **3.1 days fewer** (3.84 fewer to 2.42 fewer)	⨁⨁◯◯ LOW	CRITICAL
50 % responderrate												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	95/276 (34 %)	24/278 (9 %)	**RR 3.99** (2.63 to 6.04)	-	⨁⨁◯◯ LOW	IMPORTANT
Livskvalitet (HIT-6)												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	276	279	-	mean **3.0 point lower** (3.75 lower to 2.41 lower)	⨁⨁◯◯ LOW	CRITICAL
Anfaldsbehandling												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	276	279		mean **3.1 days fewer** (3.75 fewer to 2.41 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Bivirkninger der medfører behandlingsophør												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	1/276 (0 %)	3/277 (1 %)	**RR 0.33** (0.04 to 3.20)	-	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Da den estimerede effekt er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

b. Patienter med medicinoverforbrug kunne godt blive inkluderet i studiet.

Question: Amitriptylin compared to placebo for patients with migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amitriptylin	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
1	randomised trials	serious [a]	serious [b]	not serious	not serious	none	59	59	-	mean **1.10 days fewer** (2.46 fewer to 0.26 more)	⨁⨁◯◯ LOW	CRITICAL
50 % responderrate												
1	randomised trials	serious [a]	serious [b]	not serious	not serious	none	23/59 (39.0 %)	12/59 (20.3 %)	**RR 1.92** (1.05 to 3.48)		⨁⨁◯◯ LOW	IMPORTANT
Bivirkninger der medfører behandlingsophør												
1	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	23/194 (12 %)	13/197 (7 %)	**RR 1.80** (0.94 to 3.44)	-	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Missing data, and performance and detection bias.

b. Da den estimerede effekt af amitriptylin er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

c. Brede konfidensintervaller.

Question: Valproat compared to placebo for patients with migraine and previous treatment failure

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproat	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
50 % responderrate												
1	randomised trials	serious [a]	serious[b]	not serious	not serious	none	69	36	**RR 3.44** (1.47 to 8.06)	-	⨁⨁◯◯ LOW	IMPORTANT
Bivirkninger der medfører behandlingsophør												
4	randomised trials	serious [a]	not serious	not serious	serious [c]	none	48/358 (13.4 %)	16/230 (7.0 %)	**RR 1.74** (0.85 to 3.54)	-	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Method used for randomization was unclear, and the statistical method used was not sufficiently explained.

b. Da den estimerede effekt er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

c. Brede konfidensintervaller.

Klinisk spørgsmål 3

Question: Fremanezumab monthly compared to placebo for patients with chronic migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	283	279	-	mean **3.5 days fewer** (4.19 fewer to 2.78 fewer)	⨁⨁◯◯ LOW	CRITICAL
50 % responderrate												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	97/283 (34 %)	24/278 (9 %)	**RR 3.97** (2.62 to 6.01)	**-**	⨁⨁◯◯ LOW	IMPORTANT
Livskvalitet (HIT-6)												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	283	279	-	mean **3.9 point lower** (5.40 lower to 2.40 lower)	⨁⨁◯◯ LOW	CRITICAL
Anfaldsbehandling												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	283	279		mean **3.4 days fewer** (4.03 fewer to 2.69 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Bivirkninger der medfører behandlingsophør												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	4/285 (1 %)	3/277 (1 %)	**RR 1.30** (0.29 to 5.74)	-	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Da den estimerede effekt er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

b. Der indgik også patienter med episodisk migræne i studiet. Patienter med medicinoverforbrug kunne godt blive inkluderet i studiet.

Question: Fremanezumab quarterly compared to placebo for patients with chronic migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fremanezumab	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	276	279	-	mean **3.1 days fewer** (3.84 fewer to 2.42 fewer)	⨁⨁◯◯ LOW	CRITICAL
50 % responderrate												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	95/276 (34 %)	24/278 (9 %)	**RR 3.99** (2.63 to 6.04)	-	⨁⨁◯◯ LOW	IMPORTANT
Livskvalitet (HIT-6)												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	276	279	-	mean **3.0 point lower** (3.75 lower to 2.41 lower)	⨁⨁◯◯ LOW	CRITICAL
Anfaldsbehandling												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	276	279		mean **3.1 days fewer** (3.75 fewer to 2.41 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Bivirkninger der medfører behandlingsophør												
1	randomised trials	not serious	serious [a]	serious [b]	not serious	none	1/276 (0 %)	3/277 (1 %)	**RR 0.33** (0.04 to 3.20)	-	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Da den estimerede effekt er baseret på et enkelt RCT-studie, vil der være usikkerhed i forhold til den reelle størrelsesorden på effekt. Derfor nedgraderes evidensens kvalitet et niveau pga. inkonsistens.

b. Der indgik også patienter med episodisk migræne i studiet. Patienter med medicinoverforbrug kunne godt blive inkluderet i studiet.

Question: Botulinum type A toxin compared to placebo for patients with chronic migraine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Botox	Placebo	Relative (95 % CI)	Absolute (95 % CI)		
Månedlige migrænedage												
2	randomised trials	not serious	not serious	serious [a]	not serious	none	688	696	-	mean **2 days fewer** (2.67 fewer to 1.27 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
50 % responderrate												
2	randomised trials	not serious	not serious	serious [a]	not serious	none	332/688 (48.3 %)	253/696 (36.4 %)	**RR 1.33** (1.17 to 1.50)	-	⨁⨁⨁◯ MODERATE	IMPORTANT
Livskvalitet (HIT-6)												
2	randomised trials	not serious	not serious	not serious	not serious	none	688	696	-	mean **2.4 point lower** (3.11 lower to 1.72 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Anfaldsbehandling												
2	randomised trials	not serious	not serious	serious [a]	not serious	none	688	696		mean **0.77 days fewer** (2.67 fewer to 1.45 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Bivirkninger der medfører behandlingsophør												
2	randomised trials	not serious	not serious	not serious	not serious	none	26/687 (3.8 %)	8/692 (1.2 %)	**RR 3.27** (1.49 to 7.18)	-	⨁⨁⨁⨁ HIGH	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Patienter med medicinoverforbrug kunne godt blive inkluderet i studiet.

18 Bilag 2: oversigt over "lægemiddelrekommandationer til forebyggelse af migræne" i Danmark

	Dansk Hovedpine Selskab (2010)	Dansk Neurologisk Selskab (2016)	SST (2015)	Pro.medicin.dk
1.Valg	1. Betablokkere (metoprolol 50-200 mg eller propranolol 40-240 mg) - Antiepileptika (topiramat 25-100(200) mg eller valproat 500-1800 mg) - Flunarizin 5-10 mg	- Betablokkere (metoprolol 50-200 mg, propranolol 40-240 mg) - Candesartan 16-32 mg - Antiepileptika (topiramat 25-100(200) mg, valproat 500-1.800 mg) - Flunarizin 5-10 mg	1. Betablokkere (metoprolol 50-200 mg, propranolol 40-240 mg) - Candesartan 16 mg - Antiepileptika (topiramat 25-100(200) mg, valproat 500-1.800 mg) - Flunarazin 5-10 mg	- Betablokkere (metoprolol 50-200 mg, propranolol 40-240 mg)
2.Valg	- Amitriptylin 10-100 mg - Naproxen 500 x2 - Bisoprolol 5-10 mg	* Henvises til Dansk Hovedpine Selskab		- Candesartan 16 (24-32 mg)
3.Valg	- Candesaratn 16 mg - Lisinopril 20 mg - Pizotifen 1,5-3 mg - 6 andre "off-label"	* Henvises til Dansk Hovedpine Selskab		- Antiepileptika (topiramat 25-100(200) mg, valproat 500-1.800 mg) - Flunarizin 5-10 mg
Andre		- Botox (ved kronisk migræne)	- Amitriptylin - Naproxen - Lisinopril - Riboflavin - Coenzym Q10 - Pizotifen	

	IRF (2009)
Rekommanderet	Candesartan 16 mg Lisinopril 20 mg Metoprolol 150 mg Propranolol 160 mg
Rekommanderet med forbehold eller i særlige tilfælde	Flunarizin 10 mg Naproxen 1.000 mg Pizotifen 1,5 mg Topiramat 100 mg Valproat 100 mg
Ikke rekommanderet	Clonidin

SST: "Der er endnu ikke demonstreret en effekt af at kombinere flere former for profylaktiske midler, og der er ikke sikker evidens for, at en type profylaktisk migrænemedicin virker bedre ved en bestemt migræne-subtype. Der er heller ikke sikker evidens for, at et præparat er mere effektivt end andre, så valg må bero på de forskellige stoffers bivirkningsprofil, komorbiditet og kontraindikationer". (7)

19 Bilag 3: Udvalgte studie- og baselinekarakteristika fra de inkluderede studier

Studie	Behandlingsarme‡, n	Studie-population†	Inklusionskriterier for migræne	Migrænefrekvens~		Studievarighed*, uger	Klinisk spørgsmål
				MMD/MMA	MHD		
Fremanezumab							
Bigal et al., 2015	fremanezumab 225 mg q1m., n = 95 fremanezumab 675 mg q3m., n = 96 placebo, n = 104	EM	≥ 8 MHD 8-14 MMD	11,5 ± 1,9 11,3 ± 2,2 11,5 ± 2,2	12,6 ± 3,1 12,5 ± 2,7 12,4 ± 2,3	12 uger	1
Dodick et al., 2018	fremanezumab 225 mg q1m., n = 290 fremanezumab 675 mg q3m., n = 291 placebo, n = 294	EM	≥ 8 og ≤ 14 MHD ≥ 4 MMD	8,9 ± 2,6 9,3 ± 2,7 9,1 ± 2,7	-	12 uger	1
Bigal et al., 2015	fremanezumab 675/225 mg q1m., n = 88 fremanezumab 900 mg q1m., n = 87 placebo, n = 89	CM	CM efter ICHD-III beta version, 2013	17,2 ± 5,4 16,4 ± 5,3 16,8 ± 5,0	16,5 ± 6,7 15,9 ± 6,5 16 ,5 ± 6,3	12 uger	1
Silberstein et al., 2017	fremanezumab 675/225 mg q1m., n = 379 fremanezumab 675 mg q3m., n = 376 placebo, n = 375	CM	≥ 15 MHD ≥ 8 MMD	16,0 ± 5,2 16,2 ± 4,9 16,4 ± 5,2	20,3 ± 4,3 20,4 ± 3,9 20,3 ± 4,2	12 uger	1
Ferrari et al., 2019	fremanezumab 225 mg q1m., n = 283 fremanezumab 675 mg q3m., n = 276 placebo, n = 279	EM CM (60 %)	EM: 6-14 MHD, heraf min. 4 MMD CM: ≥ 15 MHD heraf ≥ 8 MMD	14,1 ± 5,6 14,1 ± 5,6 14,3 ± 6,1	-	12 uger	2, 3
Propranolol							
Diener et al., 1996	propranolol 160 mg qd., n = 78 placebo, n = 55	EM	2-10 MMA	MMA 4 ± 2 MMA 4 ± 2	-	Titrering: 2 uger 12 uger	1
Diener et al., 2004	propranolol 160 mg qd., n = 143 placebo, n = 143	EM	3-12 MMA < 15 MHD	6,1 ± 2,6 6,1 ± 2,7	-	Titrering: 8 uger 18 uger	1
Stovner et al., 2014	propranolol 160 mg qd., n = 61 candesartan 16 mg qd., n = 59 placebo, n = 61	EM CM (2 %)	≥ 2 MMA	4,8 ± 3,4	-	12 uger	1
Candesartan							
Tronvik et al., 2003	candesartan 16 mg qd., n = 59 placebo, n = 58	EM	2-6 MMA	5,7 ± 2,9	8,4 ± 3,9	12 uger	1

Studie	Behandlingsarme‡, n	Studie-population†	Inklusionskriterier for migræne	Migrænefrekvens~		Studievarighed*, uger	Klinisk spørgsmål
				MMD/MMA	MHD		
Stovner et al., 2014	propranolol 160 mg qd., n = 61 candesartan 16 mg qd., n = 59 placebo, n = 61	EM CM (2 %)	≥ 2 MMA	4,8 ± 3,4	-	12 uger	1
Lisinopril							
Schrader et al., 2001	lisinopril 20 mg qd., n = 47 placebo, n = 47	EM	2-6 MMA	6,8 ± 3,0	9,4 ± 3,0	12 uger	1
Topiramat							
Storey et al., 2001	topiramat 200 mg qd., n = 19 placebo, n = 21	EM	≥ 2 MMA	5,1 ± 1,6 4,4 ± 2,0	-	Titrering: 8 uger 8 uger	1
Diener et al., 2004	topiramat 200 mg qd., n = 143 topiramat 100 mg qd., n = 139 placebo, n = 143	EM	3-12 MMA < 15 MHD	6,2 ± 2,8 5,8 ± 2,2 6,1 ± 2,7	-	Titrering: 8 uger 18 uger	1
Mei et al., 2004	topiramat 100 mg qd., n = 58 placebo, n = 57	EM	2-6 MMA	5,3 ± 1,3 5,8 ± 1,0	-	Titrering: 4 uger 12 uger	1
Brandes et al., 2004	topiramat 200 mg qd., n = 117 topiramat 100 mg qd., n = 120 topiramat 50 mg qd., n = 117 placebo, n = 114	EM	3-12 MMA < 15 MHD	6,1 ± 2,5 6,9 ± 3,0 6,4 ± 2,9 6,7 ± 2,8	-	Titrering: 8 uger 18 uger	1
Silberstein et al., 2004	topiramat 200 mg qd., n = 112 topiramat 100 mg qd., n = 125 topiramat 50 mg qd., n = 117 placebo, n = 115	EM	3-12 MMA < 15 MHD	6,6 ± 3,1 6,4 ± 2,7 6,4 ± 2,7 6,4 ± 2,6	-	Titrering: 8 uger 18 uger	1
Silberstein et al., 2006	topiramat 200 mg qd., n = 138 placebo, n = 73	EM	3-8 MMA ≤ 15 MHD	MMA 4,8 ± 1,5 MMA 5,2 ± 1,7	-	Titrering: 8 uger 12 uger	1
Silberstein et al., 2007	topiramat 100 mg qd., n = 153 placebo, n = 153	CM	≥ 15 MHD ≥ 8 MMD	15,2 ± 6,4 15,1 ± 5,8	20,4 ± 4,8 20,8 ± 4,6	Titrering: 4 uger 12 uger	1
Diener et al., 2007	topiramat 100 mg qd., n = 32 placebo, n = 27	CM	≥ 15 MMD	15,5 ± 4,6 16,4 ± 4,4	-	Titrering: 4 uger 12 uger	1
Lipton et al., 2011	topiramat 100 mg qd., n = 159 placebo, n = 171	EM	9-14 MMD < 15 MHD	11,6 ± 2,0 11,8 ± 2,2	13,0 ± 2,5 13,1 ± 2,6	Titrering: 6 uger 20 uger	1
Amitriptylin							

Studie	Behandlingsarme‡, n	Studie-population†	Inklusionskriterier for migræne	Migrænefrekvens~		Studievarighed*, uger	Klinisk spørgsmål
				MMD/MMA	MHD		
Couch et al., 2011	amitriptylin 100 mg qd., n = 194 placebo, n = 197	EM	≥ 2 MMA af moderat sværhedsgrad	-	-	Titrering: 4 uger 12 uger	2
Goncalves et al., 2016	amitriptylin 25 mg qd., n = 59 placebo, n = 59	EM	≥ 3 MMA eller ≥ 3 MMD < 15 MHD	-	7,3 ± 3,1 7,2 ± 2,5	12 uger	2
Valproat							
Jensen et al., 1994	valproat 1500 mg qd, n = 34 placebo, n = 34	EM (og CM)	2-10 MMD	6,6 (3-10)	-	12 uger	2
Mathew et al., 1995	valproat 1000 mg qd, n = 70 placebo, n = 37	EM	≥ 2 MMA	6,9 7,2	-	12 uger	2
Klapper J, 1997	valproat 1500 mg qd, n = 44 valproat 1000 mg qd, n = 43 valproat 500 mg qd, n = 45 placebo, n = 44	EM	≥ 2 MMA	MMA 4,7 MMA 4,7 MMA 4,5 MMA 6,1	-	12 uger	2
Freitag et al., 2002	valproat 500/1000 mg qd, n = 122 placebo, n = 115	EM	> 2 MMA < 15 MHD	6,3 ± 2,8 5,8 ± 2,9	-	12 uger	2
Botulinum type A toxin							
Aurora et al., 2010	botulinum type A toxin, n = 341 placebo, n = 338	CM	> 15 MHD > 50 % af MHD er MMD	19,1 ± 4,0 19,1 ± 4,1	20,0 ± 3,7 19,8 ± 3,7	24 uger	3
Diener et al., 2010	botulinum toxin type A, n = 347 placebo, n = 358	CM	> 15 MHD > 50 % af MHD er MMD	19,2 ± 3,9 18,7 ± 4,1	19,9 ± 3,6 19,7 ± 3,7	24 uger	3

‡ q1m.: månedlig dosering; q3m.: kvartalsvis dosering; qd: én gang daglig

† EM: Episodisk migræne; CM: Kronisk migræne

~ MMD**:** Månedlige migrænedage; MHD: Månedlige hovedpinedage; MMA: Månedlige migræne anfald

* Den angivne varighed er længden af den placebokontrollerede periode i studiet.

En overblik over andre studie- og populationskarakteristika fremgår af appendix 1.

20 Bilag 4: Bestemmelse af hændelsesrater og beregning af absolutte effektforskelle fra relative indirekte effektestimater

De anvendte hændelsesrater er bestemt ud fra medianen af observerede hændelsesrater i komparatorgruppen fra de inkluderede studier.

Effektmål	Propranolol	Candesartan	Lisinopril	Topiramat	Amitriptylin	Valproat	Botulinum type A toxin
50 % responderrate	0,4	0,416	0,298	0,3021855	0,390	0,478	0,48
Bivirkninger der medfører behandlingsophør	0,155	NA	NA	0,1875	0,119	0,123	0,038

Indirekte effektestimater fra den endelige ansøgning

Komparator	vs. fremanezumab 225 mg q1m	vs. fremanezumab 675 mg q3m
Effektmål: 50 % responderrate		
Propranolol	1,02 (0,57; 1,84)	0,93 (0,51; 1,69)
Candesartan	0,42 (0,06; 2,99)	0,38 (0,05; 2,72)
Lisinopril	0,38 (0,11; 1,24)	0,34 (0,1; 1,13)
Topiramat	0,66 (0,07; 6,04)	0,60 (0,07; 5,5)
Amitriptylin	2,07 (1,00; 4,29)	2,08 (1,00; 4,31)
Valproat	1,15 (0,45; 2,97)	1,16 (0,45; 2,98)
Botulinum type A toxin	2,99 (1,94; 4,61)	3,00 (1,95; 4,64)
Effektmål: Bivirkninger der medfører behandlingsophør		
Propranolol	0,44 (0,17;1,16)	0,37 (0,14; 1,01)
Topiramat	0,35 (0,15; 0,85)	0,3 (0,12; 0,74)
Amitriptylin	0,72 (0,14; 3,66)	0,19 (0,02; 1,95)
Valproat	0,75 (0,14; 3,88)	0,19 (0,02; 2,05)
Botulinum type A toxin	0,4 (0,07; 2,13)	0,1 (0,01; 1,12)

Beregnede absolutte effektforskelle

Komparator	vs. fremanezumab 225 mg q1m	vs. fremanezumab 675 mg q3m
Effektmål: 50 % responderrate		
Propranolol	0,80 %-point (-17,20; 33,60)	-2,80 %-point (-19,60; 27,60)
Candesartan	-24,13 %-point (-39,11; 82,79)	-25,79 %-point (-39,52; 71,56)
Lisinopril	-18,47 %-point (-26,51; 7,15)	-19,66 %-point (-26,81; 3,87)
Topiramat	-10,27 %-point (-28,10; 152,30)	-12,09 %-point (-28,10; 135,98)
Amitriptylin	41,71 %-point (0,03; 128,25)	42,10 %-point (0,18; 129,03)
Valproat	7,17 %-point (-26,30; 94,22)	7,65 %-point (-26,30; 94,70)
Botulinum type A toxin	95,52 %-point (45,12; 173,28)	96,00 %-point (45,60; 174,72)
Effektmål: Bivirkninger der medfører behandlingsophør		
Propranolol	-8,66 %-point (-12,84; 2,47)	-9,74 %-point (-13,30; 0,15)
Topiramat	-12,19 %-point (-15,94; -2,81)	-13,13 %-point (-16,50; -4,88)
Amitriptylin	-3,32 %-point (-10,20; 31,54)	-9,60 %-point (-11,62; 11,26)
Valproat	-3,08 %-point (-10,59; 35,46)	-9,97 %-point (-12,06; 12,93)
Botulinum type A toxin	-2,27 %-point (-3,52; 4,28)	-3,41 %-point (-3,75; 0,45)

21 Bilag 5: Indirekte sammenligning af erenumab og fremanezumab

Resultaterne er præsenteret pr. effektmål, opsummeret i metaanalyser og hvor det er passende er der foretaget indirekte sammenligninger.

For dikotome mål anvendes RR, og for kontinuerte mål anvendes mean difference (MD). Der er ikke gjort forsøg på at imputere manglende data. I de tilfælde, hvor de to behandlinger er sammenlignet direkte i mere end et studie, sammenstilles resultaterne på tværs af studier med metaanalyser baseret på inverse variance-metoden, med antagelse om "fixed effects". Til indirekte sammenligning anvendes Buchers metode [45].

Buchers metode er en statistisk metode, der kan bruges til at sammenligne behandlinger, som ikke har været sammenlignet i head to head-studier. Det er et krav for at kunne bruge metoden, at to behandlinger, uden direkte sammenligning, har været sammenlignet med samme alternative behandling eller placebo (fælles komparator). Indirekte estimater for forskellen mellem de to aktuelle behandlinger kan beregnes med udgangspunkt i estimater på forskelle fra de direkte sammenligninger med den fælles komparator sammen med deres tilhørende standard error (SE). For relative mål (OR, RR og HR) laves alle beregninger på logaritmeskalaen, og resultaterne transformeres bagefter til OR/RR/HR-skala. Ved brug af denne metode bliver usikkerheden knyttet til estimatet på effekt kvantificeret, hvilket ikke er tilfældet ved en naiv indirekte sammenligning, men samtidig er usikkerheden større, dvs. konfidensintervaller er bredere end ved direkte sammenligninger.

For sammenligning mellem fremanezumab og erenumab er forskellige doser af samme lægemiddel anset som værende samme behandling. Det vil sige, at for fremanezumab er effektestimater for månedlig dosering slået sammen med effektestimater fra den kvartalsvise dosering; tilsvarende er effektestimaterne for de to forskellige doser for erenumab slået sammen i de statistiske analyser. For dikotome effektmål er resultater for de to forskellige doser i samme studie slået sammen ved at lægge antal hændelser og antal deltagere sammen for de to doser. For kontinuerte effektmål er anvendt formlerne som angivet i nedenstående tabel.

	Group 1 (e.g. males)	Group 2 (e.g. females)	Combined groups
Sample size	N_1	N_2	$N_1 + N_2$
Mean	M_1	M_2	$\frac{N_1M_1 + N_2M_2}{N_1 + N_2}$
SD	SD_1	SD_2	$\sqrt{\frac{(N_1 - 1)\,SD_1^2 + (N_2 - 1)\,SD_2^2 + \frac{N_1N_2}{N_1 + N_2}\left(M_1^2 + M_2^2 - 2M_1M_2\right)}{N_1 + N_2 - 1}}$

I nogle studier er standard error of the mean (SE) rapporteret i stedet for SD. I disse tilfælde beregnes SD som $\sqrt{N} * SE$.

Sammenligningen mellem fremanezumab og erenumab er foretaget som en indirekte justeret sammenligning ved brug af Buchers metode med placebo som fælles komparator.

Konklusion

På tværs af de undersøgte populationer og effektmål er der ingen statistisk signifikante forskelle mellem erenumab og fremanezumab i den indirekte analyse. Der er dermed ikke dokumenteret forskelle i effekt eller sikkerhed.

1. Studiekarakteristika

Intevention	Studie	Population	Antal randomiserede	Behanlingsarme	n	Længde, måneder	Fase	Primær(e) effektmål	Relevante sekundær(e) effektmål
Erenumab	*ARISE, Dodick et al. 2018 NCT02483585*	Episodisk migræne	577	erenumab 70 mg q.m.t.	286	3	3	- Change From Baseline in Monthly Migraine Days at Week 12	- Percentage of Participants With at Least a 50% Reduction From Baseline in Monthly Migraine Days at Week 12 - Change From Baseline in Monthly Acute Migraine-specific Medication Treatment Days at Week 12 - Number of Participants With Adverse Events
				placebo	291				
	STRIVE, Goadsby et al. 2017 NCT02456740	Episodisk migræne	955	erenumab 70 mg q.m.t.	317	6	3	- Change From Baseline in Mean Monthly Migraine Days to the Last 3 Months of the Double-blind Treatment Period	- Percentage of Participants With at Least a 50% Reduction From Baseline in Monthly Migraine Days in the Last 3 Months of the Double-blind Treatment Phase - Change From Baseline in Monthly Acute Migraine-specific Medication Treatment Days to the Last 3 Months of the Double-blind Treatment Period
				erenumab 140 mg q.m.t.	319				
				placebo	319				
	Studie 178, Sun et al. 2016 NCT01952574	Episodisk migræne	483	erenumab 7 mg q.m.t.	108	3	2	- Change From Baseline in Monthly Migraine Days at Week 12	- Percentage of Participants With at Least a 50% Reduction From Baseline in Monthly Migraine Days at Week 12 - Change From Baseline in Monthly Migraine Attacks at Week 12
				erenumab 21 mg q.m.t.	108				
				erenumab 70 mg q.m.t.	107				
				placebo	160				
	LIBERTY, Reuter et al. 2018 NCT03096834	Episodisk migræne	246			3	3b	- Percentage of patients with a 50% response in the reduction of Monthly Migraine Days (MMD)	- Change in the number of monthly migraine days (MMDs) from baseline to month 3 - Change in the number of monthly acute migraine-specific medication treatment days
				erenumab 140 mg q.m.t.	121				
				placebo	125				
	Studie 295, Tepper et al. 2017 NCT02066415	Kronisk migræne	667	erenumab 70 mg q.m.t.	191	3	2	- Change From Baseline in Monthly Migraine Days	- Percentage of Participants With at Least a 50% Reduction in Monthly Migraine Days - Change From Baseline in Monthly Acute Migraine-specific Medication Treatment Days
				erenumab 140 mg q.m.t.	190				
				placebo	286				
Fremanezumab	*Fase II EM, Bigal et al. 2015 NCT02025556*	Episodisk migræne	297	fremanezumab 225 mg q.m.t.	95	3	2b	- Mean change from baseline in the monthly migraine days during the 28-day post treatment period ending with week 12	- mean change from baseline on the number of days with headache of any severity during the 28-day post treatment period ending with week 12
				fremanezumab 675 mg q.m.t.	96				
				placebo	104				
	HALO EM, Dodick et al. 2018 NCT02629861	Episodisk migræne	875	fremanezumab 225 mg q.m.t.	290	3	3	- Change From Baseline in the Monthly Average Number of Migraine Days During the 12-Week Period After the First Dose of Study Drug - Participants With Adverse Events	- Percentage of Participants With At Least 50% Reduction In Monthly Average Number of Migraine Days - Change From Baseline in the Monthly Average Number of Days of Use of Any Acute Headache Medicine
				fremanezumab 675 mg q3month	291				
				placebo	294				
	Fase II CM, Bigal et al. 2015 NCT02021773	Kronisk migræne	264	fremanezumab 675/225 mg q.m.t.	88	3	2b	- Mean change from baseline in the number of monthly cumulative headache hours of any severity on headache days - Safety as determined by the presence of AEs	- Mean change from baseline in the number of headache days of at least moderate severity
				fremanezumab 900 mg q.m.t.	87				
				placebo	89				
	HALO CM, Silberstein et al. 2017 NCT02621931	Kronisk migræne	1130	fremanezumab 675/225 mg q.m.t.	379	3	3	- Change From Baseline in the Monthly Average Number of Headache Days of At Least Moderate Severity - 2.Participants With Treatment-Emergent AEs	- Change From Baseline in the Monthly Average Number of Migraine Days - Percentage of Participants With At Least 50% Reduction In Monthly Average Number of Headache Days of At Least Moderate Severity
				fremanezumab 675 mg q3month	376				
				placebo	375				
	FOCUS, NCT03308968	Episodisk og kronisk migræne	838	fremanezumab 225 mg q.m.t.	283	3	3b	- Mean change from baseline in the monthly average number of migraine days	- Proportion of patients reaching at least 50% reduction in the monthly average number of migraine days - mean change from baseline in the monthly average number of headache days
				fremanezumab 675 mg q3month	276				
				placebo	279				

2. Baselinekarakteristika

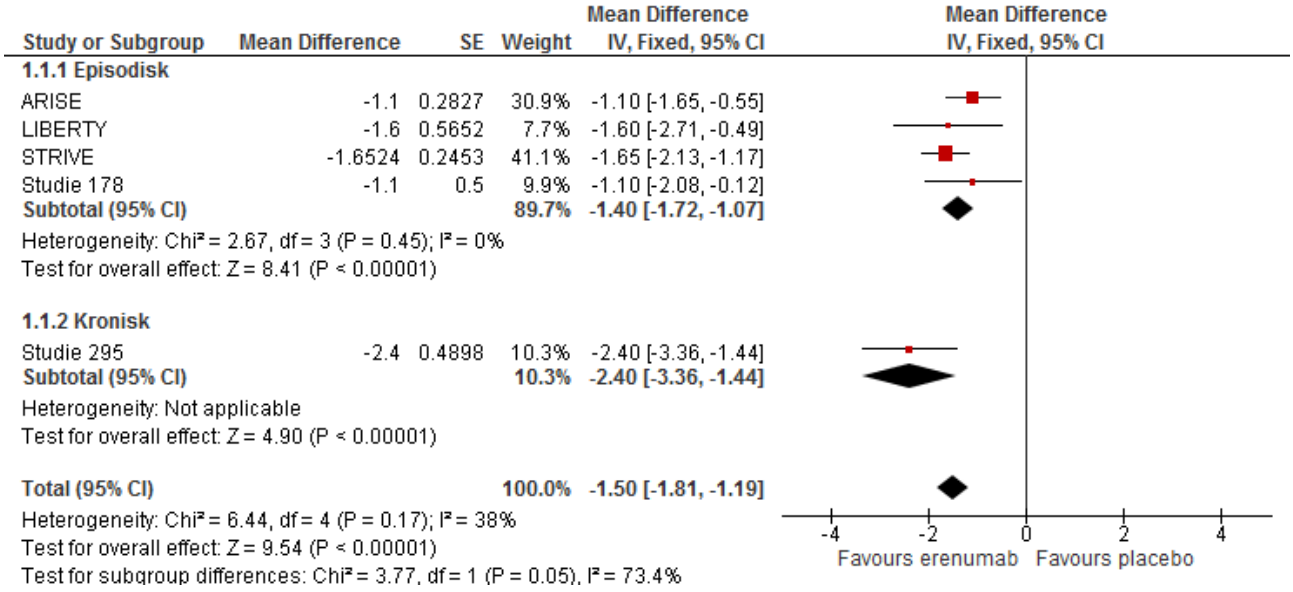
						Migræne/hovedpine frekvens		Tidligere profylaktisk behandling, no (%)		
Intevention	**Studie**	**Behandlingsarme**	**Alder, år**	**Kvinder, n (%)**	**Sygdomsvarighed, år**	**MMD, dage**	**MHD, dage**	**Aldrig**	**Tidligere**	**Nuværende**
Erenumab	*ARISE, Dodick et al. 2018*	erenumab 70 mg q.m.t.	42 ± 11	245 (85,7)	20 ± 12	8,1 ± 2,7	9,1 ± 2,7	144 (50,3)	123 (43,0)	19 (6,6)
	NCT02483585	placebo	42 ± 12	247 (84,9)	22 ± 13	8,4 ± 2,6	9,3 ± 2,7	150 (51,5)	125 (43,0)	16 (5,5)
	STRIVE, Goadsby et al. 2017	erenumab 70 mg q.m.t.	41 ± 11	268 (84,5)	21,4 ± 11,0*	8,3 ± 2,5	9,1 ± 2,6	175 (55,2)	133 (42,0)	10 (3,1)
		erenumab 140 mg q.m.t.	40 ± 11	272 (85,3)	20,7 ± 9,9*	8,3 ± 2,5	9,3 ± 2,5	187 (58,6)	124 (38,9)	9 (2,8)
	NCT02456740	placebo	41 ± 11	274 (85,9)	21,2 ± 10,2*	8,2 ± 2,5	9,3 ± 2,6	178 (55,8)	131 (41,1)	8 (2,5)
	Studie 178, Sun et al. 2016	erenumab 7 mg q.m.t.	40 ± 11	88 (81)	19,0 ± 11,4	8,6 ± 2,8		61 (56)	47 (44)	
		erenumab 21 mg q.m.t.	40 ± 12	87 (81)	20,1 ± 12,5	8,9 ± 2,9		63 (58)	45 (42)	
	NCT01952574	erenumab 70 mg q.m.t.	43 ± 10	82 (77)	21,5 ± 11,7	8,6 ± 2,5		60 (56)	47 (44)	
		placebo	41 ± 10	132 (83)	20,7 ± 11,5	8,8 ± 2,7		94 (59)	66 (41)	
	LIBERTY, Reuter et al. 2018	erenumab 140 mg q.m.t.	45 ± 11	97 (80)		9,2 ± 2,6	10,1 ± 2,8			
	NCT03096834	placebo	44 ± 11	103 (82)		9,3 ± 2,7	10,1 ± 2,7			
	Studie 295, Tepper et al. 2017	erenumab 70 mg q.m.t.	41 ± 11	166 (87)	20,7 ± 12,8	17,9 ± 4,4	20,5 ± 3,8			
		erenumab 140 mg q.m.t.	43 ± 11	160 (84)	21,9 ± 11,8	17,8 ± 4,7	20,7 ± 3,8			
	NCT02066415	placebo	42 ± 11	226 (79)	22,2 ± 12,6	18,2 ± 4,7	21,1 ± 3,9			
Fremanezumab	*Fase II EM, Bigal et al. 2015*	fremanezumab 225 mg q.m.t.	41 ± 12	87 (91)	18,9 ± 12,9	11,5 ± 1,9	12,6 ± 3,1			
		fremanezumab 675 mg q.m.t.	41 ± 12	82 (85)	16,9 ± 12,3	11,3 ± 2,2	12,5 ± 2,7			
	NCT02025556	placebo	42 ± 12	92 (88)	21,1 ± 14,1	11,5 ± 2,2	12,4 ± 2,3			
	HALO EM, Dodick et al. 2018	fremanezumab 225 mg q.m.t.	43 ± 13	244 (84)	20,7 ± 12,9	8,9 ± 2,6				62 (21,4)
		fremanezumab 675 mg q3month	41 ± 11	251 (86)	20,0 ± 12,1	9,3 ± 2,7				58 (19,9)
	NCT02629861	placebo	41 ± 12	247 (84)	19,9 ± 11,9	9,1 ± 2,7				62 (21,1)
	Fase II CM, Bigal et al. 2015	fremanezumab 675/225 mg q.m.t.	40 ± 12	76 (86)	15,8 ± 11,2	17,2 ± 5,4	16,5 ± 6,7			
		fremanezumab 900 mg q.m.t.	42 ± 13	75 (86)	18,8 ± 12,2	16,4 ± 5,3	15,9 ± 6,5			
	NCT02021773	placebo	41 ± 12	76 (85)	20,4 ± 13,1	16,8 ± 5,0	16,5 ± 6,3			
	HALO CM, Silberstein et al. 2017	fremanezumab 675/225 mg q.m.t.	41 ± 12	330 (87)	20,1 ± 12,0	16,0 ± 5,2	20,3 ± 4,3			85 (22)
		fremanezumab 675 mg q3month	42 ± 12	331 (88)	19,7 ± 12,8	16,2 ± 4,9	20,4 ± 3,9			77 (20)
	NCT02621931	placebo	41 ± 12	330 (88)	19,9 ± 12,9	16,4 ± 5,2	20,3 ± 4,2			77 (21)
	FOCUS, NCT03308968	fremanezumab 225 mg q.m.t.	46 ± 11	238 (84)	24,0 ± 13,7	14,1 ± 5,6				
		fremanezumab 675 mg q3month	46 ± 11	229 (83)	24,3 ± 12,8	14,1 ± 5,6				
		placebo	47 ± 11	233 (84)	24,3 ± 13,6	14,3 ± 6,1				

*Alder ved symptomdebut

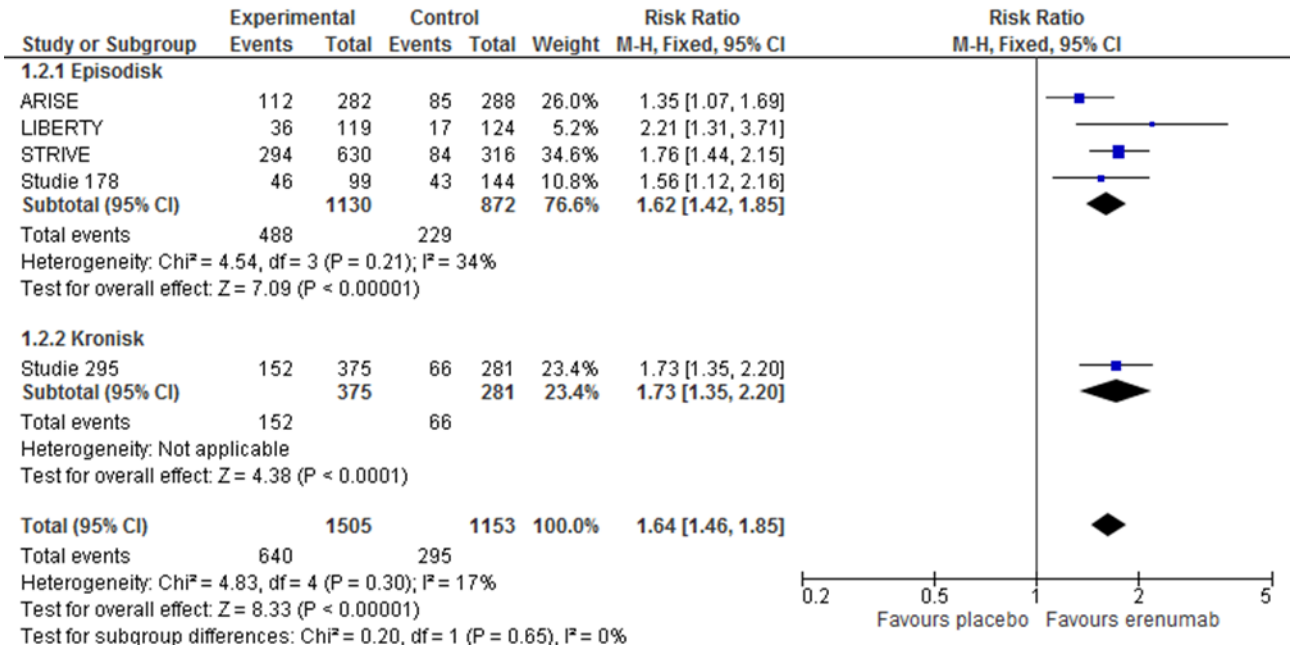
3. Metaanalyser baseret på placebokontrollerede studier for patienter med minimum 4 månedlige migrænedage

Erenumab

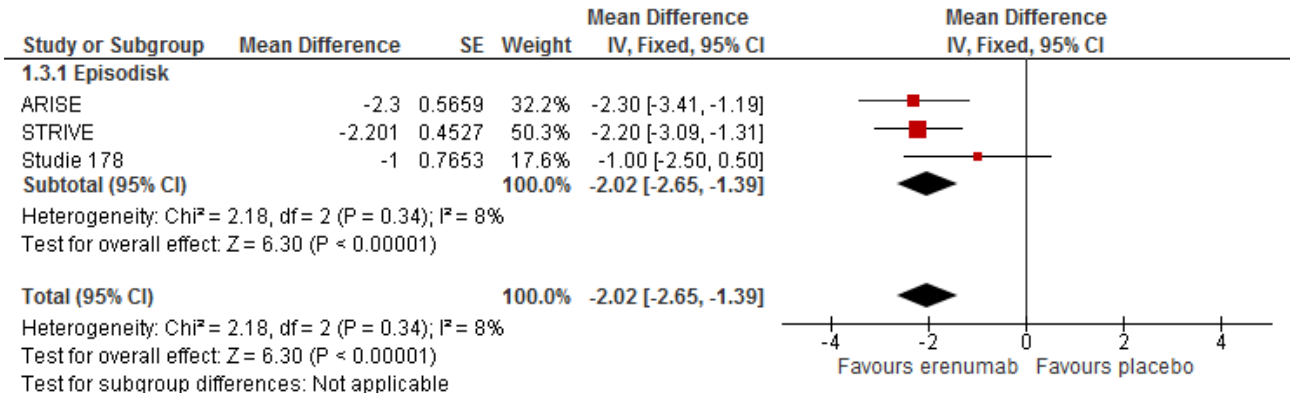
Reduktion af månedlige migrænedage



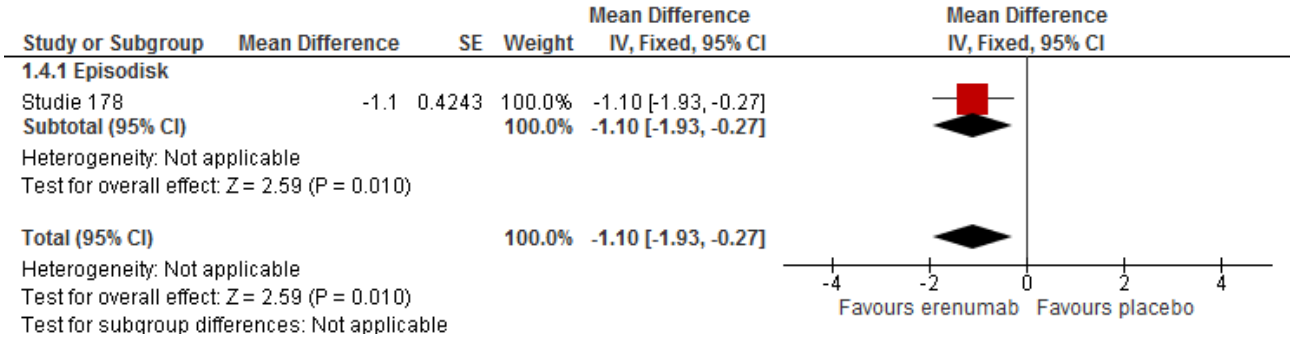
50 % responderrate



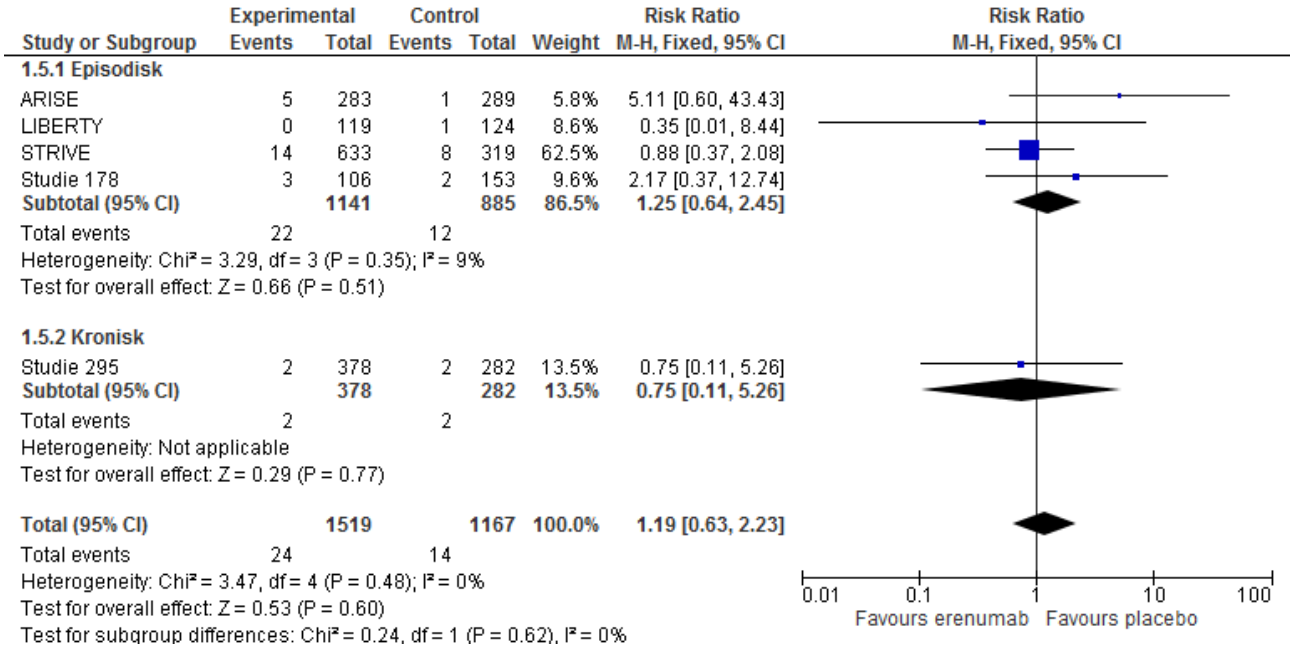
Livskvalitet



Anfaldssværhedsgrad

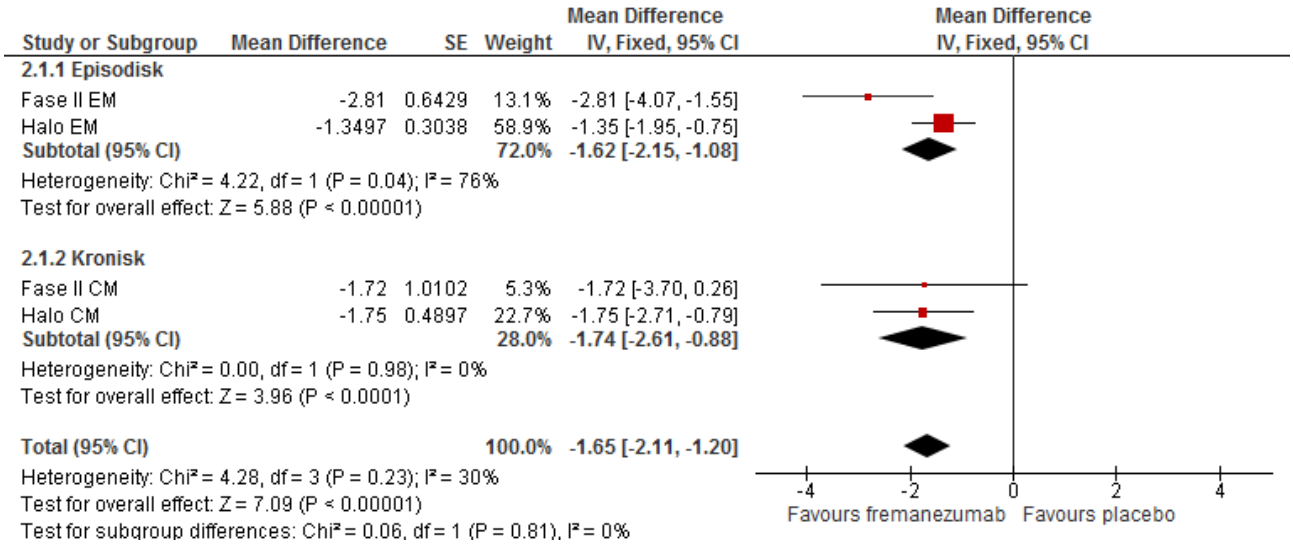


Bivirkninger

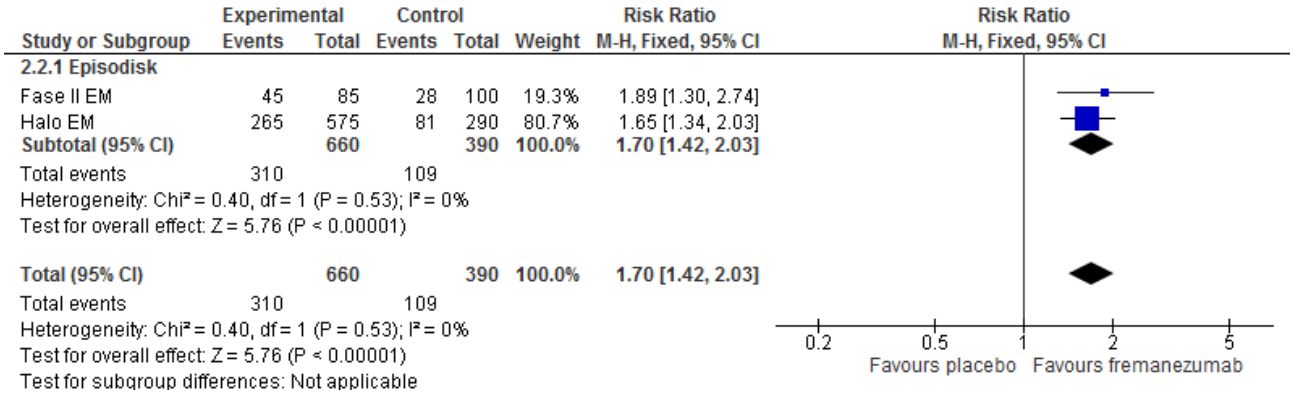


Fremanezumab

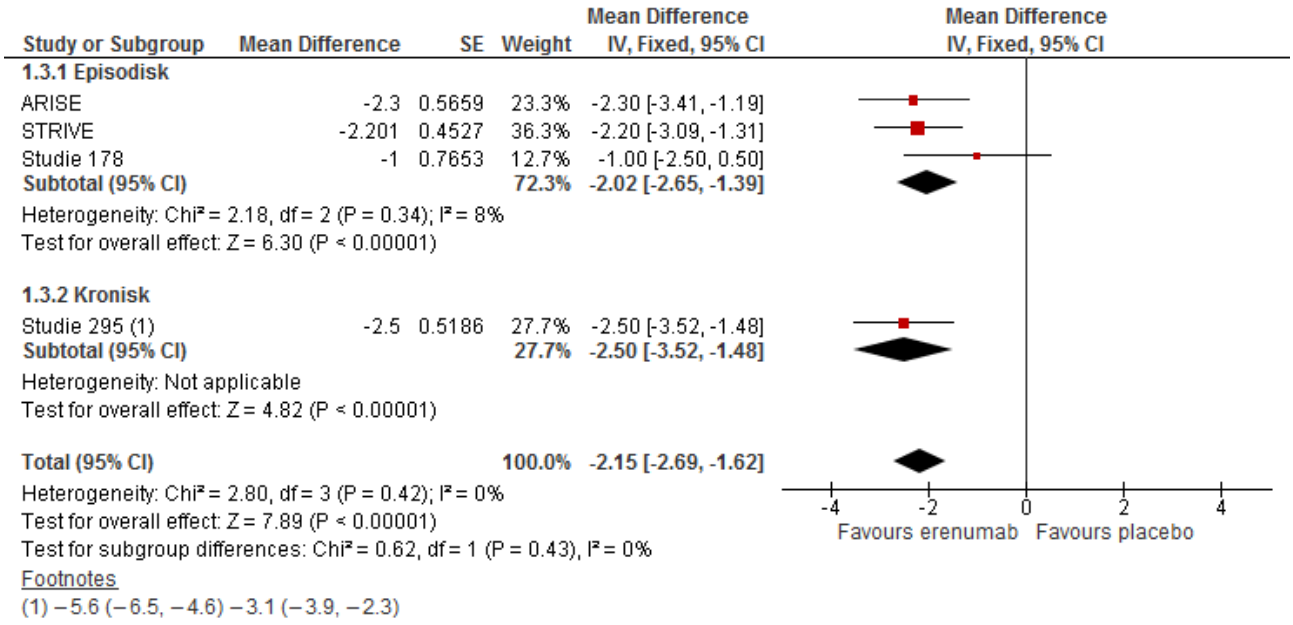
Reduktion af månedlige migrænedage



50 % responderrate



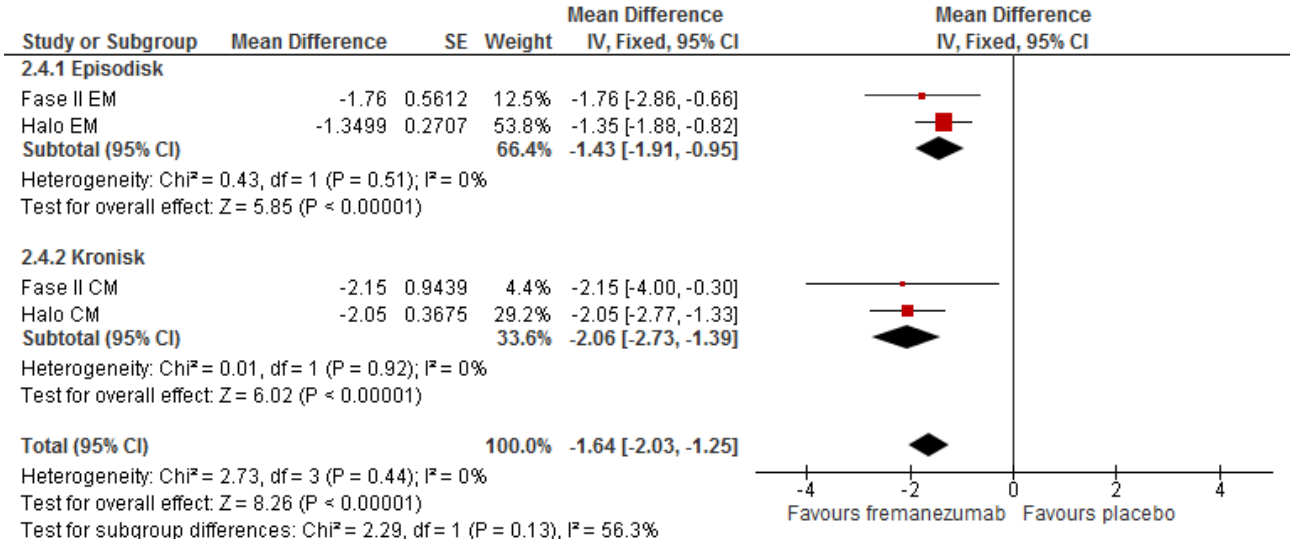
Livskvalitet



Footnotes

(1) −5.6 (−6.5, −4.6) −3.1 (−3.9, −2.3)

Anfaldssværhedsgrad



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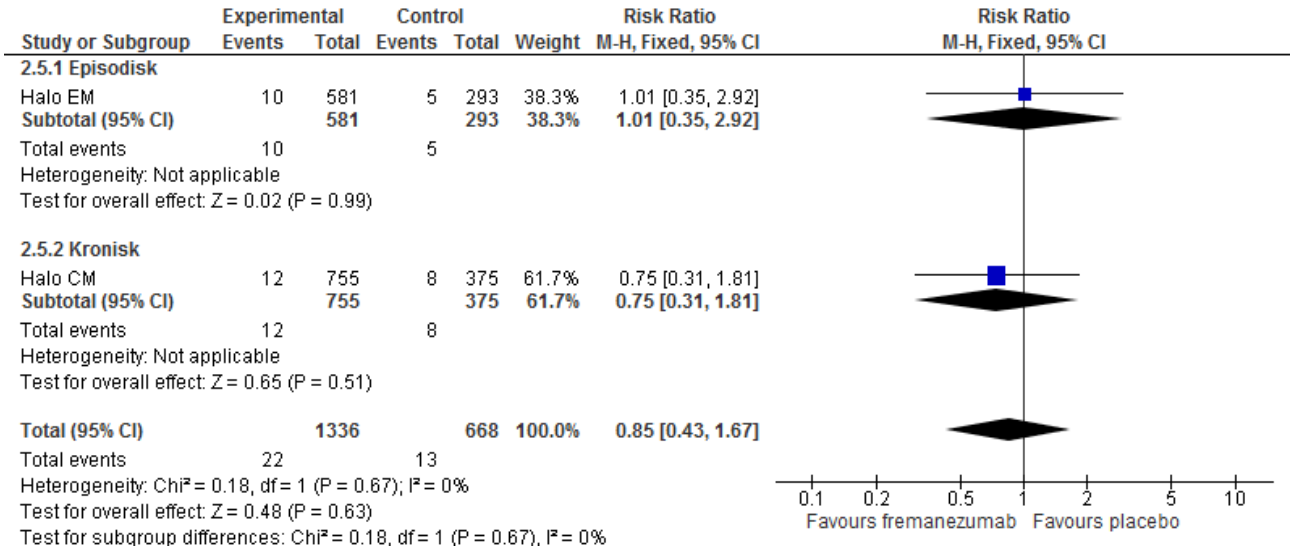
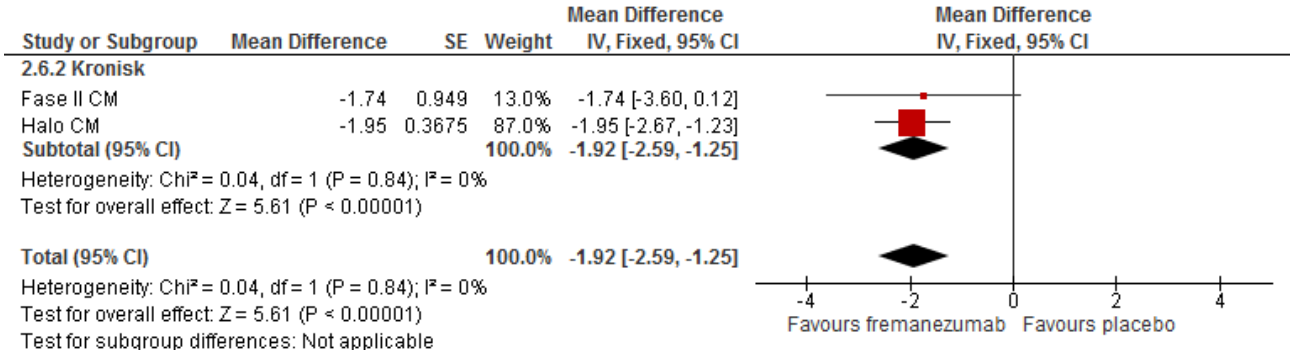


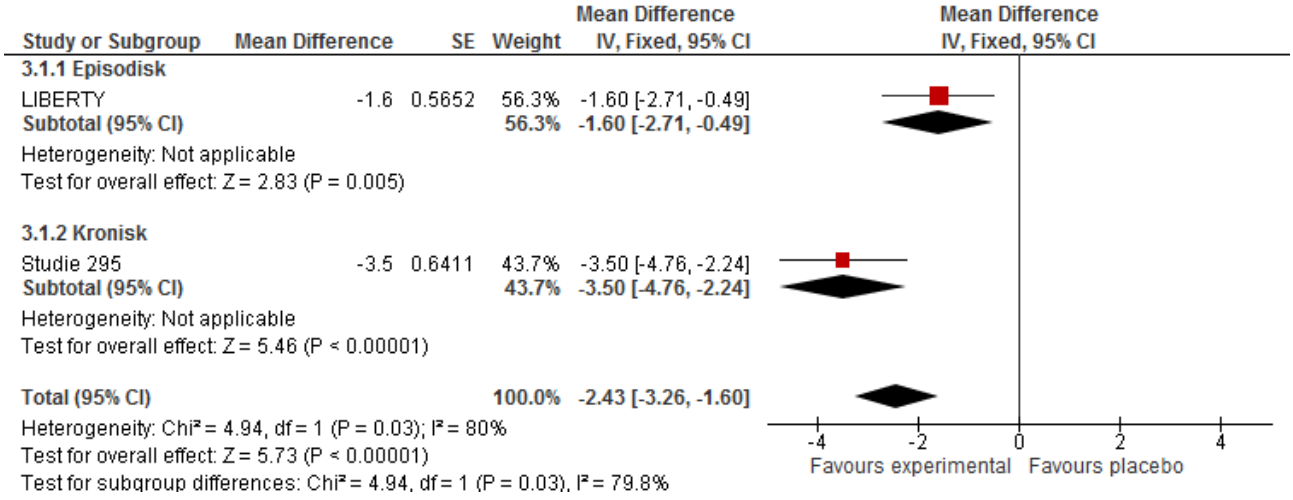
Frekvens af hovedpinedage



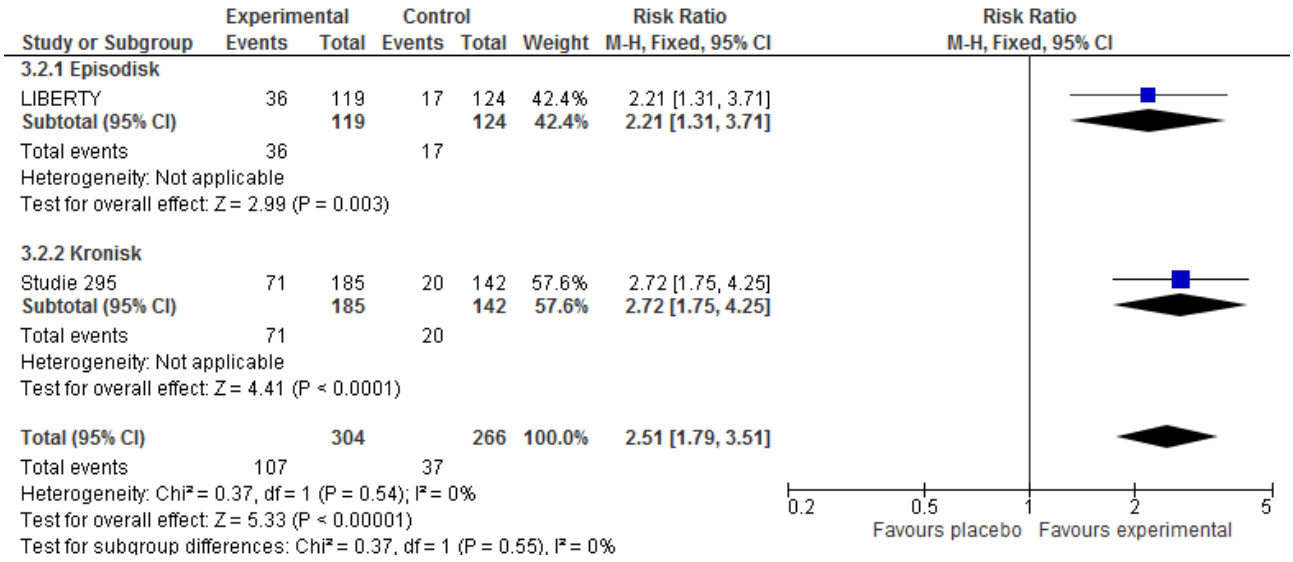
4. Metaanalyser baseret på placebokontrollerede studier for patienter med minimum 4 månedlige migrænedage som har oplevet behandlingssvigt på minimum 2 tidligere forebyggende behandlinger.

Erenumab

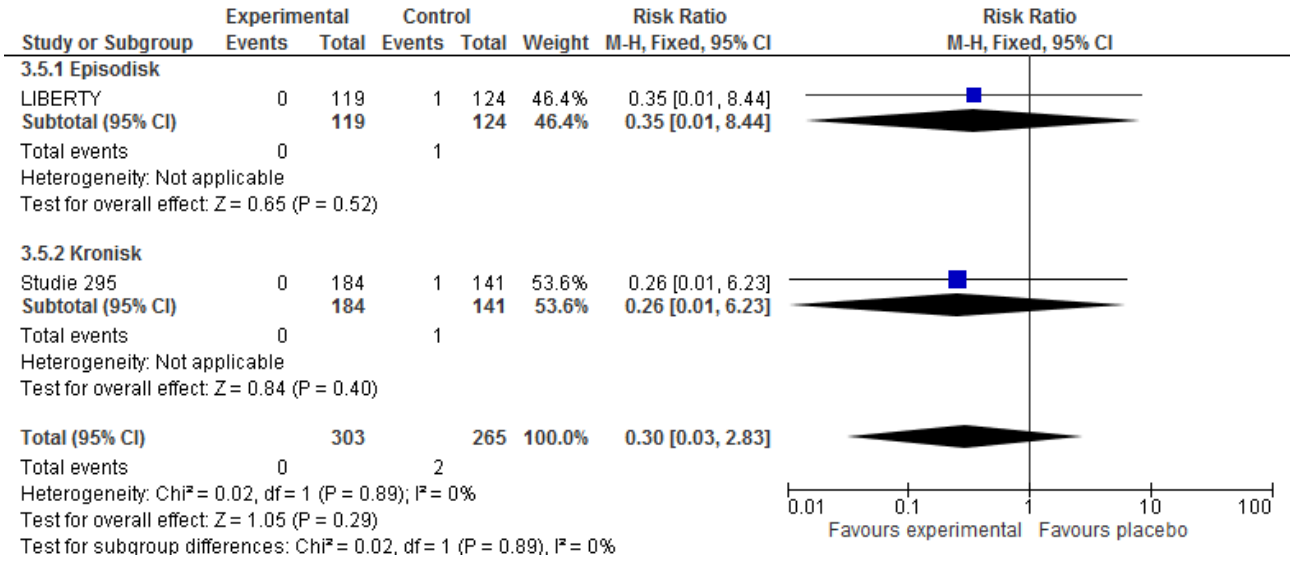
Reduktion af månedlige migrænedage



50 % responderrate

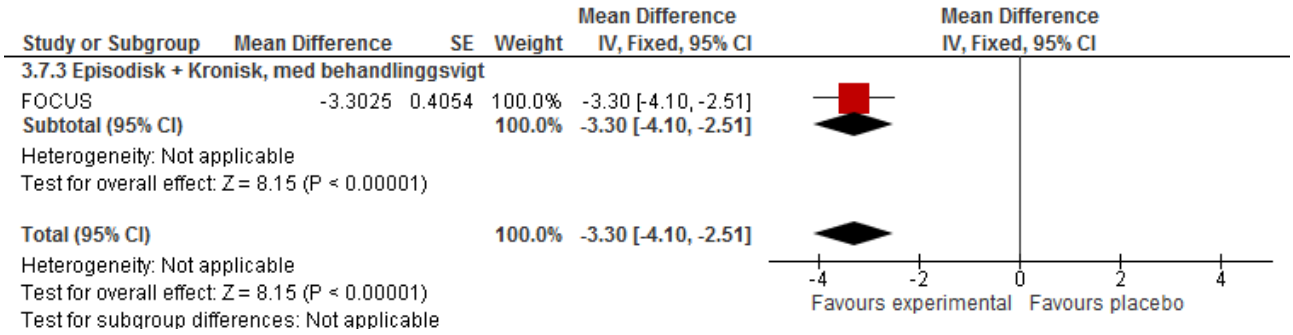


Bivirkninger

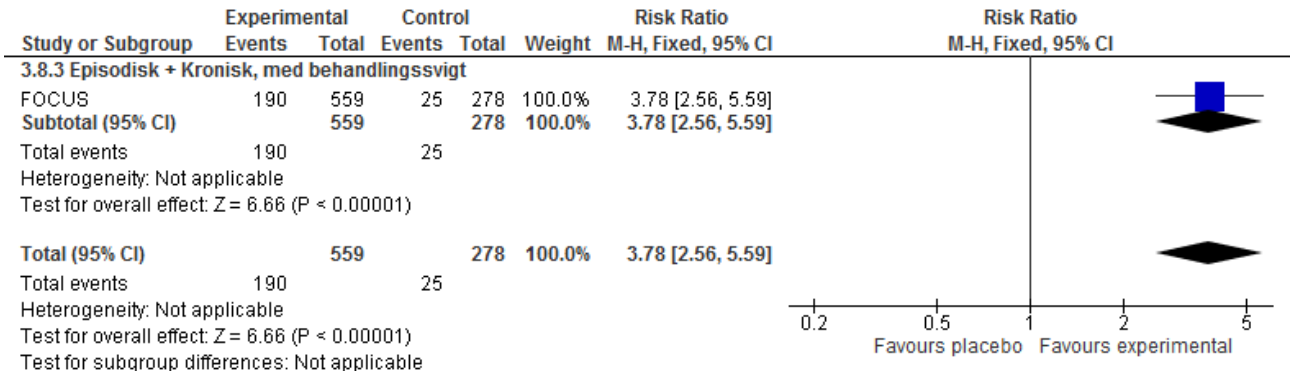


Fremanezumab

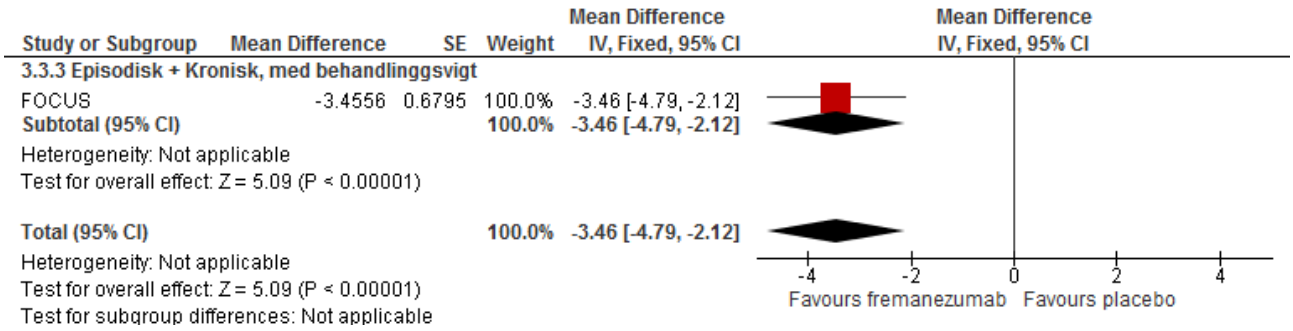
Reduktion af månedlige migrænedage



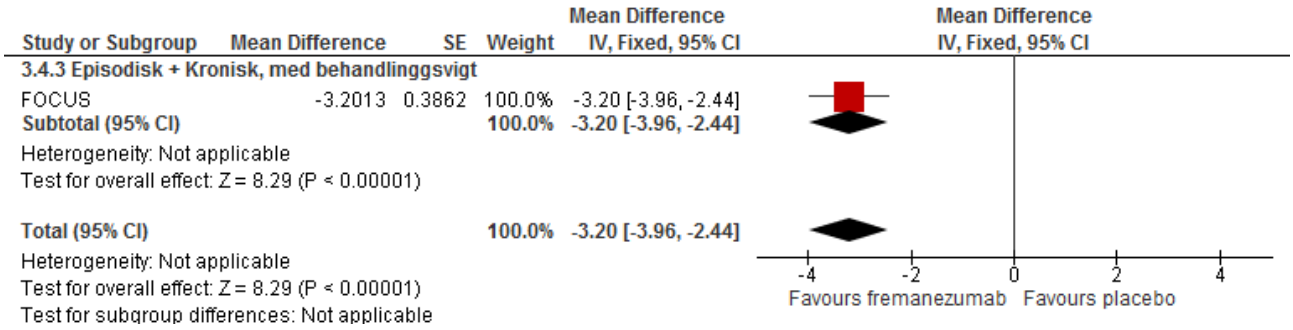
50 % responderrate



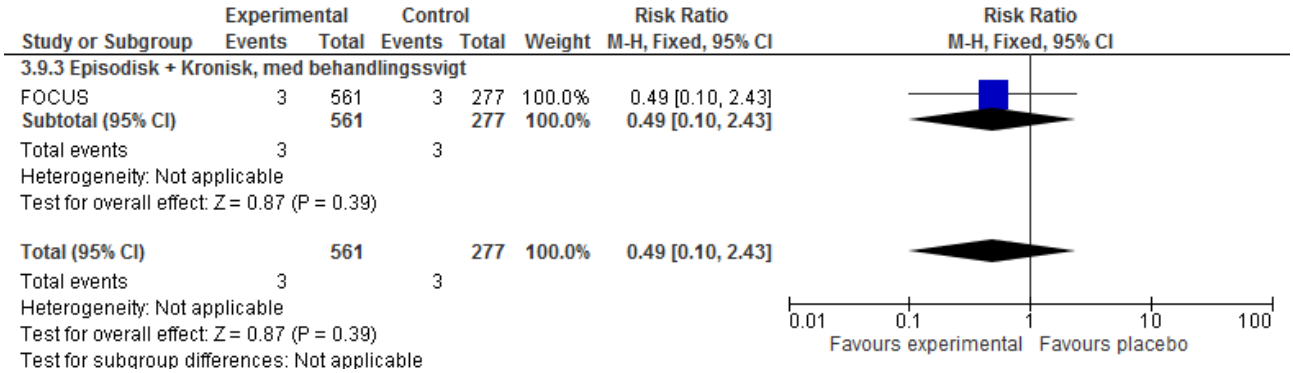
Livskvalitet



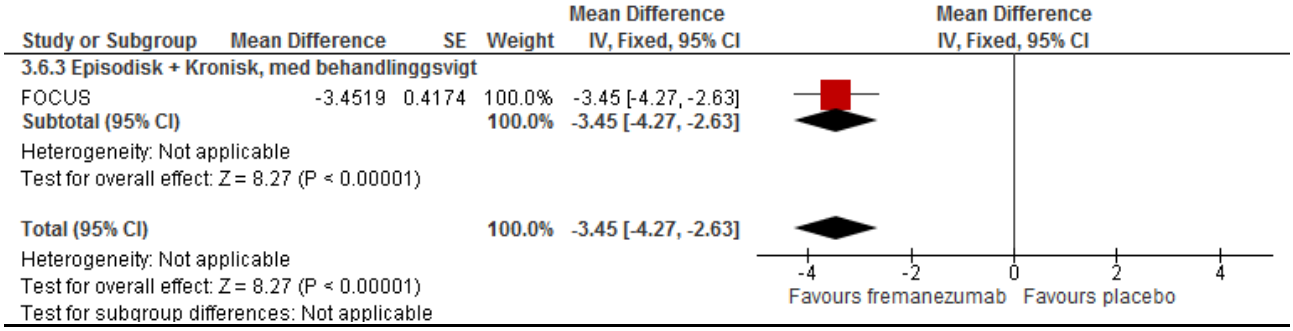
Anfaldssværhedsgrad



Bivirkninger



Frekvens af hovedpinedage



5. Indirekte sammenligninger ved Buchers metode

Sammenligning	Enhed	Erenumab vs. placebo	Fremanezumab vs. placebo	Erenumab vs. fremanezumab Indirekte estimat
Patienter med episodisk migræne				
Reduktion af månedlige migrænedage	MD	-1,40 [-1,72; -1,07]	-1,62 [-2,15; -1,08]	0,22 [-0,41; 0,85]
50 % responderrate	RR	1,62 [1,42; 1,85]	1,70 [1,42; 2,03]	0,95 [0,76; 1,19]
Livskvalitet	MD	-2,02 [-2,65; -1,39]	-	-
Anfaldssværhedsgrad	MD	-1,10 [-1,93; -0,27]	-1,43 [-1,91; -0,95]	0,33 [-0,63; 1,29]
Bivirkninger	RR	1,25 [0,64; 2,45]	1,01 [0,35; 2,92]	1;24 [0;35; 4;34]
Frekvens af hovedpinedage	MD	-	-	-
Patienter med kronisk migræne				
Reduktion af månedlige migrænedage	MD	-2,40 [-3,36; -1,44]	-1,74 [-2,61; -0,88]	-0,66 [-1,95; 0,63]
50 % responderrate	RR	1,73 [1,35; 2,20]	-	-
Livskvalitet	MD	-2,50 [-3,52; -1,48]	-2,10 [-3,26; -0,94]	-0,40 [-1,94; 0,51]
Anfaldssværhedsgrad	MD	-	-2,06 [-2,73; -1,39]	-
Bivirkninger	RR	0,75 [0,11; 5,26]	0,75 [0,31; 1,81]	1,00 [0,12; 8,38]
Frekvens af hovedpinedage	MD	-	-1,92 [-2,59; -1,25]	-
Patienter med episodisk og kronisk migræne				
Reduktion af månedlige migrænedage	MD	-1,50 [-1,81; -1,19]	-1,65 [-2,11; -1,20]	0,15 [-0,40; 0,70]
50 % responderrate	RR	1,64 [1,46; 1,85]	1,70 [1,42; 2,03]	0,96 [0,78; 1;20]
Livskvalitet	MD	-2,15 [-2,69; -1,62]	-2,10 [-3,26; -0,94]	-0,05 [-1,33; 1;23]
Anfaldssværhedsgrad	MD	-1,10 [-1,93; -0,27]	-1,64 [-2,03; -1,25]	0,54 [-0,38; 1,46]
Bivirkninger	RR	1,19 [0,63; 2,23]	0,85 [0,43; 1,67]	1,40 [0,55; 3,54]
Frekvens af hovedpinedage	MD	-	-1,92 [-2,59; -1,25]	-
Patienter med episodisk og kronisk migræne som tidligere har oplevet minimum to behandlingssvigt				
Reduktion af månedlige migrænedage	MD	-2,43 [-3,26; -1,60]	-3,30 [-4,10; -2,51]	0,87 [-0,28; 2,02]
50 % responderrate	RR	2,51 [1,79; 3,51]	3,78 [2,56; 5,59]	0,66 [0,40; 1,11]
Livskvalitet	MD	-	-3,46 [-4,79; -2,12]	-
Anfaldssværhedsgrad	MD	-	-3,20 [-3,96; -2,44]	-
Bivirkninger	RR	0,30 [0,03; 2,83]	0,49 [0,10; 2,43]	1;42 [0,04; 9,84]
Frekvens af hovedpinedage	MD	-	-3,45 [-4,27; -2,63]	-

Final application to Medicinrådet for:

Ajovy® (fremanezumab)

- For prophylaxis of migraine in adults

This revised application is submitted by Teva Denmark

August 2019

Contents

Table of captions

Basic information

TABLE 1: CONTACT INFORMATION

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Area of responsibility	Clinical/Medical
Phone	+45 23660404
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TABLE 2: OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Ajovy®
Generic name	Fremanezumab
Marketing authorization holder in Denmark	TEVA GmbH Graf-Arco-Str. 3 89079 Ulm Germany
ATC code	N02
Pharmacotherapeutic group	Analgesics
Active substance(s)	Fremanezumab
Pharmaceutical form(s)	Solution for injection. Clear to opalescent, colourless to slightly yellow solution with a pH of 5.5 and an osmolality of 300-450 mOsm/kg.
Mechanism of action	Fremanezumab is a humanized monoclonal antibody that binds to the vasodilatating neuropeptide calcitonin gene-related peptide (CGRP), thus preventing the peptide from binding the CGRP receptor [1,2].
Dosage Regimen	Injection: 225 mg/1.5 mL solution in a prefilled syringe.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	AJOVY is indicated for 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	Fremanezumab can be administered as monotherapy and as an add-on therapy to current migraine preventatives Co-medication: acute headache medication
Packaging – types, sizes/number of units, and concentrations	Packaging: 1 prefilled syringe Strength: 225 mg Solution for injection, subcutaneous use Emballage: Pre-filled syringe (glass) Concentration: 1.5 mL (150 mg/mL)
Orphan drug designation	No

Abbreviations

ACR: Assumed control group rates

AEs: Adverse Events

CI: Confidence interval

CGRP: Calcitonin gene-related peptide

CM: Chronic Migraine

EM: Episodic Migraine

EMA: European Medicines Agency

HIT: Headache Impact Test

***ICHD*-3-beta:** *International Classification of Headache Disorders 3* beta version

ITC: Indirect treatment comparison

LSM: Least-square mean

MIDAS: Migraine Disability Assessment

MSQ: Migraine-Specific Quality of Life

SC.: Subcutaneous

SD: Standard deviation

SE: Standard Error

SmPC: Summary of product characteristics

Executive Summary

Migraine is the third most common disease in the world, and is associated with reduced functionality, quality of life and increased absenteeism [3,4]. Migraine is a neurovascular neurological disease presumably with a genetic basis [5].

All current migraine prophylactics were originally developed for other purposes (e.g. antihypertensive, antiepileptic, or antidepressant conditions), and most of these prophylactics are used off-label in migraine treatment [6–16]. Currently there are often challenges with finding the correct prophylactic drug, including the optimal dosage after titration. These prophylactics have high discontinuation rates, and the onset of action takes months [17–19]. Moreover, most of the current prophylactics are taken orally on a daily basis, and have several contraindications, a long lists of potential burdensome adverse events and/or drug-drug interactions [6,7,9–13] which also results in low adherence to the treatment [17].

The anti-CGRP antibodies (anti-CGRPs) are the only class of medication specifically designed and targeted for the prophylactic treatment of migraine [18]. The anti-CGRPs appear to overcome all the above-mentioned challenges providing a promising efficacy profile, and a favorable safety profile. Fremanezumab (Ajovy®), is a monoclonal antibody which binds CGRP. Fremanezumab is approved in the US [20] and was approved in Europe 28 March 2019 [21].

Fremanezumab is clinically different from other anti-CGRPs, in that:

- Fremanezumab provides the choice of a once monthly (225 mg of fremanezumab) or a once quarterly dosing regimen (675 mg of fremanezumab, i.e. 3 x 225 mg) [22,23] [See preliminary application]
- Fremanezumab can be given both as monotherapy and as add-on therapy [24] [See preliminary application]
- Fremanezumab is the only anti-CGRP that has shown to significantly reduce all migraine related debilitating symptoms, i.e. photophobia, phonophobia, nausea or vomiting [25,26] [See preliminary application]

This application provides efficacy and safety data of fremanezumab from the HALO phase 3 registration studies, the FOCUS phase 3b study and two phase 2 studies, which investigated fremanezumab compared with placebo for prevention of episodic and chronic migraine (EM and CM, respectively) with both a once monthly and once quarterly dosing regimen. The HALO trials significantly met all primary and secondary endpoints in both CM and EM, and fremanezumab demonstrated that both monthly and quarterly dosing of fremanezumab was associated with a statistically significant improvements in all efficacy outcomes compared to placebo over a three-month period. [22,23,27–30]

The included patients in the FOCUS study had responded inadequately to 2 to 4 classes of prior preventive treatments. The topline FOCUS phase 3b trial data has been announced, in which all primary and secondary endpoints were significantly met [31].

Clinical question 1

Fremanezumab is compared with propranolol, candesartan, lisinopril and topiramate in patients with episodic and chronic migraine.

Table 17 and Table 18 outline the favored treatment based on the indirect treatment comparison (ITC).

Overall, the results from the ITC favors fremanezumab compared to the comparators for the population in clinical question 1.

The ITC results comparing fremanezumab with topiramate are significantly favoring fremanezumab, with regards to the monthly days with reduction in number of days with acute headache medication (important outcome) in the monthly dosing regimen of fremanezumab, and with regards to the proportion of patients who experiences adverse events leading to discontinuation (important outcome) in both the monthly and quarterly dosing regimen of fremanezumab.

Fremanezumab in a monthly dosing regimen is significantly favored compared to propranolol, with regards to the percent reduction of mean monthly migraine days (critical outcome), and monthly days with reduction in number of days with acute headache medication (important outcome).

Hence, based on the ITC data, on some parameters, fremanezumab is significantly favored over topiramate and propranolol, and none of the comparators are significantly favored over fremanezumab in any parameter.

Where ITC has been possible to do, fremanezumab is (favored) considered more tolerable than the comparators topiramate and propranolol (proportion of patients who experiences adverse events leading to discontinuation), and **fremanezumab appears (is favored) to have a better effect on the burden of migraine than topiramate (MIDAS and HIT-6), for a monthly dosing regime of fremanezumab**.

Descriptive comparisons of the SmPCs of fremanezumab and all the comparators suggest, that fremanezumab has a better tolerability and safety profile than the comparators (Note: no head to head studies have been made between fremanezumab and the said comparators).

Moreover, the following should be noted with regards to the ITC and the said comparators:

- It is important to note that large differences exist between studies used in the ITC in terms of follow-up time, patient characteristics, size of population and study design.
- Lisinopril is used off label, and not recommended as first line prophylactic treatment in any current Danish treatment guideline of migraine.
- Candesartan is also used off-label.
- Amongst the many precautions stated in the SmPC for topiramate, the report concerning suicidal thoughts and suicidal behavior can be highlighted as those have been seen in various cases with patients being treated with antiepileptic medication. [10]

Clinical question 2

Fremanezumab is compared with amitriptyline and valproate in patients with episodic and chronic migraine who have responded inadequately to 2 to 4 classes of prior preventive treatments.

Table 21 and Table 22 outline the favored treatment based on the ITC.

All the results from the ITC favors fremanezumab compared to the comparators, amitriptyline and valproate, for the population in clinical question 2.

Based on the ITC data, fremanezumab is significantly favored over amitriptyline with regards to the percent reduction of mean monthly migraine days (critical outcome) and proportion of patients who achieve ≥50% reduction in monthly migraine days (important outcome), in both the monthly and quarterly dosing regimen of fremanezumab.

Based on the ITC data, fremanezuamb is favored over valproate on all the measured parametres.

Based on the ITC data, fremanezumab is (favored) considered more tolerable than amitriptyline and valproate (proportion of patients who experiences adverse events leading to discontinuation), **in both the monthly and quarterly dosing regimen of fremanezumab.**

Descriptive comparisons of the SmPCs of fremanezumab, valproate and amitriptyline suggest, that fremanezumab has a better tolerability and safety profile than valproate and amitriptyline (Note: no head to head studies have been made between fremanezumab and valproate and amitriptyline).

Moreover, the following should be noted with regards to the ITC and the said comparators:

- It is important to note that large differences exist between studies used in the ITC in terms of follow-up time, patient characteristics, size of population and study design.
- The use of amitriptyline is debated and it is used as second line prophylactic treatment [15], i.e. prior to the population relevant for clinical question 2.
- Nortriptyline is currently not recommended in any Danish treatment guideline.
- Valproate is used off-label. According to the SmPC, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. [9]

Clinical question 3

Fremanezumab is compared with botox in patients with chronic migraine who have responded inadequately to at least 2 classes of prior preventive treatments.

Table 25 and Table 26 outline the favored treatment based on the ITC.

On all measured parametres, the ITC favors fremanezumab compared to the botox population in clinical question 3.

The ITC results comparing fremanezumab to botox are significantly favouring fremanezumab with regards to the percent reduction of mean monthly migraine days (critical outcome), the proportion of patients who achieve ≥50% reduction in monthly migraine days (important outcome), and the monthly days with reduction in number of days with acute headache medication (important outcome) in both a monthly and quarterly dosing of fremanezumab.

Based on the ITC data, fremanezumab is (favored and) considered to be more effective than botox, in both the monthly and quarterly dosing regimen of fremanezumab.

Based on the ITC data, fremanezumab is (favored and) considered to have a better effect on the burden of migraine than botox (HIT-6), in both the monthly and quarterly dosing regimen of fremanezumab.

Based on the ITC data, fremanezumab is (favored and) considered to be more tolerable than Botox (proportion of patients who experiences adverse events leading to discontinuation), in both the monthly and quarterly dosing regimen of fremanezumab.

1. Literature search

The literature search was conducted based on a prespecified search string provided from the Danish Medicines Council (hereafter referred to as the Council) and stated in the protocol. MEDLINE (via PubMed) and CENTRAL (via Cochrane Library) databases were searched for relevant literature. The European Public Assessment Report (EPAR) for fremanezumab was consulted, however, no EPARs were identified for the comparators why the Danish summary of product characteristics (SmPC) were consulted [6,7,10,12,32,33].

The electronic search was performed in MEDLINE and CENTRAL on **April 10th, 2019**. The literature search included terms representative for the therapeutic area and drugs specified in the protocol and with no limitations to the time period. Inclusion criteria, and PRISMA flow diagram are outlined in Appendix A.

The literature search resulted in 750 hits. Two investigators independently screened and reviewed citations for inclusion based on the criteria shown in section 1.1. 43 publications were selected for full text reading.

Based on the full text reading and the consulted EPAR and SmPCs, 28 publications met the criteria for inclusion. In Table 5, a full overview of the included articles is outlined.

To answer the clinical question 1, 20 publications are identified. Four publications for fremanezumab [22,23,29,34], 12 for topiramate [35–43], one for lisinopril [44], two for candesartan [45,46], and three for propranolol [37,47,48].

To answer the clinical question 2, one publication for fremanezumab [30,49] and two publications for amitriptyline [50,51] and four for valproate were included [52–55].

When answering the clinical question 3, one publication for fremanezumab [30,49] and two publications for botox were included [56,57]. Data from these two trials were pooled in a publication which was used as results per study and for the ITC for this comparator [58].

1.1 *Databases and search strategy*

Table 3 and

Table 4 contain the search strings done in MEDLINE and CENTRAL at April 10th.

Note that two significant changes have been made to the search string for MEDLINE delivered by Medicinrådet. These are distinguished with red font, **bold** and underlining at the search string number #4 and #12 in

Table 3.

TABLE 3 SEARCH STRING IN MEDLINE (PUBMED), APRIL 10TH

#	Search terms and word variations	Description	#citations
#1	Migraine Disorders[Mesh] OR migrain*[tiab]	Disease area	
#2	prophyl*[tiab] OR prevent*[tiab]		
#3	1 and 2	Treatment population	5,337
#4	fremanezumab[nm] OR fremanezumab[tiab] OR TEV-48125[tiab] OR Ajovy[tiab]	Intervention	
#5	propranolol[MeSH] OR propranolol[tiab]	Comparators for clinical question 1	
#6	metoprolol[MeSH] OR metoprolol[tiab] OR metoprololsuccinat*[tiab]		
#7	lisinopril[MeSH] OR lisinopril[tiab]		
#8	Candesartan cilexetil[nm] OR candesartan[nm] OR "candesartan cilexetil"[tiab] OR candesartan*[tiab]		
#9	Topiramate[MeSH] OR topiramat*[tiab]		
#10	amitriptyline[MeSH] OR amitriptylin*[tiab]	Comparators for clinical question 2	
#11	nortriptyline[MeSH] OR nortriptylin*[tiab]		
#12	Valproic Acid[MeSH] OR valproat*[tiab] OR valproic*[tiab]		
#13	Botulinum Toxins, Type A[MeSH] OR botulinum*[tiab] OR onabotulinum*[tiab]	Comparator clinical question 3	
#14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	All comparators	109,128
#15	3 and 14	Treatment population and all comparators	1,468
#16	randomized controlled trial[pt]	Cochrane RCT filter	1,153,089
#17	controlled clinical trial[pt]		
#18	randomized[tiab] OR randomised[tiab]		
#19	placebo[tiab]		
#20	clinical trials as topic[mesh:noexp]		
#21	randomly[tiab]		
#22	trial[ti]		
#23	16 or 17 or 18 or 19 or 20 or 21 or 22		
#24	animals[mh] NOT humans [mh]		
#25	23 not 24		
#26	#15 and #25	**Full search**	**561**

TABLE 4 SEARCH STRING IN CENTRAL (COCHRANE), APRIL 10TH

#	Search terms and word variations	Description	#citations
#1	[mh "Migraine Disorders"]	Disease area	
#2	migrain*:ti,ab,kw		
#3	(prophyl* or prevent*):ti,ab or prophylaxis:kw		
#4	(#1 or #2) and #3	Treatment population	1,977
#5	(fremanezumab or TEV-48125 or Ajovy):ti,ab,kw	Intervention	
#6	[mh Propranolol]	Comparators for clinical question 1	
#7	propranolol:ti,ab,kw		
#8	[mh Metoprolol]		
#9	metoprolol:ti,ab,kw		
#10	[mh Lisinopril]		
#11	lisinopril:ti,ab,kw		
#12	candesartan*:ti,ab,kw		
#13	topiramat*:ti,ab,kw		
#14	[mh Amitriptyline]	Comparators for clinical question 2	
#15	amitriptylin*:ti,ab,kw		
#16	[mh Nortriptyline]		
#17	nortriptylin*:ti,ab,kw		
#18	[mh "Valproic Acid"]		
#19	(valproic* or valproat*):ti,ab,kw		
#20	[mh "Botulinum Toxins, Type A"]	Comparators for clinical question 3	
#21	(botulinum* or onabotulinum*):ti,ab,kw		
#22	{or #5-#21}	All comparators	20,163
#23	#4 and #22	Treatment population and all comparators	698
#24	("conference abstract" or review):pt OR NCT*:au	Conference abstract filter	303,445
#25	#23 not #24	Treatment population and all comparators with conference abstract filter	498
#26	"Pubmed":an		1,532,625
#27	#25 not #26 in Trials	**Full search**	**189**

1.2 Relevant studies

Four studies are included for fremanezumab. These constitutes the HALO EM & CM trials, the two phase IIb trials of episodic and chronic migraine [22,29,34,59] and the phase IIIb trial FOCUS [30]. The studies are summarized in Table 5.

TABLE 5: RELEVANT STUDIES INCLUDED FOR FREMANEZUMAB

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Table number – main characteristics in appendix	Relevant for clinical question
	Fremanezumab				
Effect of fremanezumab compared with placebo for prevention of episodic migraine, Dodick et al., JAMA, 2018	*HALO EM*	*NCT02629861*	*Start: March 23, 2016* *Actual completion date: April 10, 2017*	*Table 29*	*1*
Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Bigal et al., Lancet Neurology, 2015	-	*NCT02025556*	*Start: January 2014* *Actual completion date: March 2015*	*Table 30*	*1*
Fremanezumab for the preventive treatment of chronic migraine. Silberstein et al., NEJM, 2017	*HALO CM*	*NCT02621931*	*Start: March 22, 2016* *Actual completion date: April 11, 2017*	*Table 31*	*1*
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	-	*NCT02021773*	*Start: January 2014* *Actual completion date: March 2015*	*Table 32*	*1*
Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomized, double-blind, placebocontrolled, phase 3b trial. Ferrari et al., Lancet, 2019	*FOCUS*	*NCT03308968*	*Start: October 2017* *Actual primary completion date: October 2018*	*Table 33*	*2 and 3*

TABLE 6 RELEVANT STUDIES INCLUDED FOR TOPIRAMATE

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Table number – main characteristics	Relevant for clinical question
	Topiramate				
Topiramate in migraine prevention: a double-blind, placebo-controlled study. Storey et al., Headache, 2001	-	*Not stated in publication*	-	*Table 34*	*1*
Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. Mei et al., Neurological sciences, 2004	-	*Not stated in publication*	-	*Table 35*	*1*
Topiramate in migraine prophylaxis - results from a placebo-controlled trial with propranolol as an active control. Diener et al., Journal of neurology, 2004	-	*Not stated in publication*	-	*Table 36*	*1*
Topiramate for migraine prevention: a randomized controlled trial. Brandes et al., JAMA, 2004	-	*Not stated in publication*	-	*Table 37*	*1*
Assessing the ability of topiramate to improve the daily activities of patients with migraine. Brandes et al., Mayo Clinic proceedings, 2006	-	*Not stated in publication*	*Start: March 1, 2001* *Actual completion date: April 4, 2002*	*Table 38*	*1*
Topiramate in migraine prevention: results of a large controlled trial. Silberstein et al., Archives of neurology, 2004	-	*Not stated in publication*	-	*Table 39*	*1*
The impact of migraine on daily activities: effect of topiramate compared with placebo. Silberstein et al., Current medical research and opinion, 2006	-	*Not stated in publication*	-	*Table 40*	*1*
Efficacy and tolerability of topiramate 200 mg/d in the	-	*Not stated in publication*	*Start: October 2000*	*Table 41*	*1*

prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. Silberstein et al., Clinical therapeutics, 2006			*Actual completion date: December 2001*		
Efficacy and Safety of Topiramate for the Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. Silberstein et al., Headache, 2007	*-*	*NCT00210912*	*Start: September 2003* *Actual completion date: April 2005*	*Table 42*	*1*
Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Silberstein et al., Headache, 2009	*-*	*NCT00210912*	*Start: September 2003* *Actual completion date: April 2005*	*Table 43*	*1*
Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Diener et al., Cephalalgia, 2007.	*-*	*NCT02639598*	*Start: November 10, 2003 Actual completion date: July 17, 2005*	*Table 44*	*1*
Topiramate intervention to prevent transformation of episodic migraine: The topiramate INTREPID study. Lipton et al., Cephalalgia, 2011	*INTREPID*	*NCT00212810*	*Start: September 2005. Actual completion date: August 2007*	*Table 45*	*1*

TABLE 7: RELEVANT STUDIES INCLUDED FOR CANDESARTAN

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Table number – main characteristics	Relevant for clinical question
	Candesartan				
Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. Tronvik et al., JAMA, 2003	-	*Not stated in publication*	*Start: January 2001* *Actual completion date: February, 2002*	*Table 46*	*1*
A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Stovner et al., Cephalalgia, 2014	-	*NCT00884663*	*Start: April 2009* *Actual completion date: March 2012*	*Table 47*	*1*

TABLE 8 RELEVANT STUDIES INCLUDED FOR LISINOPRIL

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Table number – main characteristics	Relevant for clinical question
	Lisinopril				
Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. Schrader et al., BMJ (Clinical research ed.), 2001	-	*Not stated in publication*	*Start: April 1998* *Actual completion date: December, 1999*	*Table 48*	*1*

TABLE 9 RELEVANT STUDIES INCLUDED FOR PROPRANOLOL

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Table number – main characteristics	Relevant for clinical question
	Propranolol				
Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group. Diener et al., Cephalalgia, 1996	-	*Not stated in publication*	-	*Table 49*	*1*
Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. Diener et al., Journal of neurology, 2004	-	*Not stated in publication*	-	*Table 50*	*1*
A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Stovner et al., Cephalalgia, 2014	-	*NCT00884663*	*Start: April, 2009* *Actual completion date: March, 2012*	*Table 51*	*1*

TABLE 10 RELEVANT STUDIES INCLUDED FOR VALPROATE

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Table number – main characteristics in appendix	Relevant for clinical question
	Valproate				
Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study. Jensen et al., Neurology, 1994	-	*Not stated in publication*	-	*Table 52*	2
Migraine Prophylaxis with Divalproex. Mathew et al., Arch Neurology, 1995.	-	*Not stated in publication*	-	*Table 53*	2
Divalproex sodium in migraine prophylaxis: a dose-controlled study. Klapper J., Cephalalgia, 1997.	-	*Not stated in publication*	-	*Table 54*	2
A randomised trial of divalproex sodium extended-release tablets in migraine prophylaxis. Freitag et al., 2002	-	*Not stated in publication*	-	*Table 55*	2

TABLE 11 RELEVANT STUDIES INCLUDED FOR AMITRIPTYLINE

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Table number – main characteristics	Relevant for clinical question
	Amitriptyline				
Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Couch et al., Headache, 2011	-	*Not stated in publication*	*Start 1977 Actual completion date: 1979*	*Table 56*	2
Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. Goncalves et al., Journal of neurology, neurosurgery, and psychiatry, 2016.	*EDUMAP*	*NCT01357031*	*Start: December 2011* *Actual completion date: December 2012*	*Table 57*	2

TABLE 12 RELEVANT STUDIES INCLUDED FOR BOTOX

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Table number – main characteristics in appendix	Relevant for clinical question
	Botox				
OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Aurora et al., Cephalalgia, 2010	*PREEMPT I*	*NCT00156910*	*Start: February 2006 Actual completion date: July 2008*	*Table 58*	*3*
OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Diener et al., Cephalalgia, 2010	*PREEMPT II*	*NCT00168428*	*Start: March 2006 Actual completion date: August 2008*	*Table 59*	*3*

TABLE 13 EXCLUDED STUDIES

Reference (title, author, journal, year)	Relevant for clinical question	Reasoning for exclusion
Excluded due to outcomes		
Propranolol		
Comparison of propranolol LA 80 mg and propranolol LA 160 mg in migraine prophylaxis: a placebo controlled study. al-Qassab HK & Findley LJ, Cephalalgia 1993	1	In this trial, an assessment was made of headache frequency, headache severity, duration of attacks of headache, nausea frequency, nausea severity, frequency of analgesics used, and frequency rescue medications. Adverse events were assessed by direct questioning and by the patients completing detailed questionnaires on each visit. Compliance was checked by measuring pulse and blood pressure during the various treatment periods. This trial did not report any outcome measures which is prespecified in the protocol.
Double blind study of propranolol for migraine prophylaxis. Diamond S & Medina JL, Headache, 1976	1	The recorded outcomes in terms of Headache Units, Relief Medication Units, Headache Index, Relief Medication Index, Headache Index Ratio, and Relief Medication Index Ratio. This trial did not report any outcomes measures which is prespecified in the protocol.
Propranolol for migraine prophylaxis. Forssman et al., Headache, 1976	1	In this trial, no outcome measures of interest were reported for the placebo arm. This trial did not report any outcome measures which is prespecified in the protocol.
Propranolol in acute migraine: a controlled study. Fuller GN & Guiloff RJ, Cephalalgia, 1990.	1	In this trial, the outcome measure was the response to treatment evaluated by no effect, poor, fair, good, or excellent. Also, the difference in score of headache severity and the duration of headache. These measures were evaluated with deterioration and improvement scores and duration in minutes, respectively. This trial did not report any outcome measures which is prespecified in the protocol.

Propranolol prophylaxis of migraine. Malvea et al., Headache, 1973	1	In this trial, the outcome measures were 1) final preference with propranolol, placebo or neither, 2) average headache units, 3) average symptomatic drugs, 4) adverse events are only reported for propranolol. This trial did not report any outcomes measures which is prespecified in the protocol.
Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. Pradalier et al., Cephalalgia, 1989	1	This trial did not report any outcome measures which is prespecified in the protocol.
Topiramate		
The Impact of Topiramate on Health-Related Quality of Life Indicators in Chronic Migraine. Dodick et al., Headache, 2007	1	For the relevant QoL outcome reported in this study, MSQ, no baseline or confidence intervals were reported. Thus, no absolute differences could be estimated.
Amitriptyline		
Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. Gomersall JD & Stuart A., 1973	2	This trial did not report any outcome measures which is prespecified in the protocol.
Metoprolol		
Symptoms of classic migraine attacks: modifications brought about by metoprolol. Hedman et al., Cephalalgia, 1988	1	In this trial, the outcome measures were 1) pain intensity (mild, moderate, severe), 2) mean intensity (1-3), global rating, duration, and analgesic consumption, 3) reporting of symptoms during migraine attacks, and 4) adverse events which was measured before and during headache. This trial did not report any outcome measures which is prespecified in the protocol.
Classic migraine: effective prophylaxis with metoprolol. Kangasniemi et al., Cephalalgia, 1987	1	This trial did not report any outcome measures which is prespecified in the protocol.
Excluded due to intervention/comparator		

Propranolol		
The prophylactic effect of timolol versus propranolol and placebo in common migraine: beta-blockers in migraine. Standness, B., Cephalalgia, 1982	1	The comparator in this trial is A: timolol 10 mg + propranolol placebo, B: propranolol 80 mg + timolol placebo, or C: timolol placebo + propranolol placebo. This trial is excluded as propranolol is not compared to placebo.
Excluded due to study design		
Metoprolol		
Metoprolol in the prophylaxis of migraine: parallel-groups comparison with placebo and dose-ranging follow-up. Steiner et al., Headache, 1988	1	The follow-up period in this trial is 8 weeks. Thus, this does not fulfill the prespecified follow-up period of at least 3 months (i.e. 12 weeks)
Prophylactic treatment of classical and non-classical migraine with metoprolol-a comparison with placebo. Andersson PG et al., Cephalalgia, 1983	1	The follow-up period in this trial is 8 weeks. Thus, this does not fulfill the prespecified follow-up period of at least 3 months (i.e. 12 weeks)
Botox		
OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Aurora et al., Acta neurologica Scandinavica, 2014	3	Excluded due to pooled data analysis.
Excluded due to population		
Valproate		
Sodium valproate in migraine without aura and medication overuse headache: a randomized controlled trial. Sarchielli P et al., European neuropsychopharmacology	2	Excluded due to the population which includes patients with medication overuse headache.

1.3 Main characteristics of included studies

The main characteristics for the 30 included studies are described in detail in Table 29 to Table 59 in appendix B (APPENDIX B: Main characteristics of included studies).

2 Data and methods

The following sections are descriptions of the methods used when processing data.

2.1 Endpoints

This analysis is comprised of comparisons made on both binary and continuous outcomes. The endpoints are classified as follows:

Binary:

- Frequency of migraine days: Proportion of patients who achieve ≥50% reduction in monthly migraine days
- Adverse events: Proportion of patients who experiences adverse events leading to discontinuation

Continuous:

- Frequency of migraine days: % reduction in monthly migraine days
- Quality of life: Point reduction in Headache Impact Test (HIT)-6 score, MIDAS or MSQ
- Severity of attacks: % reduction in number of days with any acute headache medication
- Adverse events: % reduction in monthly headache days

Quality of life measures

Some of the included studies use different measures than HIT-6 for quality of life (QoL), including MSQ and MIDAS scores. Only those studies which reported either HIT-6 or MIDAS were used in the analysis. Some of the studies also reported MSQ scores, however these were excluded from the main analysis and only assessed for heterogeneity as the MSQ score has three domains. Thus, the three domains were not comparable with the single outcome from HIT-6 and MIDAS.

If the QOL measures differed from HIT-6 for a particular comparison (i.e., both HIT-6 and MIDAS QOL scores were given), then the analysis was based on the standardized mean difference (SMD). The meta-analysis was performed on the SMD calculated for each study. The SMD from the ITC was converted to the preferred scale for the outcome measure; the HIT-6 scale. This conversion was performed using the pooled standard deviation used to standardize the mean of the included study in the ITC that used the HIT-6 questionnaire.

2.2 Pooling of doses for comparators

Where the endpoints for a comparator (i.e., any drugs apart from fremanezumab) were reported for more than one dose, estimates of the endpoints and their associated standard deviations were calculated for the overall treatment, across doses. Standard deviations for individual doses were therefore pooled across all doses using a weighted average.

For binary outcomes, the weighted average calculation is indicated in section 2.2.

For continuous outcomes, let $\bar{x}$ and s be the mean and standard deviation based on a sample of size n, and let the subscripts D1 and D2 denote the different doses for the treatment. For continuous endpoints the pooled sample mean was calculated by taking a weighted average of the individual sample means, i.e.

$$\bar{x}_{pooled} = \frac{(n_{D1} \times \bar{x}_{D1}) + (n_{D2} \times \bar{x}_{D2})}{n_{D1} + n_{D2}}.$$

2.3 Imputation of individual study results

The various studies that make up the individual data points in the data set do not necessarily report all outcome measures in a consistent fashion, i.e., some publications report a point estimate and standard error, while others report a 95% confidence interval. Consequently, an imputation step was required to ensure a consistent reporting format for all of the individual studies. The imputation of missing values for each of the statistics was performed as described in the following sections.

Note that for the binary outcomes, the imputed treatment effects and their confidence intervals (provided in the imputation excel spreadsheet) were calculated using the endpoints, whereas in the meta-analysis they were calculated using sample size and number of individuals experiencing the event of interest. If either the sample size or number of events were imputed, then there may be minor differences between the results imputed in the excel spreadsheet and the meta-analysis.

2.3.1 Imputation of sample size

For results with a missing sample size, where the proportion ($\hat{p}$) and the total number experiencing the event of interest (X) are given, the sample size can be computed as of $\frac{X}{\hat{p}}$ rounded to the nearest whole number.

2.3.2 Imputation of number of patients experiencing event

For results with a missing number of patients experiencing the event of interest (X), where the proportion ($\hat{p}$) and sample size (n) are given, the number of patients experiencing the event of interest can be calculated as $n \times \hat{p}$ rounded to the nearest whole number.

2.3.3 Imputation of endpoints

Continuous endpoints will be summarized by a sample mean, while binary endpoints will be summarized by a sample proportion.

I. If a confidence interval is reported in the absence of a point estimate, then the point estimate can be calculated as the midpoint of the confidence interval. This is applicable to the calculation of point estimates for both binary and continuous endpoints. Let LCL and UCL represent the lower and upper limits of the confidence interval respectively. The point estimate can then be calculated as:

$$point\ estimate = \frac{\text{UCL+LCL}}{2}.$$

II. Continuous endpoints may be imputed from the baseline and end of study with point estimate calculated as the difference in the sample means, i.e.:

$$\bar{x}_{endpoint} = \bar{x}_{EOS} - \bar{x}_{baseline} \ .$$

The standard deviation of the endpoint will be computed as the square-root of the sum of the variances for the baseline and end of study measurements as:

$$s_{endpoint} = \sqrt{s_{EOS}^2 + s_{baseline}^2} \ .$$

Note that the true standard deviation of the difference will be smaller than this calculation; this is a conservative method as the standard deviation is also affected by the covariance between the baseline and end of study measurements, and data on this covariance is not available. If the standard deviation is not available, it may be imputed as:

$$s = \sqrt{\boldsymbol{n}} \times SE(\bar{x}) \ .$$

III. For a binary endpoint, if the number of subjects with an event, *X,* and the sample size, *n,* are reported then the point estimate (sample proportion, $\hat{p}$) can be imputed as:

$$\hat{p} = \frac{X}{n} \ .$$

IV. For continuous endpoints, the $SE(\bar{x})$ can be imputed using the standard deviation, *s,* if reported as:

$$SE(\bar{x}) = \frac{\boldsymbol{s}}{\sqrt{\boldsymbol{n}}} \ .$$

If instead a 95% confidence interval is reported in the absence of the standard deviation, then the $SE(\bar{x})$ can be imputed as:

$$SE(\bar{x}) = \frac{\text{UCL+LCL}}{2*1.96} \ .$$

2.3.4 Imputation of confidence interval for endpoints

For continuous endpoints the 95% confidence interval for the endpoint will be calculated as:

$$\bar{x} \pm 1.96 \times SE(\bar{x}).$$

For binary endpoints the 95% confidence interval for the endpoint will be calculated as:

$$\hat{p} \pm 1.96 \times \sqrt{\frac{\hat{p} \times (1-\hat{p})}{n}}.$$

If the number of events is less than 5, then the confidence interval for the endpoint will be calculated using the exact Clopper-Pearson method.

2.3.5 Imputation of Relative Effects

Absolute effect point estimate

For continuous endpoints, the point estimate of the absolute effect will be calculated as the mean difference between the placebo and treatment groups, calculated as:

$$\bar{x}_{effect} = \bar{x}_{trt} - \bar{x}_{placebo} \ .$$

For binary endpoints, the point estimate of the absolute effect will be calculated by the difference between the sample proportions experiencing the event for the placebo and treatment groups, calculated as:

$$\hat{P}_{effect} = \hat{P}_{trt} - \hat{P}_{placebo} \ .$$

Absolute effect confidence interval:

For continuous endpoints the confidence interval for the absolute effect will be calculated under the assumption of normality:

$$\left(\bar{x}_{trt} - \bar{x}_{placebo}\right) \pm 1.96\, SE\left(\bar{x}_{trt} - \bar{x}_{placebo}\right)$$

Where,

$$SE\left(\bar{x}_{trt} - \bar{x}_{placebo}\right) = \sqrt{\frac{s_{Trt}^2}{n_{Trt}} + \frac{s_{Placebo}^2}{n_{Placebo}}} = \sqrt{SE(\bar{x}_{trt})^2 + SE\left(\bar{x}_{placebo}\right)^2} \ .$$

For binary endpoints the confidence interval for the absolute effect will be calculated

as defined in the meta package for R [60]:

$$\left(\hat{p}_{trt} - \hat{p}_{placebo}\right) \pm 1.96 \sqrt{\frac{(X_{trt}+\mathrm{q}) * ((n_{trt}-X_{trt})+\mathrm{q})}{(n_{trt}+(2*\mathrm{q}))^3} + \frac{(X_{placebo}+\mathrm{q}) * ((n_{placebo}-X_{placebo})+\mathrm{q})}{(n_{placebo}+(2*\mathrm{q}))^3}},$$

where q is an increment that takes on a value of 0.5 if any of the counts of individuals with an event are 0 (X_{trt} *or* $X_{placebo}$) and 0 otherwise.

Absolute effect p-value:

For continuous endpoints, the p-value for the absolute effect will be taken as the p-value testing the mean difference between the placebo and treatment groups is equal to zero, against the two sided alternative. The test statistic will calculated assuming normality as:

$$z = \frac{\bar{x}_{trt} - \bar{x}_{placebo}}{SE\left(\bar{x}_{trt} - \bar{x}_{placebo}\right)} \ .$$

For binary endpoints, the p-value for the absolute effect will be the p-value resulting from the hypothesis test testing the equivalence of the sample proportions for the placebo and treatment groups against the tow sided alternative. The test statistic will be calculated using the normal approximation to the binomial distribution as:

$$z = \frac{\hat{p}_{trt} - \hat{p}_{placebo}}{\sqrt{(\hat{p})(1 - \hat{p}) \times \left(\frac{1}{n_{trt}} + \frac{1}{n_{placebo}}\right)}} \ ,$$

where $\hat{p}$ is the pooled sample proportion calculated over the placebo and treatment groups found by:

$$\hat{p} = \frac{X_{placebo} + X_{trt}}{n_{placebo} + n_{trt}}$$

Relative effect point estimate

For continuous endpoints there is no measure of relative effect. Consequently, these will not be reported.

For binary endpoints the measure of relative effect will be calculated as the relative risk (RR) of the event between the placebo and treatment groups calculated as defined in the meta package [60]:

$$RR = \left(\frac{\frac{X_{trt} + \mathrm{q}}{n_{trt} + \mathrm{q}}}{\frac{X_{placebo} + \mathrm{q}}{n_{placebo} + \mathrm{q}}} \right),$$

where q is an increment that takes on a value of 0.5 if any of the counts of individuals with an event are 0 (X_{trt} *or* $X_{placebo}$) and 0 otherwise.

Relative effect 95% confidence interval

The confidence interval for the RR will be calculated on the log scale and then back transformed to the original scale. The confidence interval on the log scale will be calculated as:

$$\log(RR) \pm SE(\log(RR)) \times 1.96,$$

where the standard error is calculated as defined in the meta package [60]:

$$SE(\log(RR)) = \sqrt{\frac{1}{X_{placebo} + \mathrm{q}} + \frac{1}{X_{trt} + \mathrm{q}} - \frac{1}{n_{placebo} + \mathrm{q}} - \frac{1}{n_{trt} + \mathrm{q}}},$$

where q is an increment that takes on a value of 0.5 if any of the counts of individuals with an event are 0 (X_{trt} *or* $X_{placebo}$) and 0 otherwise.

Relative effect p-value

The p-value for the RR will be calculated for the hypothesis test that the log(RR) is equal to zero, against the two sided alternative. The test statistic will be calculated as:

$$z = \frac{\log(RR) - 0}{SE(\log(RR))}.$$

2.4 Meta-analysis and indirect treatment comparison

2.4.1 Meta-analysis

For each study, the treatment effect can be expressed as T_{AB}, where A represents the treatment and B represents placebo. For continuous outcomes, T_{AB} is the mean difference. For binary outcomes, T_{AB} is the difference in the sample proportions (risk difference) and the relative risk (RR). For each study, T_{AB} was either extracted from publication or imputed (see section 2.3 for more detail).

Where there was more than one study comparing a treatment to placebo, a meta-analysis was used to calculate a common estimate of the treatment effect ($\hat{T}_{AB}$), using both a fixed and random effect model. If however there was only one study comparing a treatment to placebo, T_{AB} was taken to be that individual study.

2.4.2 Indirect treatment comparison

An indirect treatment comparison (ITC) was then performed using the Bucher method [61] to compare fremanezumab (monthly and quarterly) to each of the comparator treatment (where applicable), via the common comparator, placebo.

For example, comparing fremanezumab quarterly to topiramate, we used meta-analysis to obtain a common treatment comparison for each treatment to placebo, $\hat{T}_{AB}$ and $\hat{T}_{CB}$, where A represents fremanezumab quarterly, C represents topiramate, and B represents placebo. Using the Bucher method [61], we then obtained the treatment effect of fremanezumab quarterly compared to topiramate using the following equation:

$$\hat{T}_{AC} = \hat{T}_{AB} - \hat{T}_{CB}$$

The variance of the indirect estimate of the treatment effect was then calculated as the sum of the variances of the direct estimates,

$$variance_{AC} = variance_{AB} + variance_{CB}$$

And the 95% two-tailed confidence intervals were calculated as,

$$\hat{T}_{AC} \pm Z_{0.975}\sqrt{variance_{AC}}$$

Where $Z_{0.975}$ is the 97.5% quantile of the standard normal distribution, which is equal to 1.96. Note that for relative effects (i.e., relative risk) the Bucher method was performed on the logarithmic scale, and back-transformed to the raw scale.

2.4.3 Percent reduction from baseline

For each continuous outcome, the endpoint measure is the change from baseline. Following the ITC, these outcomes were converted to the percentage reduction (% reduction) as follows;

$$\left(\frac{\bar{X}}{ER}\right) * 100\%$$

Where $\bar{X}$ is the estimated treatment effect, lower confidence limit or upper confidence limit, calculated from the ITC, and ER is the median of the observed event rates in the comparator group of the included studies.

2.4.4 Conversion of relative risk to risk difference

For binary outcomes, the meta-analysis and indirect treatment comparisons were performed on the RR. Estimates of the risk difference (RD), and its associated confidence interval, were calculated from the relative risk as:

$$RD = ACR \times RR - ACR,$$

where ACR is an assumed control group rate. The ACR was calculated as the median event rate (sample proportion) of the placebo groups for all included studies.

For the meta-analysis, the ACR was calculated across the placebo groups of all studies included in the analysis of a given treatment. For the ITC, the ACR for each indirect comparison of two treatments was calculated across the placebo groups of the studies included. The ACRs used for each analysis are reported as a column in the raw results file.

2.5 Heterogeneity

For each treatment comparison informed by two or more studies, the heterogeneity was assessed using the I^2 statistic, which estimated the percentage of variation across studies that is due to heterogeneity. Forest plots were produced to illustrate the variation in treatment differences across studies, with the I^2 statistic given in the plots.

Heterogeneity was also assessed for the MSQ score results for the QOL outcome in Clinical Question 1, which were excluded from the main analysis. Each domain (RP domain, EF domain, RR domain) was analysed separately. The results were plotted in forest plots to compare between studies.

2.6 Software

All data imputation and statistical analysis was performed using R statistical software [62]. The meta-analysis was carried out using the 'meta' package in R [60].

2.7 Interpretation of ITC results

A summary of the interpretation of the treatment comparison for each outcome is shown in

Table 14.

TABLE 14 INTERPRETATION OF INDIRECT TREATMENT COMPARISONS BY OUTCOME

Outcome	Measure	ITC Estimate	Interpretation
Proportion >= 50% reduction in monthly migraines	RD	*RD > 0*	*favours Fremanezumab treatment*
		RD = 0	*No difference between treatments*
		RD < 0	*favours comparator treatment*
	RR	*RR > 1*	*favours Fremanezumab treatment*
		RR = 1	*No difference between treatments*
		RR < 1	*favours comparator treatment*
Proportion of patients who experience AEs leading to discontinuation	RD	*RD > 0*	*favours comparator treatment*
		PD = 0	*No difference between treatments*
		RD < 0	*favours Fremanezumab treatment*
	RR	*RR > 1*	*favours comparator treatment*
		RR = 1	*No difference between treatments*
		RR < 1	*favours Fremanezumab treatment*
% reduction in monthly migraine days	MD	MD > 0	*favours comparator treatment*
		MD = 0	*No difference between treatments*
		MD < 0	*favours Fremanezumab treatment*
% reduction in quality of life; HIT-6 score	MD	MD > 0	*favours comparator treatment*
		MD = 0	*No difference between treatments*
		MD < 0	*favours Fremanezumab treatment*
% reduction in number of days with any acute headache medication	MD	MD > 0	*favours comparator treatment*
		MD = 0	*No difference between treatments*
		MD < 0	*favours Fremanezumab treatment*
% reduction in monthly headache days	MD	MD > 0	*favours comparator treatment*
		MD = 0	*No difference between treatments*
		MD < 0	*favours Fremanezumab treatment*

RD: Risk difference; RR: risk ratio; MD: Mean difference

3 Clinical questions

According to the protocol for the assessment of the added clinical value of fremanezumab in the prophylactic treatment of migraine, results in the final application should answer the clinical questions and be relevant for the populations described. Table 15 provides an overview of the requested outcomes that should be presented per study whenever possible.

TABLE 15 OUTCOMES REQUESTED TO BE USED IN THE ASSESSMENT OF ADDED CLINICAL VALUE OF FREMANEZUMAB.

Outcome	Results requested
Requested for both episodic and chronic migraine	
Migraine days	Reduction (%) of monthly migraine days
	Proportion of patient population who achieve ≥50% reduction in monthly migraine days
Quality of life	Mean change from baseline in HIT-6 or alternatively MSQ/MIDAS
Use of acute headache medication	Reduction (%) in days with acute headache medication use
Adverse events	Proportion of patients who experience adverse events leading to treatment discontinuation
	Qualitative review of adverse events
Requested for chronic migraine	
Headache days	Percentage reduction of monthly headache days

3.1 Clinical question 1: Hvad er den kliniske merværdi af fremanezumab til patienter med migræne, der har mindst fire migrænedage pr. måned sammenlignet med eksisterende standardbehandling?

3.1.1 Presentation of relevant studies

See Table 16 for an overview of included studies and its associated population and follow-up time. Note, large differences exist.

TABLE 16 OVERVIEW OF INCLUDED STUDIES AND FOLLOW-UP TIME

Clinical question 1	
Study	**Follow-up time**
HALO EM, Dodick et al., 2018	12 weeks
Fremanezumab EM, Bigal et al., 2015	12 weeks
HALO CM, Silberstein et al., 2017	12 weeks
Fremanezumab CM, Bigal et al., 2015	12 weeks
Topiramate EM+CM, Storey et al., 2001	16 weeks
Topiramate EM+CM, Mei et al., 2004	16 weeks
Topiramate EM, Diener et al., 2004	26 weeks
Topiramate EM, Brandes et al., 2004	26 weeks
Topiramate EM, Brandes et al., 2006	26 weeks
Topiramate EM+CM, Silberstein et al., 2004	26 weeks
Topiramate EM+CM, Silberstein et al., 2006	26 weeks
Topiramate EM+CM, Silberstein et al., 2006	20 weeks
Topiramate EM+CM, Silberstein et al., 2007	12 weeks
Topiramate EM+CM, Dodick et al., 2007	12 weeks
Topiramate CM, Diener et al., 2007	16 weeks
Topiramate CM, Silberstein et al., 2009	16 weeks
Topiramate EM, Lipton et al., 2011	26 weeks
Candesartan EM, Tronvik et al., 2003	12 weeks
Candesartan EM+CM, Stovner et al., 2014	12 weeks
Lisinopril EM+CM, Schrader et al., 2001	12 weeks
Propranolol EM, Diener et al., 1996	20 weeks
Propranolol EM, Diener et al., 2004	26 weeks
Propranolol EM+CM, Stovner et al., 2014	12 weeks

Fremanezumab

3.1.1.1 *Dodick et al, 2018 (Phase III HALO EM)*

HALO EM was a multicenter, double-blind, randomized, placebo-controlled, parallel-group phase III trial comparing the efficacy and safety of two dose regimens of fremanezumab versus placebo for prevention of episodic migraine. Study participants included women and men aged 18 to 70 with a history of migraine according to the *International Classification of Headache Disorders* 3 beta version (*ICHD*-3 beta) diagnostic criteria for at least 12 months prior to screening and with onset prior to age 50 years. Patients were required to have episodic migraine based on information collected during a 28-day pretreatment baseline period and defined as a headache occurring on day 6 to 14, with at least 4 days fulfilling ICHD-3 beta criteria for migraine with aura (code 1.2; B and C) or without aura (code 1.1; C and D), probable migraine, or use of triptans or ergot derivatives. [63,64]

Subjects (n=875) were randomized 1:1:1 into two experimental arms and one placebo arm with a treatment period of 12 weeks. The study period consisted of a screening visit, a 28-day preintervention period, and a 12-week intervention period, with a final evaluation at week 12. Patients received monthly dosing of fremanezumab (225mg at baseline, week 4, and week 8); a single higher dose of fremanezumab, as intended to support a quarterly dose regimen (675mg of fremanezumab at baseline; placebo at weeks 4 and 8); or placebo (at baseline, week 4, and week 8). 291 patients were in the fremanezumab quarterly trial group, whereas 290 and 294 patients were in the fremanezumab monthly and placebo trial group, respectively. [64]

Migraine days

The primary end point was the mean change from baseline (28-day pretreatment period) in the mean number ofmonthly migraine days during the 12-week period after the first injection. A migraine day was defined as a calendar daywith either at least 2 consecutive hours of a headache meeting criteria for migraine (with orwithout aura); probable migraine (only 1 migraine criterion absent); or a day, regardless of duration, when acute migraine-specific medication (triptans or ergots) was used to treat a headache.

Secondary efficacy end points included the proportion of patients achieving at least a 50% reduction in the mean number of monthly migraine days from baseline to week 12, the mean change from baseline to week 12 in the monthly mean number of monthly days with use of any acute headache medications, the mean change from baseline to week 4 in the number of migraine days, the mean change from baseline to week 12 in mean number of monthly migraine days in patients not receiving concomitant migraine preventive medication, and the mean change in the Migraine Disability Assessment (MIDAS) score.

Quaity of life

The MIDAS questionnaire assesses headache-related disability based on lost days of activity over the previous 3 months; possible scores range from 0 to 270, with 0 to 5 indicating little or no disability; 6 to 10, mild disability; 11 to 20, moderate disability; and 21 or higher, severe disability.

Adverse Events

Adverse events and tolerability were assessed by evaluating reported adverse events, vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate), 12-lead electrocardiogram, clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis), physical examinations, and concomitant medication use.

3.1.1.2 *Bigal et al, 2015 (Phase IIb EM)*

Between Jan 8, 2014, and Oct 15, 2014, 297 participants were enrolled: 104 were randomly assigned to receive placebo, 95 to receive 225 mg TEV-48125, and 96 to receive 675 mg TEV-48125.

Patients reported headache information daily using an electronic diary. Primary endpoints were change from baseline in migraine days during the third treatment cycle (weeks 9-12) and safety and tolerability. The secondary endpoint was change relative to baseline in headache-days during weeks 9-12. Efficacy endpoints were analyzed for the intention-to-treat population. Safety and tolerability were analyzed using descriptive statistics.

Migraine days

The primary efficacy endpoint was the mean decrease from baseline in the number of days fulfilling criteria for migraine during the third treatment cycle (weeks 9–12). A migraine-day was defined as a day on which migraine with aura, migraine without aura, or probable migraine occurred. In accordance with the ICHD-3, the minimum duration of a migraine-day was 4 h unless a triptan or drug containing ergotamine was used, in which case we specified no minimum duration.

The secondary endpoint was the mean decrease from baseline in the number of headache-days of any severity during the third treatment cycle (week 9–12). As part of the prespecified statistical analysis plan, primary and secondary parameters were also measured after the first and second treatment cycles (weeks 1–4 and weeks 5–8). A-priori defined exploratory endpoints included change in the consumption of headache acute drugs, change in the number of headache-hours of any severity, change in the number of days with nausea or vomiting, change in the number of days with photophobia and phonophobia, change in the number of headache-hours of at least moderate severity, and change in the number of headache days reaching at least moderate or severe intensity, and change in disability from baseline during any treatment cycle. In post-hoc analyses, we examined the proportion of patients achieving at least 50% and 75% decrease in the number of migraine-days relative to baseline.

Quality of life

The last clinical visit took place 28 days after the final drug administration (week 12), during which MIDAS was used to assess disability. MIDAS was used at pretreatment and after the last treatment.

3.1.1.3 *Silberstein et al, 2017 (Phase III HALO CM)*

HALO CM was a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial comparing the efficacy and safety of two dose regimens of fremanezumab versus placebo for prevention of chronic migraine. Key inclusion criteria were an age of 18 to 70, a history of migraine according to the criteria of the ICHD-3 beta for at least 12 months, and the fulfillment of the criteria for chronic migraine during the 28-day preintervention period (headache of any duration or severity on ≥15 days and headache meeting ICHD-3 beta criteria for migraine on ≥8 days). The study protocol allowed inclusion of up to 30% of patients using a stable dose of one migraine-preventive medication (hereafter referred to as preventive medication) for at least 2 months before the beginning of the preintervention period to continue these medications. [23]

Subjects (n=1,130) were randomized 1:1:1 into two experimental arms and one placebo arm with a treatment period of 12 weeks. The study period consisted of a screening visit, a 28-day preintervention period, and a 12-week intervention period, with a final evaluation at week 12. Patients received monthly dosing of fremanezumab (675mg at baseline, 225mg at week 4 and week 8); quarterly dosing of fremanezumab (675

mg at baseline and placebo at weeks 4 and 8); or placebo (at baseline, week 4, and week 8). 376 patients were in the fremanezumab quarterly trial group, whereas 379 and 375 patients were in the fremanezumab monthly and placebo trial group, respectively. [23]

Migraine days

The primary end point was the mean change in the average number of headache days (days in which headache pain lasted ≥4 consecutive hours and had a peak severity of at least a moderate level or days in which acute migraine–specific medication [triptans or ergots] was used to treat a headache of any severity or duration) 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 and 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. A migraine day was defined as a calendar day in which headache pain lasted at least 4 consecutive hours and met criteria for migraine (with or without aura) or probable migraine (subtype in which only one migraine criterion is absent), or a day in which acute migraine–specific medication (triptans or ergots) was used to treat a headache of any duration. Other secondary end points included 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.

Quality of life

The mean change in the score on the six-item HIT-6 (scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability) from baseline (day 0) to 4 weeks after administration of the last dose of the trial regimen.

Adverse Events

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 behavior as assessed by means of scores on the electronic Columbia–Suicide Severity Rating Scale.

3.1.1.4 *Bigal et al, 2015 (Phase IIb CM)*

Between Jan 8, 2014, and Aug 27, 2014, 264 participants were enrolled: 89 were randomly assigned to receive placebo, 88 to receive 675/225 mg TEV-48125, and 87 to receive 900 mg TEV-48125. Note that the dose of 900 mg of fremanezumab is excluded in the analysis in this application according to the dosages of fremanezumab provided in the protocol by Medicinrådet.

Migraine days

The primary efficacy endpoint was the mean change relative to baseline in the number of headache-hours of any severity during the third treatment cycle (weeks 9–12). As part of the prespecified statistical analysis plan (SAP), headache-hours were also measured during the first and second treatment cycles.

The secondary endpoint was the mean change from baseline in the number of headache-days of at least moderate severity during the third treatment cycle relative to baseline.

The number of headache-days of at least moderate severity was also assessed during the first and second treatment cycles. A-priori defined exploratory efficacy endpoints included decreases in the following parameters during the third treatment cycle, ending at week 12: headache hours of moderate severity; headache-days of any severity; migraine-days; and days with consumption of acute headache drugs (including triptans and other analgesics). As part of the prespecified SAP analyses, these same endpoints were measured during the first and second treatment cycles. In accordance with FDA regulatory precedence, migraine-days and headache-days required at least 4 consecutive hours of headache or the use of specific acute migraine drugs (triptans or ergotamine compounds).

Topiramate

3.1.1.5 *Storey et al, 2001*

The objective of this study was to evaluate the efficacy of topiramate in the preventative treatment of episodic migraine.

Adverse Events

At each study visit, migraine diaries were reviewed. An interim history, review of concomitant medications, and a report of any adverse events, including changes in body weight, were completed. Vital signs were recorded, and a brief neurologic examination was performed. Patients were encouraged to report treatment-emergent adverse events, spontaneously or in response to general, nondirected questioning. Symptoms associated with and occurring in conjunction with a migraine episode (e.g., nausea, photophobia) were not reported as adverse events.

3.1.1.6 *Mei et al, 2004*

The objectives of this paper are to evaluate the efficacy and tolerability of topiramate, given at the dose of 100 mg/day, in the prophylactic treatment of migraine.

Adverse Events

Drug tolerability was measured in terms of adverse events. Adverse events were reported for topiramate drop-outs, placebo drop-outs, topiramate treatment and placebo treatment. Method of obtaining adverse event information was not specified in this publication.

3.1.1.7 *Diener et al, 2004*

This study is a randomized, doubleblind, multicentre trial seeking to evaluate the efficacy and safety of two doses of topiramate vs placebo for migraine prophylaxis, with propranolol as an active control. Subjects with episodic migraine with and without aura were randomized to topiramate 100 mg/d, topiramate 200 mg/d, propranolol 160 mg/d (active control), or placebo.

Migraine days

The primary efficacy measure was the change in mean monthly migraine frequency from the baseline phase relative to the double–blind treatment phase.

The primary efficacy endpoint, change in average monthly migraine frequency (based on migraine periods), was analyzed using a linear model with baseline value as a covariate and analysis centre and treatment as factors. The least squares mean, were used to compare treatment groups. Treatment comparisons between the topiramate groups and placebo were assessed using a step-down procedure where, at each step, the Tukey-Ciminera-Heyse trend test was performed.

The following endpoints were included in the secondary efficacy evaluation:

1. change in number of migraine days per month
2. change in the average monthly rate of rescue medication use in days

The linear and unadjusted pairwise comparisons were used to analyze the secondary efficacy endpoints of change in rate of average monthly migraine days and average rate of rescue medication use.

Adverse events

Safety was evaluated on the basis of treatment-emergent adverse events (including abnormal findings in physical examinations) and changes in clinical laboratory tests, vital signs, body weight, and neurologic examination findings.

3.1.1.8 *Brandes et al, 2004*

The objective of this study was to assess the efficacy and safety of topiramate for migraine prevention in a large controlled trial (n = 468).

Migraine days

Relevant secondary efficacy measures were

- reductions in mean number of monthly migraine days
- severity, duration, and days a month requiring rescue medication
- adverse events

For all secondary variables and migraine frequencies during cumulative monthly periods, comparisons of each topiramate group with placebo were analyzed with pairwise comparisons, and nominal P values are given. The proportions of patients responding to treatment were analyzed with the Cochran-Mantel-Haenszel test stratified by analysis center. All other secondary variables were based on linear models. Estimates of various treatment effects and their graphical depictions are based on the treatments' least squares mean, which are the means adjusted for the variables in the statistical model. Analyses were done with SAS (version 6.12; SAS Institute Inc, Cary, NC) at a significance level of .05.

Use of acute headache medication

During the baseline phase, patients were permitted to take rescue medication. This continuous efficacy endpoint variable was based on linear models.

Adverse events

Adverse events during the study were recorded and followed up until resolved or until a clinically stable end point was achieved. This continuous efficacy endpoint variable was based on linear models.

3.1.1.9 *Brandes et al, 2006*

Brandes et al. performed a randomized, double-blind, placebo-controlled multicenter trial Initiated on March 1, 2001, and completed on April 4, 2002.

Quality of life

Patient-reported data from the Migraine Specific Questionnaire (MSQ) and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) were collected at baseline and at weeks 8, 16, and 26 from an intent-to-treat population receiving either topiramate, 50, 100, or 200 mg/d, or placebo. Two activity-related MSQ domains (role restrictive [MSQ-RR] and role prevention [MSQ-RP]) and 2 activity-related SF-36 domains (role physical [SF36-RP] and vitality [SF36-VT]) were the prospectively designated secondary outcome measures. The changes in MSQ and SF-36 scores for each treatment group were calculated by measuring the area under the curve from week 8 (the beginning of the maintenance period) through week 26 of the double-blind phase, relative to the prospective baseline. A mixed-effect piecewise linear regression model was used to estimate average domain score over time.

3.1.1.10 *Silberstein et al, 2004*

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter US study. Topiramate at 50, 100, or 200 mg/d or matching placebo was given for a 26-week total treatment period. Enrolled patients had an established history (≥6 months) of migraine with or without aura (International Headache Society criteria).

Migraine days

The secondary end points relevant to this analysis were mean change in migraine days per month and mean change in rescue medication days per month. Key secondary efficacy measures were analyzed using the same linear model, and unadjusted pairwise comparisons were made between placebo and each topiramate group. Efficacy analyses were conducted on the intent-to-treat population, which was defined as those randomized patients who had at least 1 postbaseline efficacy assessment. For subjects discontinuing the study early, the average monthly migraine period rate was computed based on the migraine periods observed before discontinuation.

Adverse Events

Safety was assessed by AE occurrence, physical and neurologic examinations, and clinical laboratory tests. Adverse events were recorded after study medication was initiated and were followed up until resolved or at a clinically stable end point. Clinical laboratory tests were performed at selected intervals throughout the 26-week study.

3.1.1.11 *Silberstein et al, 2006*

The primary objective of this paper was to utilize both the MSQ and the SF-36 to assess the impact of topiramate, a migraine preventive therapy, on the daily activities of patients with migraine. MSQ and SF-36 data were collected during a large 26-week randomized, double-blind, placebo-controlled trial (MIGR-001), which was conducted in order to assess the efficacy and tolerability of topiramate for migraine prevention.

Quality of life

MSQ and SF-36 data were collected during (at baseline and weeks 8, 16, and 26) a large 26-week, randomized, double-blind, placebo controlled trial that was statistically powered to detect changes in the primary efficacy outcome measure (change in mean monthly migraine frequency). The 14-item MSQ (version 2.1) is divided

into the role restrictive (RR), role prevention (RP), and emotional function (EF) domains, each of which is scored from 0 to 100, with higher scores indicating better functioning. The changes in MSQ and SF-36 scores during the double-blind phase relative to prospective baseline scores were compared between intent-to-treat (ITT) patients receiving topiramate or placebo.

The changes in MSQ and SF-36 scores for each treatment group were calculated by measuring the area under the curve (AUC) from week 8 (the beginning of the maintenance period) through week 26 of the double-blind phase, relative to the prospective baseline. A mixed-effects model with piecewise linear regression, which took into account variations in the availability of MSQ and SF-36 data throughout the double-blind phase, was used to assess between-group differences in the prospectively designated MSQ and SF-36 outcome scores.

3.1.1.12 *Silberstein et al, 2006 (pilot study)*

This paper evaluates efficacy and safety data from a randomized, double-blind, placebo-controlled pilot study of topiramate 200 mg/d as preventive therapy in adults having a history of migraine with or without aura. This trial was initiated before the 3 pivotal trials. Efficacy evaluations were based on information in the subjects' headache records. An algorithm based on International Headache Society criteria [65] was used to classify the headaches in each headache record as aura only, migraine with aura, migraine without aura, or nonmigraine headache.

In this study, the change in mean monthly (28 day) migraine frequency was reported, not the mean monthly days. The assessment of responder rate was based on migraine frequency. As the protocol states monthly migraine *days* these two efficacy outcomes were not included.

Adverse events

Safety assessments included measurement of vital signs, physical examinations, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), and evaluation of adverse events (AEs). AE data were collected by interviewing subjects in a nondirected manner at each visit. The investigator, who was blinded to treatment assignment, evaluated the relationship of each AE to study treatment.

3.1.1.13 *Silberstein et al, 2007*

The objective was to evaluate efficacy and safety of topiramate (100 mg/day) compared with placebo for the treatment of chronic migraine.

Migraine days

The primary efficacy endpoint was the change from baseline in the mean monthly number of migraine/migrainous days. The change in the mean monthly number of migraine days was also analyzed. In this study, chronic migraine was defined as the presence of at least 15 headache days per 28 days, of which at least half were migraine (International Headache Society; HIS 1.1 or 1.2) or migrainous headache.

If statistical significance was achieved, then the change in the mean monthly rate of migraine days could also be tested at the 2-sided 0.05 level. If significance again was achieved, then statistical significance would be declared at the 2-sided 0.05 level for both measures. If significance on the migraine/migrainous parameter was not achieved, then the formal testing procedure ended.

Adverse Events

Safety measures included measurement of vital signs, serial physical and brief neurologic examinations, and clinical laboratory parameters (hematology, chemistry, and urinalysis). Spontaneously reported adverse events were recorded at each visit.

3.1.1.14 *Silberstein et al, 2009*

The study previously reported that topiramate 100 mg per day produced a statistically significant reduction in mean monthly migraine/migrainous and migraine headache days compared with placebo treatment and that it was safe and generally well tolerated.

Migraine days

Subjects who experienced at least 15 headache days over the 28-day prospective baseline period and on at least half of these days experienced migraine headache (with or without aura: International Headache Society 1.1 or 1.2) or migrainous headache were randomized (1:1) to topiramate (target dose 100 mg. daily) vs placebo. [65][66]. To be eligible for participation, subjects also were required to have a baseline MIDAS score of at least 11 [67]. The treatment phase lasted 16 weeks and was followed by a taper/exit period that lasted up to 2 weeks.

Relevant secondary efficacy measures were

- Categorical response rate based on monthly migraine/migrainous, migraine, and total headache days. The categorical response was defined as the percentage of subjects with increase, no change, or >25%, >50%, or >75 reduction from baseline in mean monthly number of migraine/migrainous, migraine, and total headache days.
- Change in number of days per month requiring acute headache medication for all headache types.

The proportions of subjects in the response categories for reductions of migraine, migraine/migrainous and total headache days, and PGIC and SGIC were analyzed using the Cochran-Mantel-Haenszel test, stratified by center. The P values for the response rates, but not percent, were the result of a post hoc analysis.

Quality of life

MSQ was used to evaluate indicators of HRQoL relevant to migraine. Scores for each of the 3 domains assessed were normalized to a range from 0 to 100, with higher scores indicating better HRQoL. Changes from baseline to the final evaluations in scores on each MSQ domain (Role Function-Restrictive [RR], Role Function-Preventive [RP], and Emotional Function [EF]) were analyzed separately using the ANCOVA model, with treatment and center as qualitative independent factors and baseline value as a covariate.

MIDAS was used to evaluate headache-related disability. Changes from baseline to the final evaluations in MIDAS scores were analyzed using the ANCOVA model, with treatment and center as qualitative independent factors and baseline value as a covariate. In addition, the changes were categorized as “Worse,” “No Change,” and “Improved” and analyzed using the Cochran-Mantel-Haenszel test, stratified by center.

Adverse events

Safety measures included assessment of vital signs, physical and brief neurologic examinations, and clinical laboratory parameters. Spontaneously reported adverse events were collected and recorded at each visit.

Treatment-emergent adverse events (TEAEs) were defined as those that were new in onset or aggravated in severity or frequency between the prospective baseline and double-blind phase.

3.1.1.15 *Diener et al, 2007*

Results from the Diener study are provided as requested in the protocol for assessment of the added clinical value of fremanezumab. The primary efficacy measure was the change in number of migraine days from the 28th-day phase to the last 28 days of the double-blinded phase in the ITT population, which consisted of all patients who received at least one dose of study medication and had one outcome assessment during the double-blinded phase. HRQoL was evaluated with three different questionnaires (HIT-6, MSQ, ver. 2.1, and MIDAS).

Migraine days

The primary efficacy variable was the change in the mean number of monthly migraine days from baseline to the last 4 weeks of the double-blind phase. A migraine day was defined as a calendar day with symptoms of a migraine attack lasting at least 30 min.

Relevant secondary outcome measures included: change in monthly migraine days from baseline to the entire double-blind phase; the percentage of patients with ≥50% reduction in the mean number of monthly migraine days (categorical responder rates) and change from baseline in the mean number of days of acute medication intake.

A migraine day was defined as a calendar day with symptoms of migraine attack lasting at least 30 min. The primary endpoint was defined as the change in the mean number of monthly migraine days from baseline to the last 4 weeks of the double-blinded phase. Patients were allowed to take acute rescue medications such as analgesics, NSAIDs, triptans, and opioids during any phase in the trial. However, the use of acute rescue medication had to be specified next to the migraine attack information in the trial-specific patient diary.

Differences between treatment groups (topiramate vs. placebo) were compared using the Wilcoxon two-sample test for ordinal/continuous data and interpreted at the 5% significance level (two-tailed comparison). Differences within a treatment group were tested using the Wilcoxon signed rank test. Fisher's exact test was used to assess differences between nominal data.

Quality of life

The mean changes from baseline on the MIDAS questionnaire were measured. MIDAS is a valid and reliable short questionnaire for assessment of headache related disability. The MIDAS questionnaire has been developed by Lipton et al. and can be used to assess all associated aspects with migraine and tension type headaches disability in different domains of life. It has been extensively studied and its reliability and validity have been proved by standard methods in many countries [68].

Adverse events

Spontaneously reported treatment-emergent adverse events (TEAEs) were recorded. Vital signs, body weight changes and laboratory parameters, including bicarbonate, sodium, potassium, and chloride were measured at the start of the double-blind phase and at weeks 8 and 16.

3.1.1.16 *Lipton et al, 2011 (INTREPID)*

This was a multicenter, randomized, double-blind, placebo-controlled study comparing topiramate 100 mg/day and placebo for 26 weeks. The primary efficacy variable was new-onset CDH at month 6. Secondary

efficacy measures included migraine and headache days. Adverse events (AEs) were evaluated. A total of 159 topiramate subjects and 171 placebo subjects were efficacy evaluable.

Migraine days

The primary efficacy measure was whether a subject reported ≥15 headache days (migraine or non-migraine) per 28-day period at month 6.

The relevant secondary efficacy variables included:

- Change from baseline through the double-blind phase in 28-day rate of migraine days
- Change from baseline in acute medication use (days) per 28 days

Eligible subjects were required to be considered at risk for progression of episodic migraine to chronic migraine based on a prior history of experiencing migraines at a high monthly frequency, which, for the purpose of this study, was defined as occurrence of migraine headache on at least 9 but <15 days and <15 total headache days over the 28 days before screening visit. The migraine headaches must have met all ICHD-II diagnostic criteria for migraine except for duration. In this study, headache episodes with a duration of at least 30 minutes were included in the analysis.

All medication taken from the time of visit 1 until visit 10 was documented. Subjects were permitted to take acute headache medication as indicated throughout the study. The type and method of acute headache medication use was as consistent as possible with that used by the subject prior to enrollment. Subjects with concurrent illnesses who required prescription or over-the-counter medication within one month of entering the study were permitted, if necessary, to continue their medication or to initiate such therapy at the start of the study or any time during the study. Subjects' preexisting treatment regimens were modified only when deemed clinically appropriate by the investigator and not for the explicit purpose of entering the trial. All migraine preventive medications were discontinued at least six weeks before visit 2 and for the duration of the trial.

Adverse events

AEs were reported by the subject or when appropriate by a subject's caregiver, surrogate or legally acceptable representative for the duration of the study. An AE was defined as any untoward medical occurrence or any unfavorable and unintended sign (including an abnormal finding), symptom, or disease in a subject temporally associated with the use of a medicinal or investigational product, whether or not related to the medicinal or investigational product. This included any occurrence that was new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures including laboratory test abnormalities

Candesartan

3.1.1.17 *Tronvik et al, 2003*

The objective of this study is to determine whether treatment with the angiotensin II receptor blocker candesartan is effective as a migraine-prophylactic drug

Migraine days

The primary efficacy variable was days with headache, recorded by patients in daily diaries.

Relevant secondary efficacy outcome measures were days with migraine.

For the efficacy outcome measure, a candesartan responder was recorded when a symptom reduction of at least 50% was observed in the candesartan period compared with the placebo period, a definition that is in accordance with IHS guidelines [69] and that was used in the lisinopril study [44]. In addition, we recorded those with at least a 50% symptom reduction in the placebo period compared with the candesartan period. Analysis of responders was performed for the total treatment period as well as for the first, second, and third months separately.

To compare end-point variables and to assess carryover or period effects, the Wilcoxon signed rank test was used.

The proportion of patients who experiences adverse events leading to discontinuation was not included as an endpoint in this submission. From the Tronvik et al, 2013 it was not clear how many discontinued due to adverse events. From the Figure, Table 4 and the first paragraph in the results section inconsistencies exist in the reporting of dropouts due to adverse events in the candesartan and placebo arm. Thus, to avoid the risk of either over- or underestimating this endpoint in the ITC, it was not included.

3.1.1.18 *Stovner et al, 2014*

The objective of this article is to see whether the effect of candesartan for migraine prevention, shown in a previous study, could be confirmed in a new study, and if so, whether the effect was comparable to that of propranolol (non-inferiority analysis), and whether adverse events were different.

Migraine days

The primary efficacy variable was number of days with moderate or severe headache, lasting ≥4 hours or being treated with the patient's usual medication ('migraine days') per four weeks, which is according to the guidelines for chronic migraine studies.

Relevant secondary measures were days with monthly migraine and number of responders (≥50% decrease in migraine days compared with baseline).

The predetermined hypotheses were: H1: candesartan is better than placebo (superiority analysis). H2: candesartan is not inferior to propranolol (non-inferiority analysis). H3: candesartan has fewer AEs than propranolol (superiority analysis). In accordance with the predetermined statistical protocol, H1 (candesartan-placebo-difference) was tested with Wilcoxon's paired signed rank test, and likewise the secondary comparisons (candesartan-propranolol and placebo–propranolol).

Lisinopril

3.1.1.19 *Schrader et al, 2001*

The objective of this study was to determine the efficacy of an angiotensin converting enzyme inhibitor in the prophylaxis of migraine.

Migraine days

The relevant primary end points were number of days with headache and number of days with migraine. Responder analysis was done for patients where at least 50% in symptoms was seen.

A Wilcoxon signed rank test was used to compare end point variables. For comparison of adverse events and acceptability a McNemar's matched pairs test was used. A two-sided $P<0.05$ was considered significant.

Propranolol

3.1.1.20 *Diener et al, 1996*

To test the hypothesis that cyclandelate is more effective than placebo in the prophylaxis of migraine using the minimal effective dosage of 1200 mg/day, a randomized parallel-group double-blind multicenter study was performed. As a secondary hypothesis, comparative efficacy with propranolol (120 mg/day) was investigated.

Adverse Events

All patients kept a structued weekly diary and recorded daily migraine events: occurrence of migraine attacks; impairment of working ability; intensity of headache (measured by a visual analogue scale); duration of headache and migraine attack; intake of migraine medication during the attack; concomitant symptoms of migraine. Patients were asked to record adverse events related to the prophylactic medication.

3.1.1.21 *Diener et al, 2004*

Please see description in section 3.1.1.7.

3.1.1.22 *Stovner et al, 2014*

Please see description in section 3.1.1.17.

3.2 Results per study

Fremanezumab

3.2.1.1 *Dodick et al, 2018 (HALO EM)*

Results from the HALO trial for the population of episodic migraine are provided in Table 60.

Qualitative description of adverse events

A total of 192 patients (66%) who received fremanezumab monthly dosing and 193 patients (66%) who received a single higher dose of Fremanezumab reported at least 1 adverse event, compared with 171 patients (58%) who received placebo. Treatment-related adverse events were higher in the fremanezumab treatment groups (48% in the monthly group and 47% in the single-higher-dose group) compared with placebo (37%). The most common adverse events in patients treated with fremanezumab were injection site reactions: pain (fremanezumab monthly dosing: 87/290 [30.0%]; fremanezumab single higher dose: 86/291 [29.6%]), induration (fremanezumab monthly dosing: 71/290 [24.5%]; fremanezumab single higher dose: 57/291 [19.6%]), and erythema (fremanezumab monthly dosing: 52/290 [17.9%]; fremanezumab single higher dose: 55/291 [18.9%]). The proportion of patients with injection-site pain, induration, and erythema was higher with fremanezumab than with placebo (76/293 [25.9%], 45/293 [15.4%], and 41/293 [14.0%], respectively). Injection site hemorrhage occurred infrequently and at similar rates among treatment groups (fremanezumab monthly dosing: 3/290 [1.0%]; fremanezumab single higher dose: 9/291 [3.1%]; placebo: 6/293 [2.0%]).

3.2.1.2 *Bigal et al, 2015 (EM)*

Results for the population of episodic migraine are provided in Table 61.

Qualitative description of adverse events

Treatment-related adverse events were reported by 23% in the placebo arm, 27% in the fremanezumab 225 mg group and 25% in the fremanezumab 675 mg group. Most adverse events were minor injection-site reactions. Adverse events of moderate severity were reported in 9% receiving placebo and in 10% receiving 225 mg fremanezumab. No serious adverse events were reported.

3.2.1.3 *Silberstein et al, 2017 (HALO CM)*

Results from the HALO trial for the population of chronic migraine are provided in Table 62.

Qualitative description of adverse events

Adverse events were reported for 64% of the patients receiving placebo, 70% of those receiving fremanezumab quarterly (P = 0.06 vs. Placebo), and 71% of those receiving fremanezumab monthly (P = 0.03 vs. Placebo). Adverse events were mild to moderate in severity in 95%-96% of the patients in the three groups. Injection-site reactions were reported in 40% of the patients receiving placebo, 47% of those receiving fremanezumab quarterly (P = 0.08 vs. Placebo), and 47% of those receiving fremanezumab monthly (P = 0.03 vs. Placebo). The most common adverse event was injection-site pain which occurred in 30% of the patients in the fremanezumab quarterly group, 26% in the fremanezumab monthly group, and 28% in the placebo group.

3.2.1.4 *Bigal et al, 2015 (CM)*

Results for the population of chronic migraine are provided in Table 63. Note that the dose of 900 mg of fremanezumab is excluded in the analysis in this application according to the dosages of fremanezumab provided in the protocol by Medicinrådet.

Qualitative description of adverse events

Treatment-emergent adverse events were reported by 40% of the patients receiving placebo, 53% of the patients receiving fremanezumab (675/225 mg). The most common adverse events were mild injection-site pain (3% placebo, 7% fremanezumab [675/225 mg]) and pruritus (0% placebo, 5% fremanezumab [675/225 mg]). No relevant changes in blood pressure or vital signs were recorded.

Topiramate

3.2.1.5 *Storey et al, 2001*

All results from the trial are provided in Table 65.

Qualitative description of adverse events

Adverse events occurred more often in the topiramate arm compared to the placebo arm. The most frequent adverse events were; paresthesia, weight loss, abnormal tasting, anorexia, impaired memory, dysarthria, abnormal vision, emotional lability, worrying and frequent urination. In the topiramate arm, 53% of the patients reported weight loss compared to 29% in the placebo arm.

3.2.1.6 *Mei et al, 2004*

All results from the trial are provided in Table 66.

Qualitative description of adverse events

29% of the patients in the topiramate arm terminated the treatment due to adverse events. The reasons for treatment termination in the topiramate arm were cognitive difficulties (41% amongst those patients who ended treatment), paresthesia (29%), weight loss (12%), fatigue (12%), and abnormal tasting (6%). In the placebo arm, one patient terminated the treatment due to fatigue. In those patients completing the treatment the following adverse events were observed; paresthesia (23%), cognitive difficulties (8%), weight loss (23%), abnormal tasting (11%), and fatigue (6%).

3.2.1.7 *Diener et al, 2004*

All results from the trial are provided in Table 67.

Qualitative description of adverse events

The most common adverse events in the topiramate arm were related to the central and peripheral nervous system or had psychiatric characteristics. 28-44% of the patients randomized to the topiramate arm (100 and 200 mg, respectively) experienced adverse events. Only 10% of the patients experienced adverse events in the placebo arm. Adverse events leading to termination of the treatment in the topiramate arm (100 and 200 mg) was paresthesia (11-15%), concentration problems (4-12%), nausea (5-11%), fatigue (4-10%), insomnia (3-7%), and anorexia (4-6%). Kidney stones were reported in 3 patients treated with topiramate.

3.2.1.8 *Brandes et al, 2004*

All results are provided in Table 68 and QoL data from Brandes et al. 2006 in Table 69.

Qualitative description of adverse events

>10% of the patients in the topiramate arm (100 mg) experienced the following adverse events: paresthesia (50%), fatigue (14%), anorexia (13%), diarrhea (11%), weight loss (11%), hypoesthesia (11%), memory problems (10%), and nausea (10%). A significant larger weight loss was observed in the topiramate arms vs. placebo.

3.2.1.9 *Silberstein et al, 2004*

All results from the trial are provided in Table 70 and QoL data from Silberstein et el. 2006 in Table 71.

Qualitative description of adverse events

Paresthesia was reported in 36.4-46.9% of the patients in the topiramate arm (dose-dependent occurrence) compared to 6.9% in the placebo arm. Abnormal tasting occurred in 10.3-19.5% of the patients treated with topiramate compared to 4.3% in the placebo arm. Fatigue was reported in 9.3-17.7% patients in the topiramate versus 10.3% in the placebo arm. Lastly, concentration difficulties were observed in 2.5-9.7% of the patients in the topiramate compared to 0.9% in the placebo arm.

3.2.1.10 *Silberstein et al, 2006*

All results from the trial are provided in Table 72.

Qualitative description of adverse events

In the topiramate arm, 90% of the patients reported at least one adverse event compared to 69.9 in the placebo arm. Severe adverse events were reported in 28.6% of the patients treated with topiramate compared to 15.7% of the patients receiving placebo. Treatment-related adverse events (occurred in >10% of the patients in the topiramate arm) were; paresthesia (45%), dizziness (16%), fatigue (16%), nausea (14%), and weight loss (14%).

3.2.1.11 *Silberstein et al, 2007*

All results from the trial are provided in Table 73, Table 74 and QoL data from Silberstein et al., 2009 in Table 74.

Qualitative description of adverse events

In the topiramate arm, 82.5% of the patients experienced adverse events compared to 70.2% of the patients experiencing adverse events in the placebo arm. The most common adverse events in the topiramate arm were paresthesia (28.8% vs. placebo 7.5%), fatigue (10.6% vs. placebo 9.3%), hypoesthesia (9.4% vs. placebo 0%), concentration difficulties (9.4% vs. 2.5%), dry month (8.1% vs. placebo 2.5%), and nausea (8.1% vs. placebo 5.6%). In the topiramate arm, 16.3% of the patients reported severe adverse events compared to 11.2% in the placebo arm.

3.2.1.12 *Diener et al, 2007*

All results from the trial are provided in Table 75.

Qualitative description of adverse events

75% of the patients in the topiramate arm reported adverse events compared to 37% in the placebo arm. Paresthesia was the most common adverse event in the study (53% of all patients). A significant larger weight loss was observed in the topiramate arm compared to placebo.

3.2.1.13 *Lipton et al, 2011 (INTERPID)*

All results from the trial are provided in Table 76.

Qualitative description of adverse events

Adverse events were present in 82.4% of all patients treated with topiramate compared to 73.5% in the placebo arm. The most common adverse events were; paresthesia (32.4%), fatigue (14.8%), dizziness (11.4%), nausea (10.8%), virus infection (9.7%), and abnormal tasting (9.7%). There was no difference in the frequency of serious adverse events (SAEs). One patient in the topiramate arm was hospitalized and diagnosed with bipolar disease and suicidal thoughts. 14 patients in the topiramate arm were reported with abnormal laboratory results such as low bicarbonate values.

Candesartan

3.2.1.14 *Tronvik et al, 2003*

All results from the trial are provided in Table 77.

Qualitative description of adverse events

No difference in the occurrence of adverse events in the two arms. Four patients in total terminated the treatment due to dizziness. Three of those patients were receiving candesartan and the last patient was receiving placebo.

3.2.1.15 *Stovner et al, 2014*

All results from the trial are provided in Table 78.

Qualitative description of adverse events

The patients reported in general more discomfort related to adverse events in the candesartan and propranolol arm compared to the placebo arm. In the propranolol arm, 67 patients reported a total of 143 adverse events and in the placebo arm, 64 patients reported 90 adverse events. The most common adverse events were respiratory infections (propranolol: 39% vs. placebo: 42%), body pain (propranolol: 34% vs. placebo: 17%), dizziness (propranolol: 19% vs. placebo: 9%), sleeping problems (propranolol: 15% vs. placebo: 14%), and fatigue (propranolol: 16% vs. placebo: 2%)

Lisinopril

3.2.1.16 *Schrader et al, 2001*

All results from the trial are provided in Table 79.

Qualitative description of adverse events

Lisinopril was generally well-tolerated and with only mild adverse events compared to placebo. Mild adverse events occurred such as coughing (n = 8 vs. 3), fatigue (n = 3 vs. 3), dizziness (n = 7 vs. 4), and tendency to faint (n = 3 vs. 0). In total 24 adverse events were observed in the lisinopril arm and 13 adverse events were observed in the placebo arm.

Propranolol

3.2.1.17 *Diener et al, 1996*

All results from the trial are provided in Table 80.

Qualitative description of adverse events

24.4% of the patients in the propranolol arm reported adverse events compared to 9.1% in the placebo arm. I the propranolol arm the heart rate was reduced with 5 beats/minute on average.

3.2.1.18 *Diener et al, 2004*

All results from the trial are provided in Table 81.

Qualitative description of adverse events

The most frequent reported adverse events were fatigue (22%), nausea (13%), insomnia (13%), and paresthesia (12%).

3.2.1.19 *Stovner et al, 2014*

All results from the trial are provided in Table 82.

Qualitative description of adverse events

The patients reported in general more discomfort related to adverse events in the candesartan and propranolol arm compared to the placebo arm. In the propranolol arm, 67 patients reported a total of 143 adverse events and in the placebo arm, 64 patients reported 90 adverse events. The most common adverse events were respiratory infections (propranolol: 39% vs. placebo: 42%), body pain (propranolol: 34% vs. placebo: 17%), dizziness (propranolol: 19% vs. placebo: 9%), sleeping problems (propranolol: 15% vs. placebo: 14%), and fatigue (propranolol: 16% vs. placebo: 2%)

3.2.2 Comparative analyses

Clinically Question 1

Table 17 and Table 18 outline the favored treatment based on the ITC.

Overall, the results from the ITC favors fremanezumab compared to the comparators for the population in clinical question 1.

The ITC results comparing fremanezumab with topiramate are significantly favoring fremanezumab, with regards to the monthly days with reduction in number of days with acute headache medication (important outcome) in the monthly dosing regimen of fremanezumab, andwith regards to the proportion of patients who experiences adverse events leading to discontinuation (important outcome) in both the monthly and quarterly dosing regimen of fremanezumab.

Fremanezumab in a monthly dosing regimen is significantly favored compared to propranolol, with regards to the percent reduction of mean monthly migraine days (critical outcome) and monthly days with reduction in number of days with acute headache medication (important outcome).

Hence, based on the ITC data, on some parameters, fremanezumab is significantly favored over topiramate and propranolol, and none of the comparators are significantly favored over fremanezumab in any parameter.

Where ITC has been possible to do, fremanezumab is (favored) considered more tolerable than the comparators topiramate and propranolol (proportion of patients who experiences adverse events leading to discontinuation), and **fremanezumab appears (is favored) to have a better effect on the burden of migraine than topiramate (MIDAS and HIT-6), for a monthly dosing regime of fremanezumab**.

Descriptive comparisons of the SmPCs of fremanezumab and all the comparators suggest, that fremanezumab has a better tolerability and safety profile than the comparators (Note: no head to head studies have been made between fremanezumab and the said comparators).

Moreover, the following should be noted with regards to the ITC and the said comparators:

- It is important to note that large differences exist between studies used in the ITC in terms of follow-up time, patient characteristics, size of population and study design.
- Lisinopril is used off label, and not recommended as first line prophylactic treatment in any current Danish treatment guideline of migraine.
- Candesartan is also used off-label.
- Amongst the many precautions stated in the SmPC for topiramate, the report concerning suicidal thoughts and suicidal behavior can be highlighted as those have been seen in various cases with patients being treated with antiepileptic medication. [10]

In this section results of the comparative analysis will be outlined in regard to performed meta-analysis, ITC and narrative description of adverse events. **See**

Table 14 **(section 2.8) for how to interpret the ITC results**.

The results in Table 17 and Table 18 are based on the random effect results as data from the trials are randomized trials.

TABLE 17 INTERPRETATION OF ITC FOR CLINICAL QUESTION 1, FREMANEZUMAB MONTHLY DOSING SCHEME (RANDOM EFFECTS).

Outcome	Intervention	Comparator	Measure	Favors	Significant
Percent reduction of mean monthly migraine days	Fremanezumab monthly dosing	Candesartan	Mean Difference	Fremanezumab	
	Fremanezumab monthly dosing	Lisinopril	Mean Difference	Fremanezumab	
	Fremanezumab monthly dosing	Propranolol	Mean Difference	Fremanezumab	Yes
	Fremanezumab monthly dosing	Topiramate	Mean Difference	Fremanezumab	
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab monthly dosing	Candesartan	Risk Ratio	Candesartan	
	Fremanezumab monthly dosing	Lisinopril	Risk Ratio	Lisinopril	
	Fremanezumab monthly dosing	Propranolol	Risk Ratio	Fremanezumab	
	Fremanezumab monthly dosing	Topiramate	Risk Ratio	Topiramate	
Point reduction quality of life (MIDAS and HIT 6)	Fremanezumab monthly dosing	Topiramate	Mean Difference	Fremanezumab	
Monthly days with reduction in number of days with acute headache medication, change from baseline	Fremanezumab monthly dosing	Propranolol	Mean Difference	Fremanezumab	Yes
	Fremanezumab monthly dosing	Topiramate	Mean Difference	Fremanezumab	Yes
Proportion of patients who experiences adverse events leading to discontinuation	Fremanezumab monthly dosing	Propranolol	Risk Ratio	Fremanezumab	
	Fremanezumab monthly dosing	Topiramate	Risk Ratio	Fremanezumab	Yes
Percent reduction of mean monthly headache days	Fremanezumab monthly dosing	Candesartan	Mean Difference	Fremanezumab	
	Fremanezumab monthly dosing	Lisinopril	Mean Difference	Fremanezumab	

	Fremanezumab monthly dosing	Propranolol	Mean Difference	Fremanezumab	
	Fremanezumab monthly dosing	Topiramate	Mean Difference	Fremanezumab	

TABLE 18 INTERPRETATION OF ITC FOR CLINICAL QUESTION 1, FREMANEZUMAB QUARTERLY DOSING SCHEME (RANDOM EFFECTS AND SINGLE STUDIES).

Outcome	Intervention	Comparator	Measure	Favors	Significant
Percent reduction of mean monthly migraine days	Fremanezumab quarterly dosing	Candesartan	Mean Difference	Fremanezumab	
	Fremanezumab quarterly dosing	Lisinopril	Mean Difference	Fremanezumab	
	Fremanezumab quarterly dosing	Propranolol	Mean Difference	Fremanezumab	
	Fremanezumab quarterly dosing	Topiramate	Mean Difference	Fremanezumab	
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab quarterly dosing	Candesartan	Risk Ratio	Candesartan	
	Fremanezumab quarterly dosing	Lisinopril	Risk Ratio	Lisinopril	
	Fremanezumab quarterly dosing	Propranolol	Risk Ratio	Propranolol	
	Fremanezumab quarterly dosing	Topiramate	Risk Ratio	Topiramate	
Point reduction quality of life (MIDAS and HIT-6)	Fremanezumab quarterly dosing	Topiramate	Mean Difference	Topiramate	
Monthly days with reduction in number of days with acute headache medication, change from baseline	Fremanezumab quarterly dosing	Propranolol	Mean Difference	Fremanezumab	
	Fremanezumab quarterly dosing	Topiramate	Mean Difference	Fremanezumab	
Proportion of patients who experiences adverse events leading to discontinuation	Fremanezumab quarterly dosing	Propranolol	Risk Ratio	Fremanezumab	
	Fremanezumab quarterly dosing	Topiramate	Risk Ratio	Fremanezumab	Yes
	Fremanezumab quarterly dosing	Candesartan	Mean Difference	Fremanezumab	

Percent reduction of mean monthly headache days	Fremanezumab quarterly dosing	Lisinopril	Mean Difference	Fremanezumab	
	Fremanezumab quarterly dosing	Propranolol	Mean Difference	Fremanezumab	
	Fremanezumab quarterly dosing	Topiramate	Mean Difference	Fremanezumab	

3.2.2.1 *Meta-analysis*

The following Table 19 indicates which studies were included for the meta-analysis for each outcome. A "yes" indicate that the study was included, a "No" that the study was not included (due to insufficient data, non-reported, or incomparable outcomes).

TABLE 19 OVERVIEW OF STUDIES AND OUTCOMES INCLUDED IN THE META-ANALYSIS FOR CLINICAL QUESTION 1

Study	Outcome					
	Proportion ≥ 50% reduction in monthly migraines	**Proportion of patients who experience AEs leading to discontinuation**	**Monthly migraine days, change from baseline**	**Quality of life; Mean change from baseline in MIDAS or HIT-6 score**	**% reduction in number of days with any acute headache medication**	**% reduction in monthly headache days**
Total	**8**	**13**	**15**	**5**	**11**	**6**
HALO, Silberstein 2017 + EPAR	No	Yes	Yes	Yes	Yes	Yes
HALO, Dodick 2018 + EPAR	Yes	Yes	Yes	Yes	Yes	No
Fremanezumab, Bigal 2015 EM	Yes	No	Yes	Yes	Yes	No
Fremanezumab, Bigal 2015 CM	No	No	Yes	No	Yes	Yes
Propranolol, Diener 1996	No	Yes	No	No	No	No
Propranolol, Diener 2004	No	Yes	Yes	No	Yes	No
Propranolol, Stovner 2014	Yes	No	Yes	No	No	Yes
Lisinopril, Schrader 2001	Yes	No	Yes	No	No	Yes
Candesartan, Stovner 2014	Yes	No	Yes	No	No	Yes
Candesartan, Tronvik 2003	Yes	No	Yes	No	No	No
Topiramate, Mei 2004	No	Yes	No	No	No	No
Topiramate, Silberstein 2007	No	Yes	Yes	No	No	No

Study	Outcome					
	Proportion ≥ 50% reduction in monthly migraines	**Proportion of patients who experience AEs leading to discontinuation**	**Monthly migraine days, change from baseline**	**Quality of life; Mean change from baseline in MIDAS or HIT-6 score**	**% reduction in number of days with any acute headache medication**	**% reduction in monthly headache days**
Total	**8**	**13**	**15**	**5**	**11**	**6**
Topiramate, Dodick 2007	No	No	No	No	No	No
Topiramate, Silberstein 2006	No	Yes	No	No	No	No
Topiramate, Diener 2004	No	Yes	Yes	No	Yes	No
Topiramate, Diener 2007	Yes	Yes	Yes	Yes	Yes	No
Topiramate, Lipton 2011	No	Yes	Yes	No	Yes	No
Topiramate, Silberstein 2004	No	Yes	Yes	No	Yes	No
Topiramate, Silberstein 2006	No	No	No	No	No	No
Topiramate, Brandes 2004	No	Yes	Yes	No	Yes	No
Topiramate, Brandes 2006	No	No	No	No	No	No
Topiramate, Storey 2001	No	Yes	No	No	No	No
Topiramate, Silberstein 2009	Yes	No	No	Yes	Yes	Yes

All forests plots are presented in Appendix D in Figure 16 to Figure 34.

3.2.2.2 *ITC results*

The ITC results for Clinical Question 1 are given in Figure 1 to Figure 6. Random effect (RE) results are given, which refers to the meta-analysis; where treatments were compared to placebo using meta-analysis, the meta-analysis was performed using either FE or RE model.

See

Table 14 **(section 2.8) for how to interpret the ITC results**.

Tables with results per PICO are given in Table 90 to Table 97 in Appendix D.

Percent reduction in mean monthly migraine days

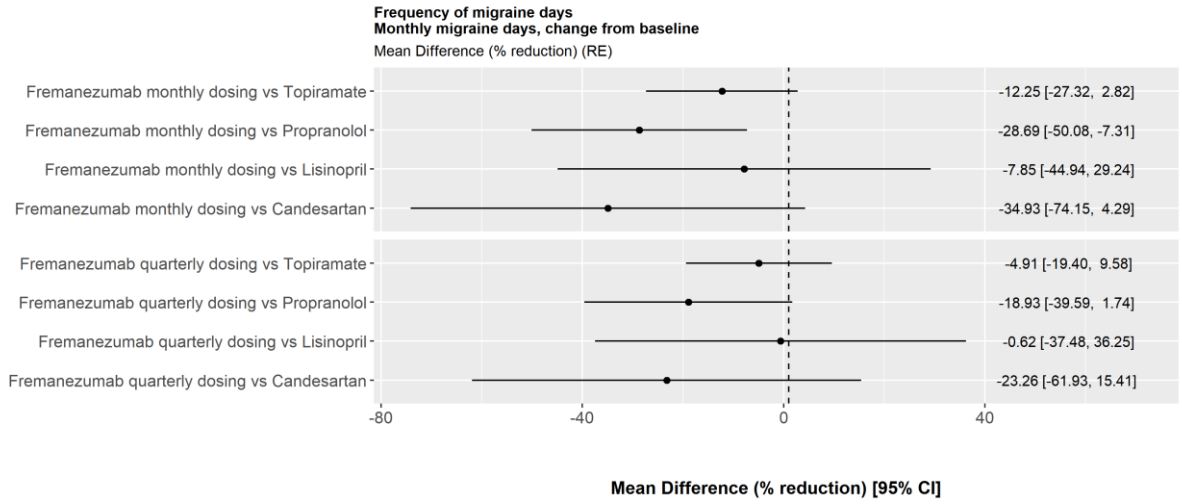

FIGURE 1 CLINICAL QUESTION 1 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO EACH COMPARATOR TREATMENT; MEAN DIFFERENCE (% REDUCTION) FOR MONTHLY MIGRAINE DAYS (RANDOM EFFECT). STATISTICAL SIGNIFICANCE OF FREMANEZUMAB MONTHLY DOSING COMPARED TO PROPRANOLOL.

Proportion of patients who achieve at least 50% reduction in monthly migraine days

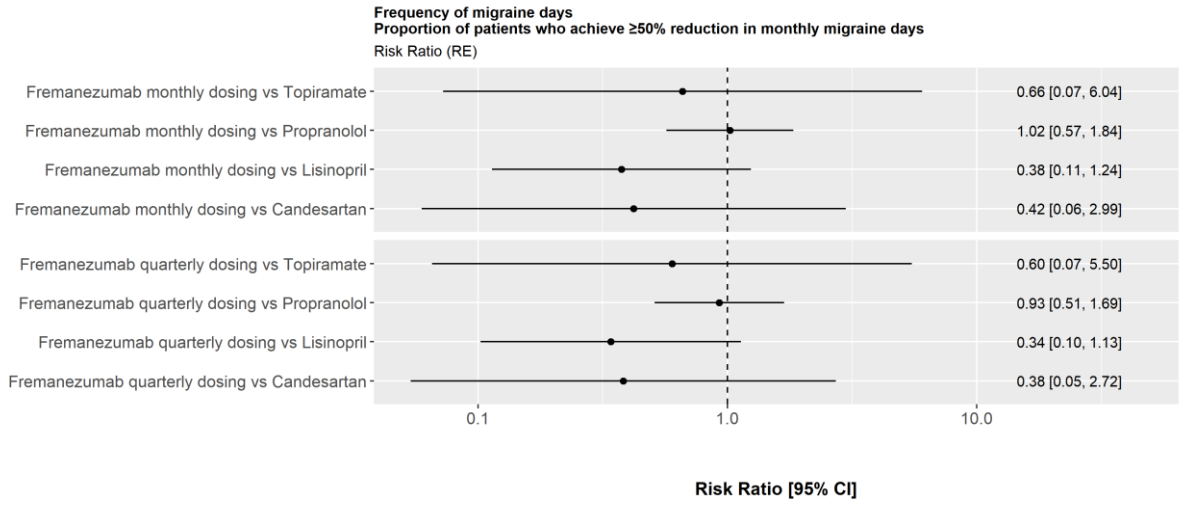

FIGURE 2 CLINICAL QUESTION 1 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO EACH COMPARATOR TREATMENT; RISK RATIO FOR THE PROPORTION OF PATIENTS WHO ACHIEVE ≥ 50% REDUCTION IN MONTHLY MIGRAINE DAYS (RANDOM EFFECT)

Point reduction in Quality of Life (HIT-6 and MIDAS)

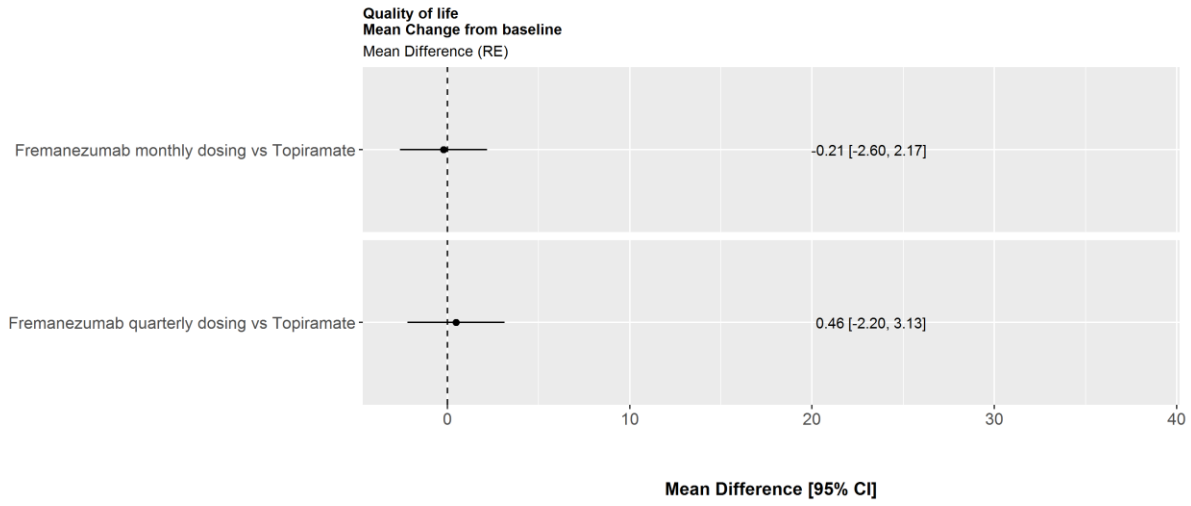

FIGURE 3 CLINICAL QUESTION 1 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO TOPIRAMATE TREATMENT; MEAN DIFFERENCE (POINT REDUCTION) FOR QUALITY OF LIFE OUTCOME MEASURES (RANDOM EFFECT)

Monthly days with reduction in number of days with acute headache medication

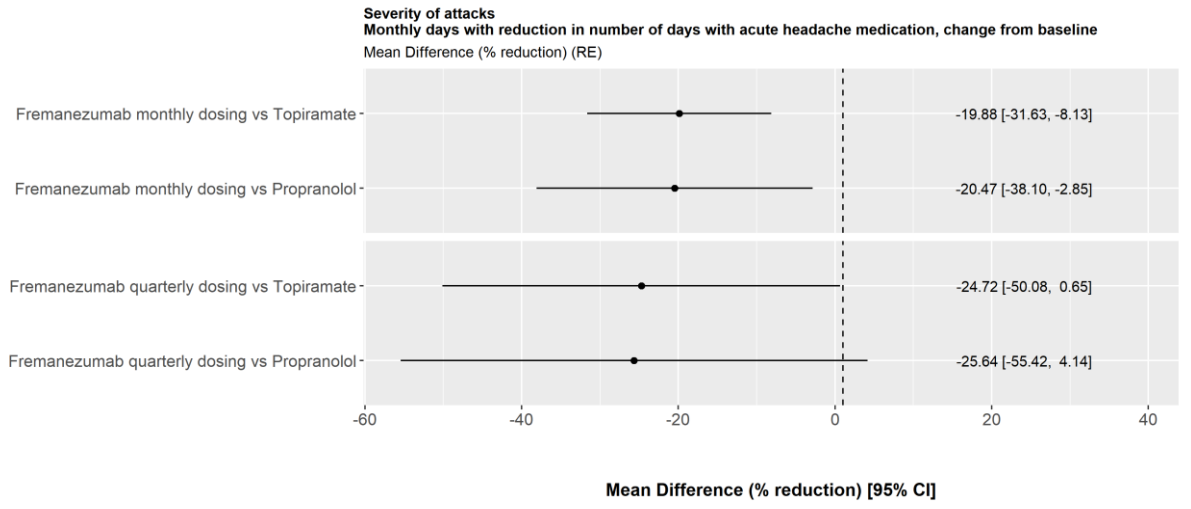

FIGURE 4 CLINICAL QUESTION 1 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO TOPIRAMATE AND PROPRANOLOL TREATMENT; MEAN DIFFERENCE (% REDUCTION) FOR MONTHLY DAYS WITH REDUCTION IN NUMBER OF DAYS WITH ACUTE HEADACHE MEDICATION (RANDOM EFFECT). STATISTICAL SIGNIFICANCE OF FREMANEZUMAB MONTHLY DOSING COMPARED TO TOPIRAMATE AND PROPRANOLOL.

Proportion of patients who experience adverse events leading to discontinuation

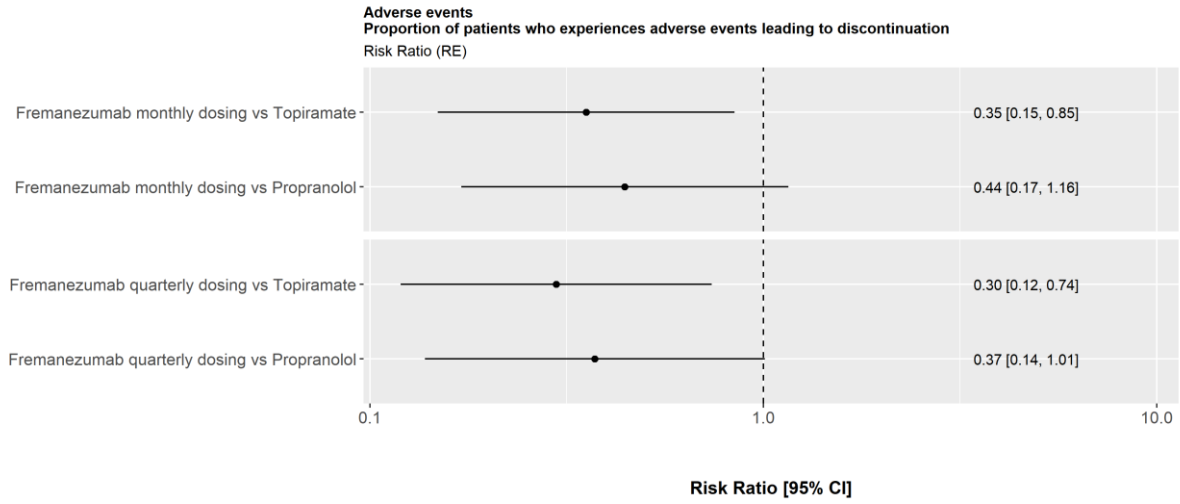

FIGURE 5 CLINICAL QUESTION 1 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO TOPIRAMATE AND PROPRANOLOL TREATMENT; RISK RATIO FOR THE PROPORTION OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS LEADING TO DISCONTINUATION (RANDOM EFFECT). STATISTICAL SIGNIFICANCE OF FREMANEZUMAB MONTHLY AND QUARTERLY DOSING COMPARED TO TOPIRAMATE.

Percent reduction in mean monthly headache days

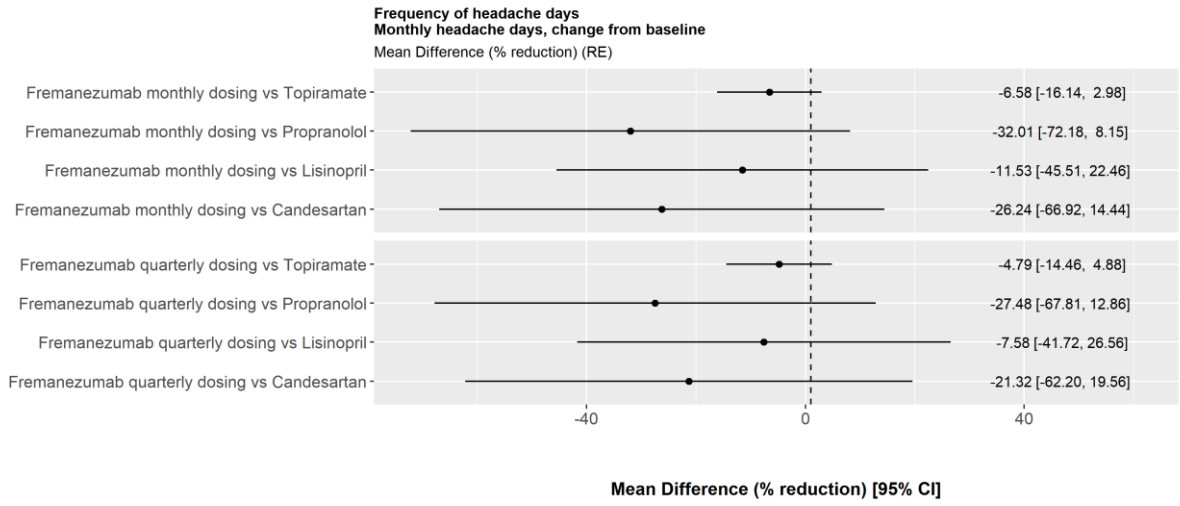

FIGURE 6 CLINICAL QUESTION 1 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO EACH COMPARATOR TREATMENT; MEAN DIFFERENCE (% REDUCTION) FOR MONTHLY HEADACHE DAYS (RANDOM EFFECT)

3.2.2.3 *Narrative description of adverse events*

Tolerability and adherence in general

Fremanezumab

A total of over 2,500 patients (more than 1,900 patient years) have been treated with AJOVY in registration studies. More than 1,400 patients were treated for at least 12 months. Commonly reported adverse drug reactions (ADRs) were local reactions at the injection site (pain [24%], induration [17%], erythema [16%] and pruritus [2%]) [70].

The very common adverse reactions were induration, and erythema. Common adverse reactions were pruritus.

Current prophylaxis treatments of migraine (incl. off-label) are often associated with a variable effect and multiple adverse events, which lead to a high level of discontinuation with the treatment in both clinical studies and in clinical practice [71–73].

E.g. in a retrospective register study with 4,634 enrolled patients, 73.4% of the patients treated with antidepressant ended their treatment after 6 months, 70.2% of the patients treated with antiepileptic ended treatment after 6 months as well and the same did 67.6% of all patients treated with beta-blockers in clinical practice [74]. In another retrospective register study of 8,707 chronic migraine patients approximately 3 out of 4 patients disrupted their treatment after 6 months independent of the type of medication. 10% of the patients disrupted treatment after 1 year. Only 13-16% of the patients were still taking the medication after 1 year [73].

Injection-site reactions

The most frequently observed local reactions at the injection site were pain, induration and erythema. All local injection site reactions were transient and predominantly mild to moderate in severity. Pain, induration and erythema were typically observed immediately after injection while pruritus and rash appeared within a median of 24 and 48 hours, respectively. All injection site reactions resolved, mostly within a few hours or days. Injection site reactions generally did not necessitate discontinuation of the medicinal product. [70]

Immunogenicity

In placebo-controlled studies, 0.4 % of patients (6 out of 1,701) treated with fremanezumab developed anti-drug antibodies (ADA). The antibody responses were of low titer. One of these 6 patients developed neutralizing antibodies. To date, 1,494 patients have completed 12 months of treatment with fremanezumab in the ongoing long-term Study 3. ADA was detected in 2% of the patients (38 out of 1,888). The safety and efficacy of fremanezumab were not affected by ADA development. [70]

Overdose

Doses up to 2,000 mg have been administered intravenously in clinical trials without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate symptomatic treatment if necessary. [70]

Comparison of adverse events, contraindications, precautions, and pregnancy

The below-mentioned information regarding comparators is obtained from Lægemiddelstyrelsens approved summary of product characteristics except if another source is cited; topiramate [10], lisinopril [11], propranolol [12], and candesartan [13].

Information regarding fremanezumab was obtained for the European Public Assessment report (EPAR) [70].

Adverse events

For fremanezumab, injection site induration, and injection site erythema are listed as “very common” adverse events (fremanezumab SmPC) which is also the case for metoprolol and topiramate. Injection site pruritus is listed as a” common” adverse event, and injection site rash is listed as an “uncommon” adverse event. Compared to beta-blockers and in particular topiramate, there are very few adverse events with fremanezumab.

Candesartan

In controlled clinical trials the adverse events related to candesartan treatment were mild and passing.

In the patient information from Dansk Hovedpinecenter in Glostrup are the following adverse events highlighted:

- Dizziness (when blood pressure is low), rare rashes, increased potassium, changes in kidney or liver functions.

According to the patients leaflet from Dansk Hovedpinecenter candesartan is generally well-tolerated but it should not be prescribed for young women with low blood pressure [75]. Lastly, it should be noted that not approved as preventive migraine treatment in Denmark (off-label) [76].

Lisinopril

Lisinopril is not approved as preventive migraine treatment in Denmark (off-label) [76].

Common adverse events in treatment with lisinopril are dizziness, headache, orthostatic manifestations (including hypotension), coughing, diarrhea, vomiting, and renal dysfunction.

Dry coughing is a common adverse event and is considered irritating in 20% of the patients.

Topiramate

Safety and tolerability were assessed in a pooled analysis of three pivotal registrations studies for topiramate enrolling 1,580 patients suffering from migraine. Paresthesia was the most common topiramate-associated adverse event (35%, 51%, and 49% of the patients treated with topiramate 50-200 mg daily compared to 6% in the placebo group). Adverse events were generally mild or moderate and were more frequent in the titration phase compared to the steady phase. Adverse events leading to discontinuation were; paresthesia (8%), tiredness (5%), nausea (2%) and difficulties concentrating (2%) [77].

In the patient information from Dansk Hovedpinecenter in Glostrup are the following adverse events highlighted:

- Paresthesia (e.g. “pins and needle' in the feet and hands), nausea, and slightly weight loss. Additionally, dizziness, tiredness, difficulties concentrating, struggling with finding the right word and depression can occur. Kidney stones can occur in some rare cases. When treated with high doses the effects of birth control (e.g. contraceptive pill) may be compromised.

Cognitive adverse events and the tendency to get a depression are highlighted as adverse events with the largest impact on the patient’s life.

Propranolol

In general, between 10 and 20% of all propranolol-treated patients will experience adverse events. The most common adverse events are tiredness/fatigue, diarrhea, nausea, vomiting, dyspepsia, and bradycardia. Muscle fatigue and cold extremities are the most irritation adverse events.

In the patient information from Dansk Hovedpinecenter I Glostrup is the following adverse events stated for the beta-blocker metoprolol, which the center finds comparable to propranolol.

- Tiredness, dizziness, decrease in blood pressure when moving, nausea, abdominal pain, diarrhea, constipation, cold hands and feet, slow pulse, heartbeat, and difficulties breathing.
- Metoprolol should not be used in patients with certain types of heart diseases (e.g. if a pacemaker is needed) and in patients with diabetes and asthma metoprolol is recommended to either be used very carefully or not used at all.

Contraindications

For fremanezumab the only contraindications are hypersensitivity to the active substance or to any of the excipients listed below:

- L-histidine
- L-histidine hydrochloride monohydrate
- Sucrose
- Disodium ethylenediaminetetraacetic acid (EDTA) dihydrate
- Polysorbate 80
- Water for injections

In contrast, especially propranolol, amitriptyline is known to have many contraindications (>10).

Precautions

Fremanezumab

Only three populations are defined as “special population”:

- **Elderly**: There is limited data available on the use of fremanezumab in patients ≥65 years of age. Based on the results of population pharmacokinetic analysis, no dose adjustment is required.
- **Renal or hepatic impairment**: No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment.
- **Pediatric population**: The safety and efficacy of AJOVY in children and adolescents below the age of 18 years have not yet been established. No data are available.

For oral prophylaxis drugs multiple precautions are stated on several pages in Lægemiddelstyrrelsens summary of product characteristics.

Topiramate

Amongst the many precautions stated in the summary of product characteristics the report concerning suicidal thoughts and suicidal behavior can be highlighted as those have been seen in various cases with patients being treated with antiepileptic medication.

Propranolol

Multiple precautions should be taken before administering propranolol. Precautions should be taken in any patient with heart diseases, both in patients with and without symptoms. Patients with diabetes mellitus should be treated with caution as well as propranolol may hide the symptoms of hypoglycemia (tachycardia and tremor). Additionally, propranolol can cause hypoglycemia in non-diabetic patients, e.g. children, elderly, dialysis patients or patients with chronic liver disease. The many precautions are mainly due to the many contraindications associated with propranolol treatment.

Lisinopril

Treatment with lisinopril is associated with multiple precautions such as double inhibition of the RAAS system, symptomatic hypotension, aorta stenosis, decreased kidney function, diabetes patients. Additionally, lisinopril can cause a higher incidence of angio-neurological edema in black patients compared to non-black patients. The summary of product characteristics from Lægemiddelstyrrelsen states a long list of precautions associated with lisinopril.

Candesartan

Treatment with candesartan is associated with similar precautions as for lisinopril, hence these will not be elaborated further.

Pregnancy

Fremanezumab

Pregnancy

There is a limited amount of data from the use of AJOVY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of AJOVY during pregnancy [70].

Breast-feeding

It is unknown whether fremanezumab is excreted in human milk. Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of fremanezumab could be considered during breast-feeding only if clinically needed [70].

Fertility

There are no fertility data in humans. Available non-clinical data do not suggest an effect on fertility [70].

Topiramate

For topiramate there are a number of important precautions in regard to pregnancy and fertility. Topiramate have been proved to be teratogenic in mice, rats, and rabbits. Topiramate passes the placenta in rats. No current studies have assessed the effects of topiramate treatment in pregnant women. Additionally, the need for treatment with antiepileptic medication must be reconsidered when a woman plans to get pregnant. Women in their fertile age should be consulted by a specialist. Topiramate can cause teratogenicity and growth inhibition in fetus if administered in a pregnant woman. Data from North American Antiepileptic Drug pregnancy register for topiramate monotherapy showed that the occurrence of serious

innate abnormalities (4.3%) were 3 times as high compared to the reference group who did not receive antiepileptic medication (1.4%).

Propranolol

Treatment with propranolol is associated with a number of important precautions in regard to pregnancy and fertility. The need for treatment with antiepileptic medication must be reconsidered when a woman plans to get pregnant. Women in their fertile age should be consulted by a specialist.

Propranolol should only be administered during pregnancy if it is absolutely necessary and only after thorough guidance about expected pros and cons. Propranolol passes the placenta, which has been related to decreased fetus growth, fetal death, abortion, and premature birth.

Candesartan

The use of candesartan is not recommended during the first trimester and is associated with contraindications in the second and third trimester.

Lisinopril

Lisinopril (and ACE inhibitors in general) is not recommended during the first trimester and is associated with contraindications in the second and third trimester.

3.3 Clinical question 2: Hvad er den kliniske merværdi af fremanezumab til patienter med migræne, der har mindst fire migrænedage pr. måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger indenfor to lægemiddelgrupper sammenlignet med eksisterende standardbehandling?

3.3.1 Presentation of relevant studies

See Table 20 for an overview of included studies and its associated population and follow-up time. Note, differences exist.

TABLE 20 OVERVIEW OF INCLUDED STUDIES AND FOLLOW-UP TIME

Clinical question 2	
Study	**Follow-up time**
Fremanezumab EM+CM, Ferrari et al. 2019	12 weeks*
Sodium Valproat (Valproat) EM+CM, Jensen et al., 1994	12 weeks
Divalproex Sodium (Valproat) EM, Mathew et al., 1995	12 weeks
Divalproex Sodium (Valproat) EM, Klapper et al., 1997	12 weeks
Divalproex Sodium (Valproat) EM, Freitag et al., 2002	12 weeks
Amitriptyline EM+CM, Couch et al., 2011	20 weeks
Amitriptyline EM, Goncalves et al., 2016	12 weeks

***For the outcome HIT-6, the follow-up time was 4 weeks after administration of the third dose of study drug**

Fremanezumab

3.3.1.1 *Ferrari et al, 2019*

The purpose of the FOCUS study was to evaluate the efficacy, safety, and tolerability of monthly and quarterly subcutaneous (sc) injections of fremanezumab compared with sc injections of placebo in patients with chronic migraine (CM) or episodic migraine (EM) who have responded inadequately to 2 to 4 classes of prior preventive treatments (beta-blockers: propranolol, metoprolol, atenolol, and bisopropol; anticonvulsants: topiramate; calcium channel blocker: flunarizine; angiotensin II receptor antagonist: candesartan; valproic acid and botox).

Approximately equal numbers of patients from each subgroup (CM and EM) are randomized in blinded-fashion 1:1:1 into one of three treatments for the subgroup - two active treatments (283 on a monthly dosing regimen and 276 on a quarterly dosing regimen) and one placebo treatment (279 patients) consisting of monthly injections for 3 months (up to week 12). Then all participants continue into an open-label extension of 3 months (weeks 13-week 24) during which everyone is administered sc injections of fremanezumab in a monthly dosing regimen [78].

Migraine days

The primary outcome measure was mean change from baseline in the monthly average number of migraine days during the double-blind period [Time Frame: Baseline (days -28 to 0), Treatment up to week 12].

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 (ie, 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 outcome was 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.

Mean change from base in the monthly average number of headache days was excluded in this analysis as the outcome was not reported for any severity (only at least moderate severity) and thereby not aligned with the protocol from Medicinrådet.

Quality of life

Mean changes from baseline at 4 weeks after administration of the third dose of study drug in the following patient-reported outcomes were also assessed as prespecified exploratory outcomes: disability scores (measured by the Migraine Disability Assessment [MIDAS] and Headache Impact Test [HIT-6]), Migraine-Specific Quality of Life (MSQOL) score, EurQol-5 Dimension (EQ-5D) health status score, 9-item Patient Health Questionnaire (PHQ-9), and Work Productivity and Activity Impairment (WPAI) questionnaire. Patient Global Impression of Change (PGIC) at 4 weeks after administration of the third dose of study drug was also assessed.

Adverse events

Adverse events, serious adverse events, and adverse events leading to discontinuation were summarised by treatment group. All adverse events were coded with the Medical Dictionary for Regulatory Activities

(MedDRA), version 18.1. Routine laboratory assessments, vital signs measurements, and physical examinations were also assessed.

Valproate

3.3.1.2 *Jensen et al, 1994*

Forty-three patients with migraine without aura were included in a triple-blind, placebo- and dose-controlled, crossover study of the prophylactic effect of slow-release sodium valproate; 34 patients completed the trial.

Migraine days

The primary endpoints were the mean number of days with migraine during sodium valproate as compared with the placebo period.

A nonparametric statistical test, Wilcoxon's rank sum test was used to test the treatment effect. A possible carryover effect was tested for by comparing the total sum of days with migraine in group A with group B by means of the Mann-Whitney two-tailed test. Analysis of variance (ANOVA) was used to test the treatment effect in relation to the duration of sodium valproate or placebo-treatment periods.

In this study, the responders were defined as having a reduction in the frequency of migraine days of 50% or less when compared with the baseline. Hence, this efficacy outcome is not included as it does not match the efficacy outcome given in the protocol, which is at least 50 %.

Adverse Events

AEs were captured. This efficacy parameter was not specified further.

3.3.1.3 *Mathew et al, 1995*

The objective of this study was to compare the effectiveness and safety of divalproex sodium (Depakote) and placebo in the prophylaxis of migraine headache.

Migraine days

The primary outcome measure was a 4-week migraine headache frequency (i.e. the number of migraine headaches with or without aura per 4 weeks) during the treatment phase.

The relevant secondary outcome measures related to migraine headaches included in the proportion of patients with a reduction of 50% or more in 4-week migraine headache frequencies compared with the baseline phase.

The nonparametric Van Elteren [79] method of linearly combining Wilcoxon test results from individual investigators, using weights recommended by Lehmann [80], was the method used to compare treatment groups with respect to the primary efficacy outcome measure.

Fisher's Exact Test was used to compare treatment groups with respect to the secondary efficacy outcome measures.

The Cochran-Mantel-Haenszel statistic was used to compare treatment groups with respect to the proportion of patients with a 50% or greater reduction in 4-week migraine headache frequencies. All hypothesis tests were two-tailed and p-values of 0.05 or less were considered significant.

Adverse events

Fisher's Exact Test was used to compare treatment groups with respect to adverse events.

3.3.1.4 *Klapper et al, 1997*

The objective of this study was to evaluate efficacy and safety of divalproex sodium (DVPX) when used as prophylactic monotherapy in patients with migraine.

Adverse events

Pairwise dose group comparisons versus placebo for the proportions of patients experiencing adverse events were performed using Fisher's exact test. All hypothesis tests were two-tailed and p-values 0.05 were considered statistically significant.

3.3.1.5 *Freitag et al, 2002*

The objective of this study was to evaluate efficacy and safety of extended-release divalproex sodium compared with placebo in prophylactic monotherapy treatment of migraine headache

Migraine days

The primary efficacy variable was the experimental phase reduction from baseline (i.e., the baseline phase) in 4-week migraine headache rate.

The secondary variables were the experimental phase percent reduction from baseline in 4-week migraine headache rate, assessing both actual percentages and the proportion of subjects achieving at least a 50% reduction, and the experimental phase reduction from baseline in the number of migraine headache days per 4 weeks.

The nonparametric van Elteren [79] method of linearly combining Wilcoxon test results from individual investigators, using weights recommended by Lehman [80], was the protocol-specified primary analysis methods for the continuous variables.

The proportions of subjects achieving at least 50% reduction in 4-week migraine headache rate were analyzed using Cochran-Mantel-Haenszel statistics with center as the stratification factor.

Adverse Events

AEs were captured. This efficacy parameter was not specified further.

Amitriptyline

3.3.1.6 *Couch et al, 2011*

This report deals with a large placebo-controlled trial of amitriptyline vs placebo of 20 weeks duration that included subjects with intermittent migraine (IM) as well as CDH. The study was carried out between 1976 and 1979; however, results have never been fully reported.

Adverse events

AEs in both the clinical and laboratory spheres were evaluated as mild, moderate or severe. These were tabulated and compared for amitriptyline and placebo groups.

3.3.1.7 *Gonçalves et al, 2016*

This study aimed to study the effect of melatonin in a double-blind, placebo-controlled trial with an active comparator.

Migraine days

The primary efficacy outcome measure was frequency in number of migraine headache days per month comparing baseline with the past 4 weeks of treatment. Analysis of the primary end point was carried out using a combination of a sequential method and a Hochberg procedure to maintain the experiment-wise α level of 0.05.

A relevant secondary efficacy variable included percentages of patients with greater than 50% reductions in migraine headache days.

Efficacy data were analyzed for the intention-to-treat population, defined as randomized patients who received at least one dose of the study medication and provided at least one post baseline efficacy assessment. No interim analysis was planned. Missing data were analyzed by three methods. The first method extended the calendar earlier into the treatment period until 28 days of non-missing data contributed to the count of migraine headache days. The second method proportionately adjusted the number of migraine headache days (multiplied by 28 and divided by the number of non-missing days). The third method treated all missing days as non-migraine headache days (used for the primary end point).

3.3.2 Results per study

Fremanezumab

All results from the trial are provided in Table 64.

3.3.2.1 *Ferrari et al, 2019*

Qualitative description of adverse events

A total of 280 patients (50%) who received fremanezumab reported at least 1 adverse event, compared with 134 patients (48%) receiving placebo. None of the serious adverse events were considered treatment-related, and no safety signals were identified. The most common adverse events in patients treated with fremanezumab were injection-site erythema (6%), injection-site induration (4%), and nasopharyngitis (4%). [81]

Individual cardiovascular or hepatobiliary adverse events were reported by no more than two (<1%) participants in any treatment group. There were no occurrences of anaphylaxis or moderate or severe hypersensitivity and no significant findings in clinical laboratory, ECG, vital signs, or physical examination analysis. Overall, no safety signals were identified in this study. [30]

Amitriptyline

3.3.2.2 *Couch et al, 2011*

All results from the trial are provided in Table 87.

Qualitative description of adverse events

The most common adverse events were daytime sleepiness (40.6% vs. 11.9%), dry month (10.2% vs. 1.7%), epigastralgia (8.5% vs. 0%), weight gain (5.1% vs. 1.7%), and constipation (6.8% vs. 6.8%). Blood pressure levels have not changed over among groups. No patients reported hypoglycemic symptoms.

3.3.2.3 *Goncalves et al, 2016*

All results from the trial are provided in Table 88.

Qualitative description of adverse events

Over the 3-month course of treatment, 77 adverse events were reported by 60 participants, 46 reports in the amitriptyline group, 16 in the melatonin group and 17 in the placebo group. No serious adverse events were observed. The majority of adverse events were either mild or moderate in intensity and occurred more commonly in the amitriptyline group compared with melatonin and placebo ($p<0.03$), whereas the melatonin and placebo groups had similar numbers (p value=not significant). The most common adverse events of amitriptyline were sleepiness, dry mouth and epigastralgia.

Valproate

3.3.2.4 *Jensen et al, 1994*

All results from the trial are provided in Table 83.

Qualitative description of adverse events

Adverse events were reported by 33% of the patients during the sodium valproate period and by 16% of the patients during placebo. The most common adverse events were; intensified nausea and dyspepsia, tiredness, increased appetite, and weigh gain. There were no serious adverse events indicating withdrawal from the study and there were no consistent changes in liver and hematologic values.

3.3.2.5 *Klapper et al, 1997*

All results from the trial are provided in Table 85.

Qualitative description of adverse events

Adverse events were similar in the divalproex sodium (DVPX) and placebo arm except for nausea, dizziness, and tremor, in which incidence rates were significantly higher in the DVPX 1500 mg group (nausea was also higher in the 500 mg group) than in the placebo arm.

3.3.2.6 *Mathew et al, 1995*

All results from the trial are provided in Table 84.

Qualitative description of adverse events

A significant difference between patients treated with divalproex and those treated with placebo was noted for the following adverse events: nausea (46% vs. 14%), asthenia (31% vs. 8%), somnolence (drowsiness) (30% vs. 5%), vomiting (19% vs. 0%), tremor (13% vs. 0%), and alopecia (13% vs. 0%).

3.3.2.7 *Freitag et al, 2002*

All results from the trial are provided in Table 86.

Qualitative description of adverse events

68% of the divalproex sodium-treated patients experienced at least one treatment-emergent adverse event compared to 70% of the patients receiving placebo. In the divalproex arm, 15% of the patients reported an infection compared to 14% in the placebo arm. 15% of the patients in the divalproex arm experienced nausea compared to 9% in the placebo arm. 7% of the patients in the divalproex arm experienced asthenia compared

to 10% in the placebo arm. Flu syndromes were observed in 8% of the patients in the divalproex arm compared to 9% in the placebo arm. None of the differences between treatment groups was significant.

3.3.3 Comparative analyses

Clinical question 2

Table 21 and Table 22 outline the favored treatment based on the ITC.

All the results from the ITC favors fremanezumab compared to the comparators, amitriptyline and valproate, for the population in clinical question 2.

Based on the ITC data, fremanezumab is significantly favored over than amitriptyline with regards to the percent reduction of mean monthly migraine days (critical outcome) and proportion of patients who achieve ≥50% reduction in monthly migraine days (important outcome), in both the monthly and quarterly dosing regimen of fremanezumab.

Based on the ITC data, fremanezuamb is favored over valproate on all the measured parametres.

Based on the ITC data, fremanezumab is (favored) considered more tolerable than amitriptyline and valproate (proportion of patients who experiences adverse events leading to discontinuation), **in both the monthly and quarterly dosing regimen of fremanezumab.**

Descriptive comparisons of the SmPCs of fremanezumab, valproate and amitriptyline suggest, that fremanezumab has a better tolerability and safety profile than valproate and amitriptyline (Note: no head to head studies have been made between fremanezumab and valproate and amitriptyline).

Moreover, the following should be noted with regards to the ITC and the said comparators:

- It is important to note that large differences exist between studies used in the ITC in terms of follow-up time, patient characteristics, size of population and study design.
- The use of amitriptyline is debated and it is used as second line prophylactic treatment [15], i.e. prior to the population relevant for clinical question 2.
- Nortriptyline is currently not recommended in any Danish treatment guideline.
- Valproate is used off-label. According to the SmPC, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. [9]

In this section results of the comparative analysis will be outlined in regard to performed meta-analysis, ITC and narrative description of adverse events. **See**

Table 14 **(sections 2.8) for how to interpret the ITC results.**

The results in

Table 21 and Table 22 are based on the random effect results as data from the trials are randomized trials.

TABLE 21 INTERPRETATION OF ITC FOR CLINICAL QUESTION 2, FREMANEZUMAB MONTHLY DOSING SCHEME (RANDOM EFFECTS AND SINGLE STUDIES)

Outcome	Intervention	Comparator	Measure	Favors	Significant
Percent reduction of mean monthly migraine days	Fremanezumab monthly dosing	Amitriptyline 25mg	Mean Difference	Fremanezumab	Yes
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab monthly dosing	Divalproex Sodium	Risk Ratio	Fremanezumab	
	Fremanezumab monthly dosing	Amitriptyline 25mg	Risk Ratio	Fremanezumab	Yes
Proportion of patients who experiences adverse events leading to discontinuation	Fremanezumab monthly dosing	Amitriptyline 25-100mg	Risk Ratio	Fremanezumab	
	Fremanezumab monthly dosing	Divalproex Sodium	Risk Ratio	Fremanezumab	

TABLE 22 INTERPRETATION OF ITC FOR CLINICAL QUESTION 2, FREMANEZUMAB QUARTERLY DOSING SCHEME (RANDOM EFFECTS AND SINGLE STUDIES)

Outcome	Intervention	Comparator	Measure	Favors	Significant
Percent reduction of mean monthly migraine days	Fremanezumab quarterly dosing	Amitriptyline 25mg	Mean Difference	Fremanezumab	Yes
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab quarterly dosing	Divalproex Sodium	Risk Ratio	Fremanezumab	
	Fremanezumab quarterly dosing	Amitriptyline 25mg	Risk Ratio	Fremanezumab	Yes
Proportion of patients who experiences adverse events leading to discontinuation	Fremanezumab quarterly dosing	Amitriptyline 25-100mg	Risk Ratio	Fremanezumab	
	Fremanezumab quarterly dosing	Divalproex Sodium	Risk Ratio	Fremanezumab	

3.3.3.1 *Meta-analysis*

The following Table 23 indicates which studies were included for the meta-analysis for each outcome. A "yes" indicate that the study was included, a "No" that the study was not included (due to insufficient data, non-reported, or incomparable outcomes).

TABLE 23 OVERVIEW OF STUDIES AND OUTCOMES INCLUDED IN THE META-ANALYSIS FOR CLINICAL QUESTION 2

Study	Outcome				
	Proportion ≥ 50% reduction in monthly migraines	**Proportion of patients who experience AEs leading to discontinuation**	**Monthly migraine days, change from baseline**	**Quality of life; Mean change from baseline in HIT-6 score**	**% reduction in number of days with any acute headache medication**
Total	**3**	**6**	**2**	**1**	**1**
Fremanezumab, Ferrari 2019	Yes	Yes	Yes	Yes	Yes
Divalproex Sodium (Valproat), Mathew 1995	Yes	Yes	No	No	No
Divalproex Sodium (Valproat), Klapper 1997	No	Yes	No	No	No
Divalproex Sodium (Valproat), Freitag 2002	No	Yes	No	No	No
Sodium Valproat (Valproat), Jensen 1994	No	Yes	No	No	No
Amitriptyline, Goncalves 2016	Yes	No	Yes	No	No
Amitriptyline, Couch 2011	No	Yes	No	No	No

The forest plot is presented in Appendix D in

Figure 35.

A note should be given concerning valproate and the monthly migraine days, change from baseline. According to study level data the mean monthly migraine days were extracted from Jensen et al, 2014, Mathew et al, 1995 and Freitag et al, 2002 (see Table 83, Table 84 and Table 86, respectively).

These data were excluded from the ITC due to limitations of the data.

- Jensen et al, 1994: Point estimate for baseline, point estimate and CI for end of study, point estimate for endpoint given. No estimate of variability for endpoint available.
- Mathew et al, 1995: Only gives point estimates for End of Study, Baseline and Endpoint, no estimates of variability.

- Freitag et al, 2002: Point estimate for baseline and endpoint given. Standard deviation for baseline given, no estimate of variability for endpoint available.

Since there were no estimates of variability for the endpoint for the above studies, these results were not combined in a meta-analysis nor were included in the ITC.

3.3.3.2 *ITC results*

The ITC results for Clinical Question 2 are given in Figure 7 to Figure 9. Random effect (RE) results are given, which refers to the meta-analysis; where treatments were compared to placebo using meta-analysis, the meta-analysis was performed using either FE or RE model.

For interpretation of the ITC results, see

Table 14 **(section 2.7) for guidance**

Tables with results per PICO are given in Table 98 to Table 101 in Appendix D.

Percent reduction in mean monthly migraine days

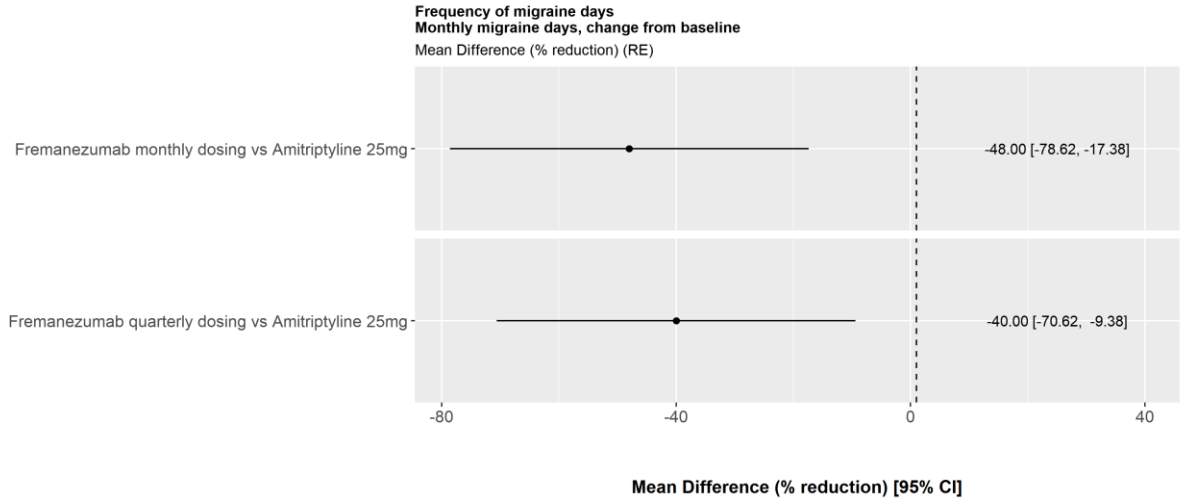

FIGURE 7 CLINICAL QUESTION 2 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO AMITRIPTYLINE TREATMENT; MEAN DIFFERENCE (% REDUCTION) FOR MONTHLY MIGRAINE DAYS. STATISTICAL SIGNIFICANCE OF FREMANEZUMAB MONTHLY AND QUARTERLY COMPARED TO AMITRIPTYLINE.

Proportion of patients who achieve at least 50% reduction in monthly migraine days

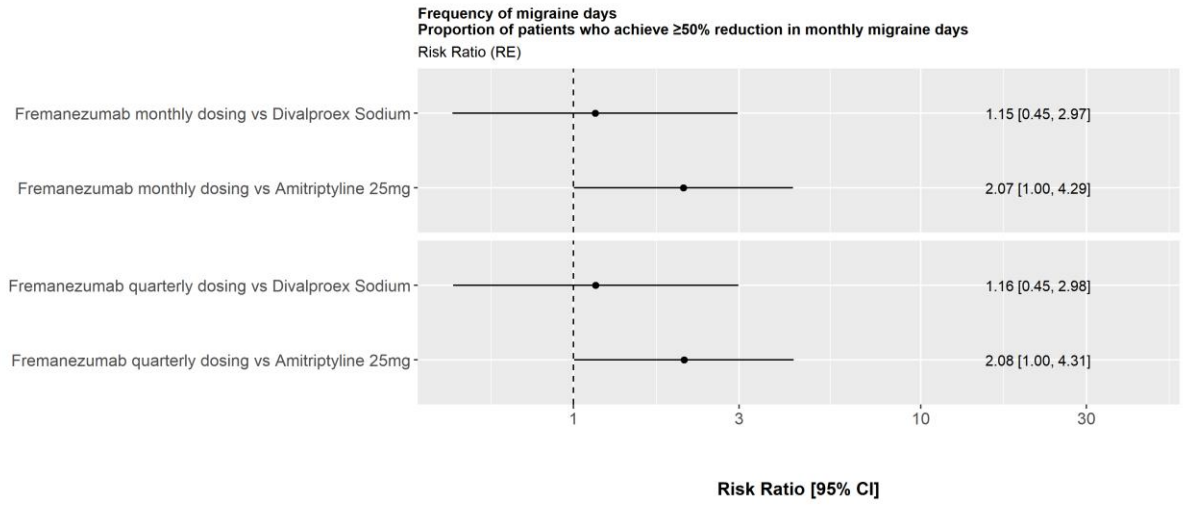

FIGURE 8 CLINICAL QUESTION 2 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO EACH COMPARATOR TREATMENT; RISK RATIO FOR PROPORTION OF PATIENTS WHO ACHIEVE ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS. STATISTICAL SIGNIFICANCE OF FREMANEZUMAB MONTHLY AND QUARTERLY DOSING COMPARED TO AMITRIPTYLINE. THE CI LOWER LIMITS IN THE COMPARISON BETWEEN FREMANEZUMAB MONTHLY AND QUARTERLY DOSING TO AMITRIPTYLINE ARE 1.0008 AND 1.0047, RESPECTIVELY.

Proportion of patients who experience adverse events leading to discontinuation

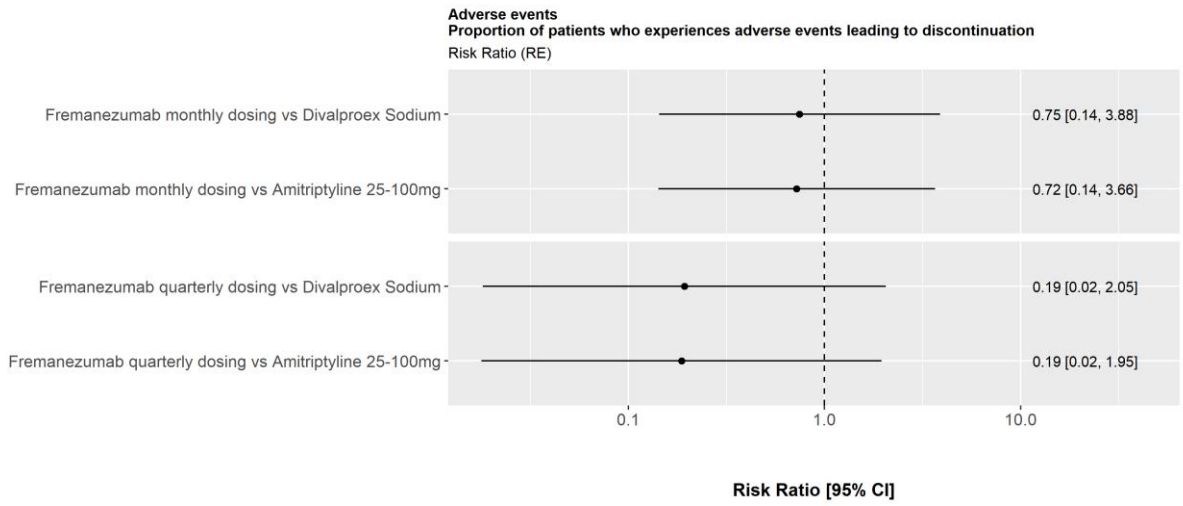

FIGURE 9 CLINICAL QUESTION 2 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO EACH COMPARATOR TREATMENT; RISK RATIO FOR PROPORTION OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS LEADING TO DISCONTINUATION (RANDOM EFFECT)

3.3.3.3 *Narrative description of adverse events*

Tolerability and adherence in general

Fremanezumab

A total of over 2,500 patients (more than 1,900 patient years) have been treated with fremanezumab in registration studies. More than 1,400 patients were treated for at least 12 months. Commonly reported adverse drug reactions (ADRs) were local reactions at the injection site (pain [24%], induration [17%], erythema [16%] and pruritus [2%]) [70].

The very common adverse reactions were induration, and erythema. Common adverse reactions were pruritus.

From the FOCUS trial, serious adverse events were reported for four (1%) of 277 participants receiving placebo, two (<1%) of 276 receiving quarterly fremanezumab, and four (1%) of 285 receiving monthly fremanezumab. No individual serious adverse event occurred in more than one participant, and no serious adverse events were considered treatment related by investigators. In participants receiving placebo, serious adverse events were thoracic vertebral fracture, uterine leiomyoma, vulval cancer, hypoaesthesia, and metrorrhagia. In participants receiving fremanezumab (either dosing regimen), serious adverse events were atrial fibrillation, cholelithiasis, clavicle fracture, foot fracture, respiratory fume inhalation, rib fracture, road traffic accident, back pain, ephrolithiasis, and vocal cord thickening. In summary, fremanezumab had comparable rates of AEs compared with placebo in patients with migraine and documented inadequate response to 2 to 4 classes of migraine preventive medications. [30,49]

Current prophylaxis treatments of migraine (incl. off-label) are often associated with a variable effect and multiple adverse events, which lead to a high level of discontinuation with the treatment in both clinical studies and in clinical practice [71–73].

E.g. in a retrospective register study with 4,634 enrolled patients, 73.4% of the patients treated with antidepressant ended their treatment after 6 months, 70.2% of the patients treated with antiepileptic ended treatment after 6 months as well and the same did 67.6% of all patients treated with beta-blockers in clinical practice [74]. In another retrospective register study of 8,707 chronic migraine patients approximately 3 out of 4 patients disrupted their treatment after 6 months independent of the type of medication. 10% of the patients disrupted treatment after 1 year. Only 13-16% of the patients were still taking the medication after 1 year [73].

Injection-site reactions

The most frequently observed local reactions at the injection site were pain, induration and erythema. All local injection site reactions were transient and predominantly mild to moderate in severity. Pain, induration and erythema were typically observed immediately after injection while pruritus and rash appeared within a median of 24 and 48 hours, respectively. All injection site reactions resolved, mostly within a few hours or days. Injection site reactions generally did not necessitate discontinuation of the medicinal product. [70]

Immunogenicity

In placebo-controlled studies, 0.4 % of patients (6 out of 1,701) treated with fremanezumab developed anti-drug antibodies (ADA). The antibody responses were of low titer. One of these 6 patients developed

neutralizing antibodies. To date, 1,494 patients have completed 12 months of treatment with fremanezumab in the ongoing long-term Study 3. ADA were detected in 2% of the patients (38 out of 1,888). The safety and efficacy of fremanezumab were not affected by ADA development. [70]

Overdose

Doses up to 2,000 mg have been administered intravenously in clinical trials without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate symptomatic treatment if necessary. [70]

Comparison of adverse events, contraindications, precautions, and pregnancy

The below-mentioned information regarding comparators is obtained from Lægemiddelstyrelsens approved summary of product characteristics except if another source is cited; amitriptyline [7] and valproate [9].

Information regarding fremanezumab was obtained for the European Public Assessment report (EPAR) [70].

Adverse events

For fremanezumab, injection site induration, and injection site erythema are listed as "very common" adverse events [82].

Valproate

Valproate is not approved as preventive migraine treatment in Denmark (off-label) [76].

Treatment with valproate is subject to additional supervision and all healthcare professionals are expected to report any suspected adverse events.

Adverse events associated with valproate treatment are dose dependent and often passing. Common adverse events include, amongst other, anemia, thrombocytopenia, tremor, cramps, dizziness, memory loss, headache, apatheia, deafness, nausea, incontinence, hypersensitivity, either weight gain or weight loss, and general confusion and hallucinations. In patients treated with valproate in longer periods, adverse events such as decreased bone density, osteoporosis, and bone fractures. How treatment with valproate affect the bone metabolism has not been clarified.

Amitriptyline

Amitriptyline is associated with adverse events similar to antidepressant. Some of the most common adverse events are headache, tremor, difficulties concentrating, obstipation and decreased libido. Treatment with amitriptyline is also associated with depression which often can explain the above-mentioned adverse events. Very common adverse events are; aggression, tiredness, dizziness, dysarthria, tachycardia, orthostatic hypotension, mouth dryness, nausea, hyperhidrosis, and weight gain.

Additionally, case reports regarding suicidal thoughts were reported either during treatment with amitriptyline or right after ended treatment.

Contraindications

For fremanezumab the only contraindications are hypersensitivity to the active substance or to any of the excipients listed below:

- L-histidine

- L-histidine hydrochloride monohydrate
- Sucrose
- Disodium ethylenediaminetetraacetic acid (EDTA) dihydrate
- Polysorbate 80
- Water for injections

In contrast, especially propranolol, amitriptyline is known to have many contraindications (>10).

Precautions

Fremanezumab

Only three populations are defined as "special population":

- **Elderly**: There is limited data available on the use of fremanezumab in patients ≥65 years of age. Based on the results of population pharmacokinetic analysis, no dose adjustment is required.
- **Renal or hepatic impairment**: No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment.
- **Pediatric population**: The safety and efficacy of AJOVY in children and adolescents below the age of 18 years have not yet been established. No data are available.

For oral prophylaxis drugs multiple precautions are stated on several pages in Lægemiddelstyrrelsens summary of product characteristics.

Valproate

Amongst the many precautions stated in the summary of product characteristics the report concerning suicidal thoughts and suicidal behavior can be highlighted as those have been seen in various cases with patients being treated with antiepileptic medication.

Amitriptyline

Cases with prolonged QT interval have been reported, thus precautions should be taken in patients with bradycardia or heart insufficiency. Treatment with amitriptyline is associated with depression which leads to an increased possibility of suicidal thoughts, self-destructive actions, and suicide (suicide related cases). This risk continues until significant remission occurs.

Pregnancy

Fremanezumab

Pregnancy

There is a limited amount of data from the use of AJOVY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of AJOVY during pregnancy [70].

Breast-feeding

It is unknown whether fremanezumab is excreted in human milk. Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of fremanezumab could be considered during breast-feeding only if clinically needed [70].

Fertility

There are no fertility data in humans. Available non-clinical data do not suggest an effect on fertility [70].

Amitriptyline

There is a limited amount of data regarding prescribing amitriptyline to pregnant women. However, studies on animals have shown reproductive toxigenicity. Therefore, amitriptyline is not recommended during pregnancy unless it is absolutely necessary and only after thorough guidance about expected pros and cons.

Valproate

Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders. Valproate is contraindicated in pregnancy and in women with childbearing potential which is the majority of the patient population. [33] According to the SmPC, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. [33] A recent Danish study concludes, that women who have used valproate during pregnancy have a higher risk of having children with ADHD. The study follows the advice from SST (2014) against the use of valproate in pregnant women [83]. EMA has tried to limit the use of valproate in women of childbearing age and raising awareness regarding the hazardous effect of valproate to children exposed in utero. The teratogenic and foetotoxic effects of valproate are well documented, and more recent studies show that there is an even greater neurodevelopmental risk to children exposed to valproate in the womb. The latest 2018 European review from the EMA, with the active participation of the European Headache Federation, concluded that not enough has been done to mitigate the risks associated with in utero exposure to valproate [84]

3.4 Clinical question 3: Hvad er den kliniske merværdi af fremanezumab til patienter med kronisk migræne, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper sammenlignet med Botox?

3.4.1 Presentation of relevant studies

See Table 24 for an overview of included studies and its associated population and follow-up time. Note, large differences exist.

TABLE 24 OVERVIEW OF INCLUDED STUDIES AND FOLLOW-UP TIME

Clinical question 3	
Study	**Follow-up time**
Fremanezumab EM+CM, Ferrari et al. 2019	12 weeks*
Aurora et al, 2010 (PREMPT I)	24 weeks
Diener et al, 2010 (PREMPT II)	24 weeks

***For the outcome HIT-6, the follow-up time was 4 weeks after administration of the third dose of study drug**

Fremanazumab

3.4.1.1 *Ferrari et al, 2019*

Please see description in section 3.3.1.1.

Botox

3.4.1.2 *Aurora et al, 2010 (PREEMPT I)*

This is the first of a pair of studies designed to assess efficacy, safety and tolerability of onabotulinumtoxinA (BOTOX) as headache prophylaxis in adults with chronic migraine.

Migraine days

The primary endpoint in PREEMPT 1 was mean change from baseline in frequency of headache episodes for the 28-day period ending with week 24.

Definition: A headache episode was defined as patient-reported headache with a start and stop time indicating that the pain lasted 4 continuous hours.

All other efficacy analyses were also based on the mean change from baseline to the 28 days ending with week 24.

For primary and secondary variables, the prespecified comparison between treatment groups was done by analysis of covariance of the change from baseline, with the same variable's baseline value as covariate, with main effects of treatment group and medication overuse strata. The baseline covariate adjustment was prespecified as the primary analysis, but sensitivity analyses (e.g., rank-sum test on changes from baseline without a baseline covariate) were also performed.

For binomial variables, the between-group comparisons were done with Pearson's Chi-square or Fisher's exact tests, except that logistic regression with the same variable's baseline as covariate was used for variables with baseline imbalance. A two-sided test with $p \leq 0.05$ was considered to be statistically significant.

Adverse events

Safety analysis was performed on all randomized patients who received at least one dose of study medication at day 0.

3.4.1.3 *Diener et al, 2010 (PREEMPT II)*

This is the second of a pair of studies designed to evaluate the efficacy and safety of onabotulinumtoxinA (BOTOX) for prophylaxis of headaches in adults with chronic migraine.

Migraine days

The primary efficacy endpoint was mean change from baseline in frequency of headache days for the 28-day period ending with week 24.

Definition: A headache day was defined as a calendar day (00:00 to 23:59) when the patient reported four or more continuous hours of a headache, per the patient diary.

All other efficacy analyses were also based on the mean change from baseline to the 28 days ending with week 24. Statistical analyses are the same as used in the PREEMPT I study (section 3.4.1.2)

Adverse events

Safety analyses were performed on all randomized patients who received at least one dose of study medication at day 0.

3.4.2 Results per study

Fremanazumab

3.4.2.1 *Ferrari et al, 2019*

All results from the trial are provided in Table 64.

Qualitative description of adverse events

Please see description in section **Fejl! Henvisningskilde ikke fundet.**.

Botox

All results from the pooled analysis of PREEMPT I and II are provided in Table 89.

3.4.2.2 *Aurora et al, 2010 (PREEMPT I)*

Qualitative description of adverse events

A total of 59.7% of onabotulinumtoxinA-treated patients experienced adverse events compared with 46.7% of the placebo-treated patients. The only individual treatment-related adverse events occurring at a rate ≥ 5% were neck pain (5.9%) and muscle weakness (5.9%) in the onabotulinumtoxinA group. The overall incidence of serious adverse events was 5.3% onabotulinumtoxinA vs. 2.4% placebo). In the onabotulinumtoxinA group, 4.1% of the patients discontinued due to adverse events compared to 0.9% in the placebo group. Treatment-related adverse events were consistent with the known tolerability profile of onabotulinumtoxinA, and no newly emerged safety finding was observed.

3.4.2.3 *Diener et al, 2010 (PREEMPT II)*

Qualitative description of adverse events

Frequency of adverse events was higher in the onabotulinumtoxinA group (65.1%) compared to the placebo group (56.4%). The only individual treatment-related adverse events in the onabotulinumtoxinA group occurring at a rate ≥ 5% were neck pain (7.5%) and muscle weakness (5.2%). Eyelid ptosis, myalgia and musculoskeletal stiffness were also higher in the onabotulinumtoxinA group than among place-treated patients. There was one treatment-related adverse event reported for onabotulinumtoxinA (migraine requiring hospitalization). Discontinuations due to adverse events were 3.5% in the onabotulinumtoxinA group and 1.4% in the placebo group.

3.4.3 Comparative analyses

Clinical question 3

Table 25 and Table 26 outline the favored treatment based on the ITC.

On all measured parametres, the ITC favors fremanezumab compared to the botox population in clinical question 3.

The ITC results comparing fremanezumab to botox are significantly favouring fremanezumab with regards to the percent reduction of mean monthly migraine days (critical outcome), the proportion of patients who achieve ≥50% reduction in monthly migraine days (important outcome), and the monthly days with reduction in number of days with acute headache medication (important outcome) in both a monthly and quarterly dosing of fremanezumab.

Based on the ITC data, fremanezumab is (favored and) considered to be more effective than botox, in both the monthly and quarterly dosing regimen of fremanezumab.

Based on the ITC data, fremanezumab is (favored and) considered to have a better effect on the burden of migraine than botox (HIT-6), in both the monthly and quarterly dosing regimen of fremanezumab.

Based on the ITC data, fremanezumab is (favored and) considered to be more tolerable than Botox (proportion of patients who experiences adverse events leading to discontinuation), in both the monthly and quarterly dosing regimen of fremanezumab.

In this section results of the comparative analysis will be outlined in regard to performed meta-analysis, ITC and narrative description of adverse events. **See**

Table 14 **(section 2.7) for how to interpret the ITC results.**

Table 25 and Table 26 are based on the random effect results as data from the trials are randomized trials.

TABLE 25 INTERPRETATION OF ITC FOR CLINICAL QUESTION 3, FREMANEZUMAB MONTHLY DOSING SCHEME (SINGLE STUDY)

Outcome	Intervention	Comparator	Measure	Favors	Significant
Percent reduction of mean monthly migraine days	Fremanezumab monthly dosing	Botox	Mean Difference	Fremanezumab	Yes
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab monthly dosing	Botox	Risk Ratio	Fremanezumab	Yes
Point reduction quality of life (HIT-6)	Fremanezumab monthly dosing	Botox	Mean Difference	Fremanezumab	
Monthly days with reduction in number of days with acute headache medication, change from baseline	Fremanezumab monthly dosing	Botox	Mean Difference	Fremanezumab	Yes
Proportion of patients who experiences adverse events leading to discontinuation	Fremanezumab monthly dosing	Botox	Risk Ratio	Fremanezumab	

TABLE 26 INTERPRETATION OF ITC FOR CLINICAL QUESTION 3, FREMANEZUMAB QUARTERLY DOSING SCHEME (SINGLE STUDY)

Outcome	Intervention	Comparator	Measure	Favors	Significant
Percent reduction of mean monthly migraine days	Fremanezumab quarterly dosing	Botox	Mean Difference	Fremanezumab	Yes
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab quarterly dosing	Botox	Risk Ratio	Fremanezumab	Yes
Point reduction quality of life (HIT-6)	Fremanezumab quarterly dosing	Botox	Mean Difference	Fremanezumab	
Monthly days with reduction in number of days with acute headache medication, change from baseline	Fremanezumab quarterly dosing	Botox	Mean Difference	Fremanezumab	Yes
Proportion of patients who experiences adverse events leading to discontinuation	Fremanezumab quarterly dosing	Botox	Risk Ratio	Fremanezumab	

3.4.3.1 *Meta-analysis*

The following Table 27 indicates which studies were included for the meta-analysis for each outcome. A "yes" indicate that the study was included, a "No" that the study was not included (due to insufficient data, non-reported, or incomparable outcomes).

TABLE 27 OVERVIEW OF INCLUDED STUDIES AND OUTCOMES IN THE META-ANALYSIS FOR CLINICAL QUESTION 3

Study	Outcome				
	Proportion ≥ 50% reduction in monthly migraines	**Proportion of patients who experience AEs leading to discontinuation**	**Monthly migraine days, change from baseline**	**Quality of life; Mean change from baseline in HIT-6 score**	**% reduction in number of days with any acute headache medication**
Total	**2**	**2**	**2**	**2**	**2**
Fremanezumab, Ferrari 2019	Yes	Yes	Yes	Yes	Yes
Botox, Aurora 2011	Yes	Yes	Yes	Yes	Yes

3.4.3.2 *ITC results*

The ITC results for Clinical Question 3 are given in Figure 10 to Figure 14. Random effect (RE) results are given, which refers to the meta-analysis; where treatments were compared to placebo using meta-analysis, the meta-analysis was performed using either FE or RE model.

For interpretation of the ITC results, see

Table 14 **(section 2.7) for guidance**

Tables with results per PICO are given in Table 102 and Table 103 in Appendix D.

Percent reduction in mean monthly migraine days

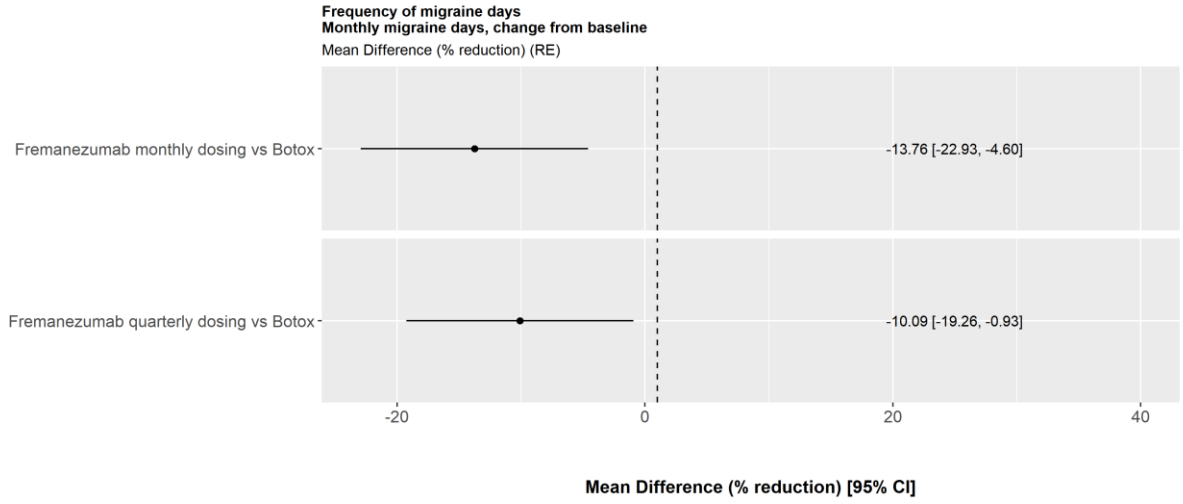

FIGURE 10 CLINICAL QUESTION 3 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO BOTOX TREATMENT; MEAN DIFFERENCE (% REDUCTION) FOR MONTHLY MIGRAINE DAYS (RANDOM EFFECT). STATISTICAL SIGNIFICANCE OF FREMANEZUMAB MONTHLY AND QUARTERLY DOSING COMPARED TO BOTOX.

Proportion of patients who achieve at least 50% reduction in monthly migraine days

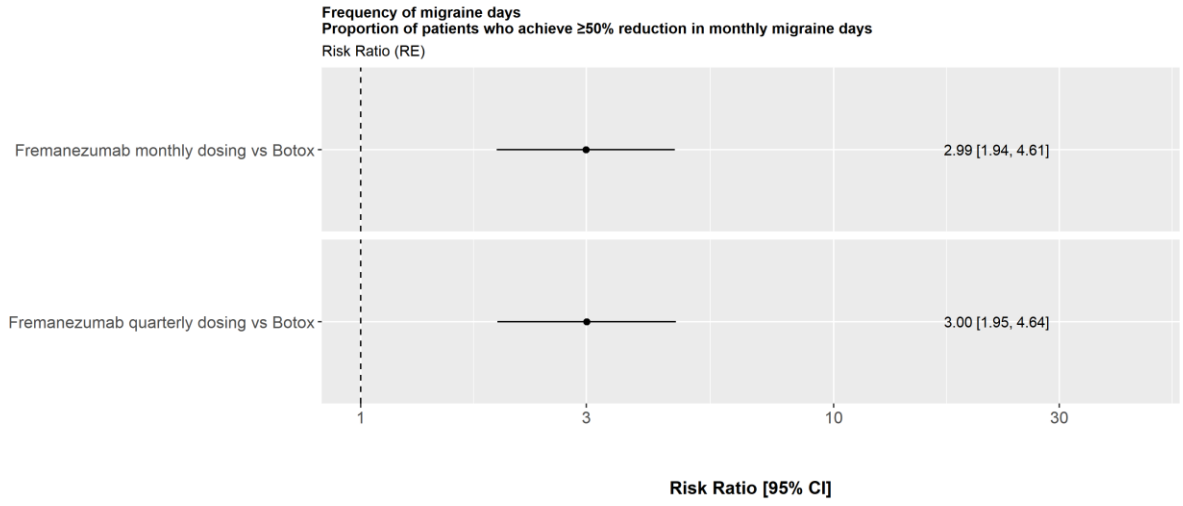

FIGURE 11 CLINICAL QUESTION 3 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO BOTOX TREATMENT; RISK RATIO FOR PROPORTION OF PATIENTS WHO ACHIEVE ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS (RANDOM EFFECT). STATISTICAL SIGNIFICANCE OF FREMANEZUMAB MONTHLY AND QUARTERLY DOSING COMPARED TO BOTOX.

Point reduction in Quality of Life (HIT-6)

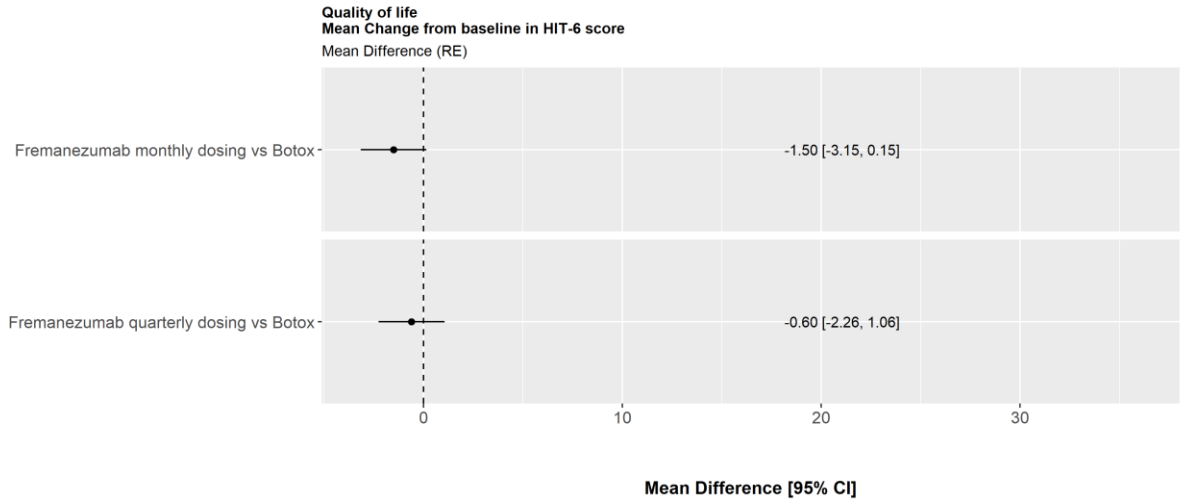

FIGURE 12 CLINICAL QUESTION 3 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO BOTOX TREATMENT; MEAN DIFFERENCE (POINT REDUCTION) FOR QUALITY OF LIFE, HIT-6 SCORE (RANDOM EFFECT).

Monthly days with reduction in number of days with acute headache medication

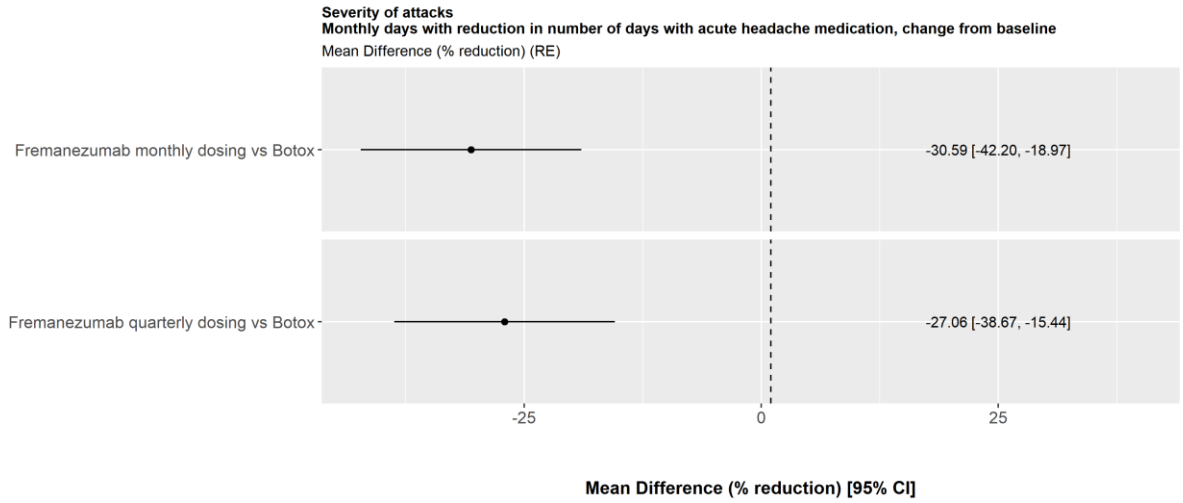

FIGURE 13 CLINICAL QUESTION 3 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO BOTOX TREATMENT; MEAN DIFFERENCE (% REDUCTION) FOR MONTHLY DAYS WITH REDUCTION IN NUMBER OF DAYS WITH ACUTE HEADACHE MEDICATION (RANDOM EFFECT). STATISTICAL SIGNIFICANCE OF FREMANEZUMAB MONTHLY AND QUARTERLY DOSING COMPARED TO BOTOX.

Proportion of patients who experience adverse events leading to discontinuation

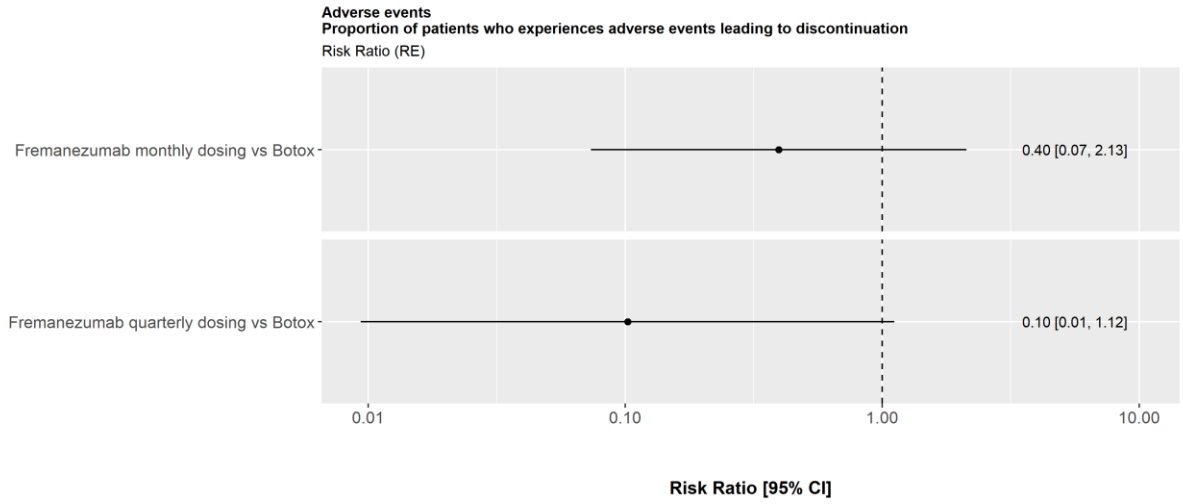

FIGURE 14 CLINICAL QUESTION 3 INDIRECT TREATMENT COMPARISON OF FREMANEZUMAB (MONTHLY AND QUARTERLY DOSING) TO BOTOX TREATMENT; RISK RATIO FOR PROPORTION OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS LEADING TO DISCONTINUATION (RANDOM EFFECT)

3.4.3.3 *Narrative description of adverse events*

Tolerability and adherence in general

Fremanezumab

A total of over 2,500 patients (more than 1,900 patient years) have been treated with AJOVY in registration studies. More than 1,400 patients were treated for at least 12 months. Commonly reported adverse drug reactions (ADRs) were local reactions at the injection site (pain [24%], induration [17%], erythema [16%] and pruritus [2%]) [70].

The very common adverse reactions were induration, and erythema. Common adverse reactions were pruritus.

From the FOCUS trial, serious adverse events were reported for four (1%) of 277 participants receiving placebo, two (<1%) of 276 receiving quarterly fremanezumab, and four (1%) of 285 receiving monthly fremanezumab. No individual serious adverse event occurred in more than one participant, and no serious adverse events were considered treatment related by investigators. In participants receiving placebo, serious adverse events were thoracic vertebral fracture, uterine leiomyoma, vulval cancer, hypoaesthesia, and metrorrhagia. In participants receiving fremanezumab (either dosing regimen), serious adverse events were atrial fibrillation, cholelithiasis, clavicle fracture, foot fracture, respiratory fume inhalation, rib fracture, road traffic accident, back pain, ephrolithiasis, and vocal cord thickening. In summary, fremanezumab had comparable rates of AEs compared with placebo in patients with migraine and documented inadequate response to 2 to 4 classes of migraine preventive medications. [30,49]

Current prophylaxis treatments of migraine (incl. off-label) are often associated with a variable effect and multiple adverse events, which lead to a high level of discontinuation with the treatment in both clinical studies and in clinical practice [71–73].

Injection-site reactions

The most frequently observed local reactions at the injection site were pain, induration and erythema. All local injection site reactions were transient and predominantly mild to moderate in severity. Pain, induration and erythema were typically observed immediately after injection while pruritus and rash appeared within a median of 24 and 48 hours, respectively. All injection site reactions resolved, mostly within a few hours or days. Injection site reactions generally did not necessitate discontinuation of the medicinal product. [70]

Immunogenicity

In placebo-controlled studies, 0.4 % of patients (6 out of 1,701) treated with fremanezumab developed anti-drug antibodies (ADA). The antibody responses were of low titer. One of these 6 patients developed neutralizing antibodies. To date, 1,494 patients have completed 12 months of treatment with fremanezumab in the ongoing long-term Study 3. ADA was detected in 2% of the patients (38 out of 1,888). The safety and efficacy of fremanezumab were not affected by ADA development. [70]

Overdose

Doses up to 2,000 mg have been administered intravenously in clinical trials without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate symptomatic treatment if necessary. [70]

Comparison of adverse events, contraindications, precautions, and pregnancy

The below-mentioned information regarding botox is obtained from Lægemiddelstyrelsens approved summary of product characteristics except if another source is cited [6].

Information regarding fremanezumab was obtained for the European Public Assessment report (EPAR) [70].

Adverse events

For fremanezumab, injection site induration, and injection site erythema are listed as "very common" adverse events (fremanezmab SmPC).

Botox

Botox is not approved as preventive migraine treatment in patients with episodic migraine (EM) in Denmark (off-label). Botox is only approved as preventive treatment in patients with chronic migraine [76].

Botox treatment is associated with multiple adverse events often presenting within a few days after the injection. Generally, the adverse events are short-term, but some can last for several months and sometimes even longer. Very common adverse events include virus infections and ear infections, ptosis, dysphagia, muscle weakness, general pain and discomfort, urinary tract infections, dysuria, and pain around the injection site. Fever and influenza symptoms have been reported as adverse events as well. Only the most common adverse events are stated here, but in general, Botox treatment is associated with multiple both common and rarer adverse events such as pain in the extremities, falling accidents, difficulties walking, rashes, edema, and dysphagia

Contraindications

For fremanezumab the only contraindications are hypersensitivity to the active substance or to any of the excipients listed below:

- L-histidine
- L-histidine hydrochloride monohydrate
- Sucrose
- Disodium ethylenediaminetetraacetic acid (EDTA) dihydrate
- Polysorbate 80
- Water for injections

In contrast, especially propranolol, amitriptyline is known to have many contraindications (>10).

Precautions

Fremanezumab

Only three populations are defined as "special population":

- **Elderly**: There is limited data available on the use of fremanezumab in patients ≥65 years of age. Based on the results of population pharmacokinetic analysis, no dose adjustment is required.
- **Renal or hepatic impairment**: No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment.
- **Pediatric population**: The safety and efficacy of AJOVY in children and adolescents below the age of 18 years have not yet been established. No data are available.

For oral prophylaxis drugs multiple precautions are stated on several pages in Lægemiddelstyrelsen summary of product characteristics.

Botox

The recommended doses and administrations frequency for Botox should not be exceeded due to a potential risk of overdose, aggressive muscle weakness, spread of the toxin removed from the administration site, and the potential development of neutralizing antibodies.

Pregnancy

Fremanezumab

Pregnancy

There is a limited amount of data from the use of AJOVY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of AJOVY during pregnancy [70].

Breast-feeding

It is unknown whether fremanezumab is excreted in human milk. Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of fremanezumab could be considered during breast-feeding only if clinically needed [70].

Fertility

There are no fertility data in humans. Available non-clinical data do not suggest an effect on fertility [70].

Botox

There is no sufficient data regarding the use of botox in pregnant women. Studies in animals have shown reproductive toxicity but the potential risk in human is unknown. Botox should not be used in pregnant women or in women in the fertile age who are not using contraceptions unless it is absolutely necessary.

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5 Appendices

APPENDIX A: Literature search

TABLE 28 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	Population: Patients with episodic or chronic migraine with at least 4 monthly migraine days. Intervention(s): fremanezumab Comparator(s): metoprolol, propranolol, lisinopril, candesartan, topiramate, valproate, TCA or botox Outcomes: at least one of the outcomes outlined in the protocol Study design: RCT, placebo-controlled Language restrictions: English or Danish
Exclusion criteria	Population: other types of headaches or the inclusion of medication overuse headache Intervention(s): Comparator(s): Outcomes: follow-up period less than 3 months Settings (if applicable): Study design: Language restrictions: Other search limits or restrictions applied: other languages than English or Danish

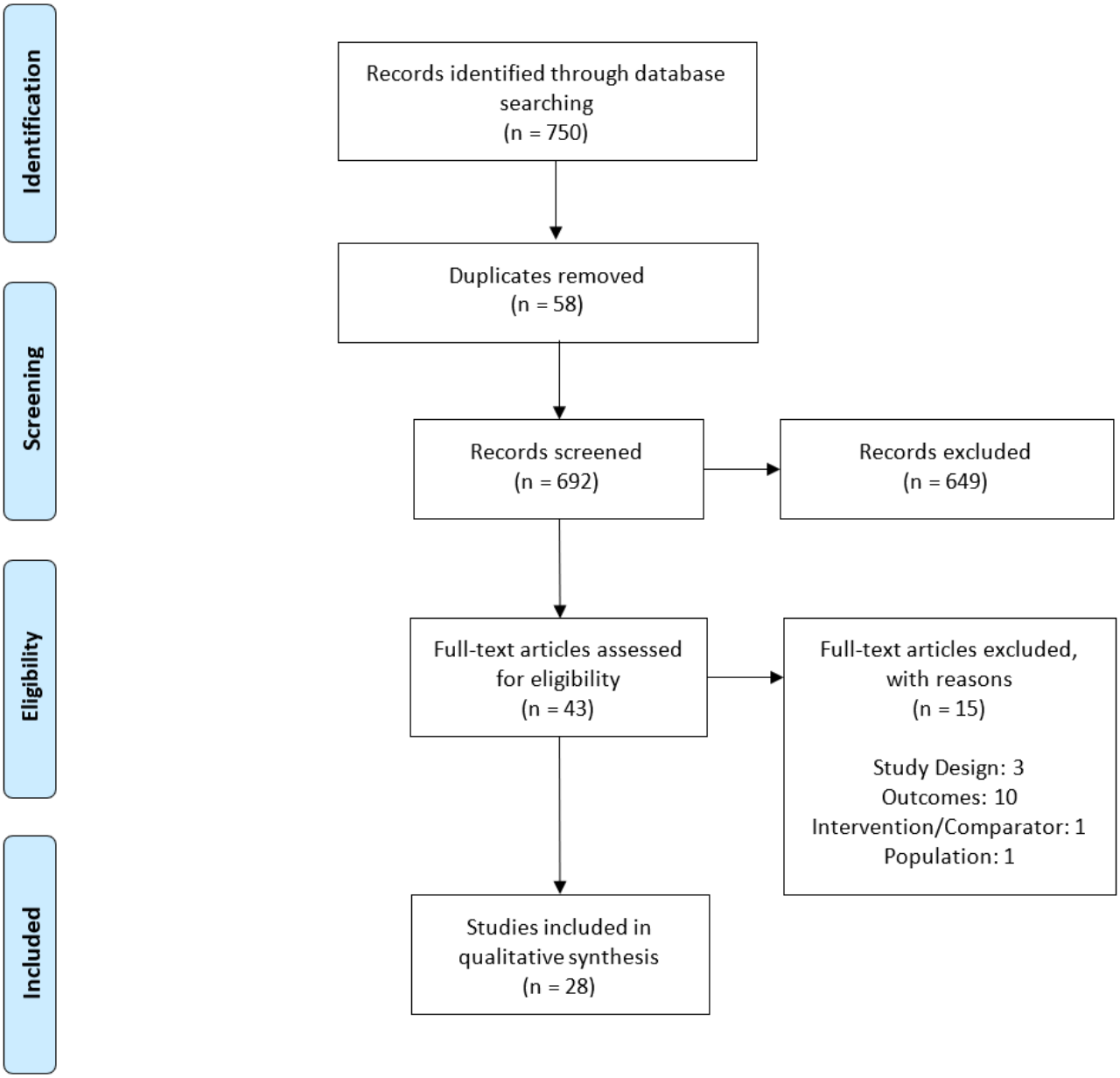

FIGURE 15: PRISMA-FLOWCHART. 28 STUDIES WERE INCLUDED IN THE QUALITATIVE SYNTHESIS. ADDITIONALLY, THE LATER PUBLISHED FOCUS TRIAL WAS INCLUDED AFTER THE LITTERATURE SEARCH.

APPENDIX B: Main characteristics of included studies

Study characteristics

5.1 Fremanezumab

5.1.1 Dodick et al, 2018 (HALO EM)

TABLE 29 MAIN CHARACTERISTICS OF PHASE III HALO EM

Trial name	*HALO EM*
NCT number	*NCT02629861*
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 sc injections of placebo in patients with episodic migraine (EM).*
Publications – title, author, journal, year	*Effect of fremanezumab compared with placebo for prevention of episodic migraine, Dodick et al., JAMA, 2018*
Study type and design	*Randomized, double-blind, placebo-controlled, parallel-group phase 3 trial. Patients with episodic migraine were randomized 1:1:1 (stratified by sex, country, and baseline preventive migraine medication use) to receive (1) fremanezumab monthly, (2) a single higher dose of fremanezumab intended to support a quarterly dose regimen, or (3) placebo. Randomization was performed using electronic interactive response technology. Patients, investigators, the sponsor, and designated personnel were blinded to treatment 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 265 lbs, inclusive* *Additional criteria apply, please contact the investigator for more information* ***Exclusion Criteria:*** • *Clinically significant hematological, 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*

<table>
<tr><td></td><td colspan="4">

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

Additional criteria apply, please contact the investigator for more information
</td></tr>
<tr><td>Intervention</td><td colspan="4">291 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.

290 participants randomized to the fremanezumab 675/225/225 mg treatment (monthly dosing) arm received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) on Days 28 and 56.

294 participants received matching placebo.</td></tr>
<tr><td rowspan="11">Baseline characteristics</td><td colspan="4">Baseline characteristics (total population)</td></tr>
<tr><td>Characteristic</td><td>Fremanezumab (monthly dosing)</td><td>Fremanezumab (quarterly dosing)</td><td>Placebo</td></tr>
<tr><td>Age, year, mean (SD)</td><td>42.9 (12.7)</td><td>41.1 (11.4)</td><td>41.3 (12.0)</td></tr>
<tr><td>Body mass index</td><td>26.2 (5.2)</td><td>27.0 (5.1)</td><td>27.2 (4.9)</td></tr>
<tr><td>Female sex, n (%)</td><td>244 (84.1)</td><td>251 (86.3)</td><td>247 (84.0)</td></tr>
<tr><td>Disease history
Time since initial migraine diagnosis, year, mean (SD)
Current preventive medication use, n (%)
Current acute headache medication use, n (%)
Prior topiramate use, n (%)</td><td>

20.7 (12.9)
62 (21.4)

279 (96.2)
64 (22.1)</td><td>

20.0 (21.1)
58 (19.9)

281 (96.6)
51 (17.5)</td><td>

19.9 (11.9)
62 (21.1)

280 (95.2)
53 (18.0)</td></tr>
<tr><td>Disease characteristics during 28-day prevention period
Migraine days
Headache days of at least moderate severity</td><td>
8.9 (2.6)
6.8 (2.9)</td><td>
9.3 (2.7)
7.2 (3.1)</td><td>
9.1 (2.7)
6.9 (3.1)</td></tr>
</table>

	Days with use of any acute headache medications *Days with use of migraine-specific acute headache medications*	*7.7 (3.4)* *6.1 (3.1)*	*7.8 (3.7)* *6.6 (3.1)*	*7.7 (3.6)* *7.1 (3.0)*
	MIDAS score, mean (SD)	*38.0 (33.2)*	*41.7 (33.0)*	*37.2 (27.6)*
Primary and secondary endpoints	*The primary end point was the mean change from baseline (28-day pretreatment period) in the mean number of monthly migraine days during the 12-week period after the first injection.* *Secondary efficacy endpoints were:* • *the proportion of patients achieving at least a 50% reduction in the mean number of monthly migraine days from baseline to week 12* • *the mean change from baseline to week 12 in the monthly mean number of monthly days with use of any acute headache medications* • *the mean change from baseline to week 4 in the number of migraine days* • *the mean change from baseline to week 12 in mean number of monthly migraine days in patients not receiving concomitant migraine preventive medication* • *the mean change in the Migraine Disability Assessment (MIDAS) score.* *Adverse events and tolerability were assessed by evaluating reported adverse events, vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate), 12-lead electrocardiogram, clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis), physical examinations, and concomitant medication use. Suicidal ideation and behavior were assessed by the electronic Columbia-Suicide Severity Rating Scale. Systematic assessment of injection sites included examination for pain, erythema, induration, and ecchymosis immediately and 1 hour after dosing.*			
Method of analysis	*Efficacy analyses were conducted in the full analysis set, which included all randomized patients (intention-to-treat population). Analyses of adverse events were performed in all randomized patients who received at least 1 dose of study drug.* *The primary end point was analyzed using an analysis of covariance method. Ninety-five percent confidence intervals were constructed for the least-squares mean (LSM) differences between each fremanezumab group and the placebo group. The Wilcoxon rank-sum test was performed as the primary analysis if there was deviation from normality assumption as assessed by the Shapiro-Wilk test. The same analyses were used for relevant secondary end points. A mixed-effects repeated-measures analysis model was implemented as a sensitivity.*			
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.*			

5.1.2 Bigal et al, 2015 (EM)

TABLE 30 MAIN CHARACTERISTICS FROM BIGAL ET AL., 2015 (EM)

Trial name	*A Multicenter Assessment of LBR-101 in High Frequency Episodic Migraine*
NCT number	*NCT02025556*
Objective	*The purpose of this study is to determine whether monthly subcutaneous administration of LBR-101 is safe and provides migraine prevention in subjects with high frequency episodic migraine.*
Publications – title, author, journal, year	*Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Bigal et al., Lancet Neurology, 2015*
Study type and design	*In this multicentre, randomised, double-blind, placebo-controlled, phase 2b study, we enrolled men and women (aged 18-65 years) from 62 sites in the USA who had migraine headaches 8-14 days per month. Using a randomisation list generated by a central computerized system and an interactive web response system, we randomly assigned patients (1:1:1; stratified by sex and use of concomitant preventive drugs) after a 28 day run-in period to three 28 day treatment cycles of subcutaneous 225 mg TEV-48125, 675 mg TEV-48125, or placebo. Investigators, patients, and the funder were blinded to treatment allocation. Patients reported headache information daily using an electronic diary. The study is completed.*
Follow-up time	*Time Frame: 12 weeks after first dose of blinded study drug*
Population (inclusion and exclusion criteria)	***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.* • *Subjects fulfilling criteria for episodic migraine as per the Second Edition of The International Headache Society (Olesen and Steiner 2004), who experience migraine at high frequency as follows:* *- History of headaches on more than 8 days per month for at least 3 months prior to screening* *- Verification of headache frequency through prospectively collected baseline information during the 28-day run-in phase demonstrating headaches (of any type) on at least 8 days with a total of 8 to 14 days* fulfilling criteria for migraine.* **Operational definition for migraine and probable migraine days are presented in the statistical section of this protocol.* • *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 by entry of headache data on a minimum of 22/28 days (80% compliance).* ***Exclusion Criteria:***

<table>
<tr><td></td><td colspan="4">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 six months prior to screening.
Subject uses 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 colspan="4">319 participants randomized to the subcutaneous LBR-101. The three arms are: Subcutaneous High Dose LBR-101 Administered Monthly x 3; Subcutaneous Low Dose LBR-101 Administered Monthly x 3; Subcutaneous Placebo Administered Monthly x 3. Between Jan 8, 2014, and Oct 15, 2014, 297 participants were enrolled: 104 were randomly assigned to receive placebo, 95 to receive 225 mg TEV-48125, and 96 to receive 675 mg TEV-48125.</td></tr>
<tr><td rowspan="12">Baseline characteristics</td><td colspan="4">Baseline characteristics (total population)</td></tr>
<tr><td>Characteristic</td><td>Placebo (n=104)</td><td>TEV-48125 225 mg (n=96)</td><td>TEV-48125 675 mg (n=97)</td></tr>
<tr><td>Age, years</td><td>42·0 (11·6)</td><td>40·8 (12·4)</td><td>40·7 (12·6)</td></tr>
<tr><td>Height, cm</td><td>165·3 (9·2)</td><td>165·1 (6·3)</td><td>166·2 (8·9)</td></tr>
<tr><td>Body mass index, kg/m²</td><td>27·2 (5·2)</td><td>26·9 (5·2)</td><td>27·4 (5·1)</td></tr>
<tr><td>Female sex, n (%)</td><td>92 (88%)</td><td>87 (91%)</td><td>82 (85%)</td></tr>
<tr><td>Preventive drug use (yes)</td><td>28 (27%)</td><td>32 (34%)</td><td>26 (27%)</td></tr>
<tr><td>Discontinued past preventive drug use owing to absence of effi cacy</td><td>28 (27%)</td><td>32 (33%)</td><td>28 (29%)</td></tr>
<tr><td>Patients using triptans ≥11 days per month</td><td>13 (13%)</td><td>11 (12%)</td><td>7 (7%)</td></tr>
<tr><td>Migraine-days per month</td><td>11·5 (2·24)</td><td>11·5 (1·9)</td><td>11·3 (2·2)</td></tr>
<tr><td>Headache-days per month</td><td>12·4 (2·3)</td><td>12·6 (3·1)</td><td>12·5 (2·65)</td></tr>
<tr><td>Days using acute drugs per month</td><td>10·4 (3·6)</td><td>10·4 (3·6)</td><td>9·8 (4·0)</td></tr>
<tr><td>Days using triptans per month</td><td>8·5 (3·4)</td><td>8·2 (4·0)</td><td>6·9 (3·5)</td></tr>
</table>

	Medium or severe headache-days per month	*9·8 (2·7)*	*10·0 (3·1)*	*9·6 (2·9)*
	Headache-hours per month	*82·1 (49·3)*	*76·1 (36·7)*	*80·4 (36·6)*
	Migraine Disability Assessment score	*48·4 (47·5)*	*45·7 (42·6)*	*48·4 (46·1)*
	Data are mean (SD) or number of patients (%)			
Primary and secondary endpoints	*The primary endpoints:* *1. Efficacy of two distinct doses of subcutaneous LBR-101 in the preventive treatment of HFEM, measured by mean change from baseline in the monthly migraine days during the 28-day post treatment period ending with week 12 [Time Frame: 12 weeks after first dose of blinded study drug]* *2. Evaluate the safety and tolerability (i.e.: by measuring the change from baseline in the frequency and severity of adverse events) of LBR-101 in the preventive treatment of HFEM. [Time Frame: 12 weeks after first dose of blinded study drug]* *Secondary efficacy endpoint: Efficacy of two distinct doses of subcutaneous LBR-101 in the preventive treatment of HFEM, measured by mean change from baseline on the number of days with headache of any severity during 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 for the primary endpoint to provide at least 90% power to detect a difference of 1·5 days between placebo and active treatment (SD 3 days).* *Change from baseline in the number of migraine-days in 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; acute drug use and years since onset of disease were covariates; and patient was treated as a random effect. We used an unstructured covariance matrix for repeated findings within patients and constructed 95% CIs for the least square mean difference between each group. Since MIDAS is used to assess disability during a 3 month period and was measured only twice (pre-treatment and after the last treatment), the change from baseline in total MIDAS scores to week 12 was analysed using an ANCOVA model with treatment group, baseline preventive drug use, and sex as fixed effects and baseline MIDAS total scores and years since onset of disease as covariates.* *The post-hoc analyses of the proportion of responders were done using χ^2 tests. 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 participants who were randomly assigned to treatment group, received at least one dose of study drug, and provided at least one endpoint measurement. All treated participants were included in the safety analysis. We used SAS version 9.1.3 for all statistical analyses*			

Subgroup analyses	*N/A*

5.1.3 Silberstein et al, 2017 (HALO CM)

TABLE 31 MAIN CHARACTERISTICS OF PHASE III 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 sc 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, inclusive* *Additional criteria apply, please contact the investigator for more information* ***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*

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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
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

Additional criteria apply, please contact the investigator for more information
</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.

379 participants randomized to the fremanezumab 675/225/225 mg treatment (monthly dosing) arm received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) 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
Time since initial migraine diagnosis, year
Current use of preventive medication, n (%)
Current use of acute headache medication, n (%)
Previous use of topiramate, n (%)
Previous use of onabotulinumtoxinA, n (%)</td><td>19.7 ±12.8

77 (2)

359 (95)

106 (28)

66 (18)</td><td>20.1 ±12.0

85 (22)

360 (95)

117 (31)

50 (13)</td><td>19.9 ±12.9

77 (21)

358 (95)

117 (31)

49 (13)</td></tr>
<tr><td>Disease characteristics during 28-day prevention period
Headache days</td><td>13.2 ±5.5</td><td>12.8 ±5.8</td><td>13.3 ± 5.8</td></tr>
</table>
</td></tr>
</table>

	Days with headache of any severity and duration *Migraine days* *Days of use of any acute headache medications* *Days of use of migraine-specific acute headache medications*	*20.4 ±3.9* *16.2 ±4.9* *13.1 ±6.8* *11.3 ±6.2*	*20.3 ±4.3* *16.0 ±4.3* *13.1 ±7.2* *11.1 ±6.0*	*20.3 ± 4.2* *16.4 ±5.2* *13.0 ±6.9* *10.7 ±6.3*
	HIT-6 score	*64.3 ±4.7*	*64.6 ±4.4*	*64.1 ±4.8*
Primary and secondary endpoints	*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.* • *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 behavior 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 analyzed 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.*

5.1.4 Bigal et al, 2015 (CM)

TABLE 32 MAIN CHARACTERISTICS FROM BIGAL ET AL., 2015 (CM)

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*
Study type and design	*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.*
Follow-up time	*Time frame: 12 weeks*
Population (inclusion and exclusion criteria)	***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.*

<table>
<tr><td></td><td colspan="4">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 colspan="4">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 rowspan="15">Baseline characteristics</td><td colspan="4">Baseline characteristics (total population)</td></tr>
<tr><td>Characteristic</td><td>Placebo (n=89)</td><td>TEV-48125 675/225 mg (n=88)</td><td>TEV-48125 900 mg (n=86)</td></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>
<tr><td>Headache-hours of any severity per month</td><td>169·1 (113·11)</td><td>159·1 (90·73)</td><td>157·7 (108·16)</td></tr>
<tr><td>Headache-hours of at least moderate severity per month</td><td>91·90 (74·68)</td><td>90·7 (59·71)</td><td>96·20 (94·42)</td></tr>
<tr><td>Headache-days of at least moderate severity per month</td><td>13·9 (5·6)</td><td>13·8 (6·3)</td><td>13·1 (5·9)</td></tr>
<tr><td>Migraine-days per month</td><td>16·8 (5·0)</td><td>17·2 (5·4)</td><td>16·4 (5·3)</td></tr>
<tr><td>Days of acute drug use per month</td><td>15·7 (6·2)</td><td>15·1 (7·0)</td><td>16·2 (6·7)</td></tr>
<tr><td>Days of triptan use per month</td><td>10·0 (5·3)</td><td>9·2 (5·6)</td><td>11·8 (6·0)</td></tr>
<tr><td>Years of migraine</td><td>20·4 (13·1)</td><td>15·8 (11·2)</td><td>18·8 (12·2)</td></tr>
<tr><td>Preventive drug use (yes)</td><td>38 (43%)</td><td>35 (40%)</td><td>33 (38%)</td></tr>
<tr><td colspan="4">Data are mean (SD) or number of patients (%)</td></tr>
</table>

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.*

5.1.5 Ferrari et al, 2019 (FOCUS)

TABLE 33 MAIN CHARACTERISTICS FROM PHASE IIIB FOCUS

Trial name	*An Efficacy and Safety Study of Fremanezumab in Adults With Migraine (FOCUS)*
NCT number	*NCT03308968*
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 sc injections of placebo in patients 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 randomized, double-blind, placebo-controlled, phase 3b trial. Ferrari et al, Lancet, 2019.*
Study type and design	*A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled,Study With an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients With Inadequate Response to Prior Preventive Treatments, 838 men and women were enrolled (age 18-70 yr). The study consisted of three arms;* *Arm 1: fremanezumab monthly: During the double-blind period, participants with chronic migraine (CM) are administered Dosage A subcutaneous (sc) injection of fremanezumab at Week 0 (baseline) followed by Dosage B sc injections at Week 4 and Week 8 and participants with episodic migraine (EM) are administered Dosage B subcutaneous (sc.) injection of fremanezumab at Week 0 (baseline), Week 4, and Week 8 then followed by an open label period where all participants are administered Dosage B sc injection of fremanezumab at Weeks 12, 16 and 20. Intervention: fremanezumab.* *Arm 2: Fremanezumab quarterly: During the double-blind period, participants with chronic migraine (CM) and participants with episodic migraine (EM) are administered Dosage A sc injection of fremanezumab at Week 0 (baseline) followed by placebo sc injections at Week 4 and Week 8 followed by an open label period where all participants are administered Dosage B sc. injection of fremanezumab at Weeks 12, 16 and 20. Intervention: fremanezumab and placebo.* *Arm 3: Placebo Comparator: During the double-blind period, participants with chronic migraine (CM) and participants with episodic migraine (EM) are administered 3 placebo sc injections at Week 0, and 1 placebo injection at weeks 4 and 8 followed by an open label period where all participants are administered Dosage B sc. injection of fremanezumab at Weeks 12, 16 and 20. Intervention: fremanezumab and placebo.* *The study is completed.*
Follow-up time	*12 weeks*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *The patient has a diagnosis of migraine with onset at ≤50 years of age.* • *Body weight ≥45 kg* • *The patient has a history of migraine for ≥12 months prior to screening.* • *Women of childbearing potential (WOCBP) whose male partners are potentially fertile (i.e., 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)*

<table>
<tr><td></td><td colspan="4">

Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [e.g., 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).

Exclusion Criteria:

At the time of screening visit, patient is receiving any preventive migraine medications, regardless of the medical indication for more than 5 days and expects to continue with these medications.
Patient 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 patient has used an intervention/device (e.g., scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening.
The patient uses triptans/ergots as preventive therapies for migraine.
Patient uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (e.g., 81 mg) used for cardiovascular disease prevention is allowed.

</td></tr>
<tr><td>Intervention</td><td colspan="4">838 participants randomized in blinded-fashion 1:1:1 into one of three treatments for the subgroup - two active treatments and one 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 (weeks 13-week 24) during which everyone is administered sc injections of fremanezumab</td></tr>
<tr><td rowspan="12">Baseline characteristics</td><td colspan="4">Baseline characteristics (total population)</td></tr>
<tr><td>Characteristic</td><td>Placebo (n=279)</td><td>Quarterly fremanezumab (n=276)</td><td>Monthly fremanezumab (n=283)</td></tr>
<tr><td>Age, years</td><td>46.8 (11.1)</td><td>45.8 (11.0)</td><td>45.9 (11.1)</td></tr>
<tr><td>Height, cm</td><td>167.7 (9.0)</td><td>167.7 (8.1)</td><td>167.3 (7.7)</td></tr>
<tr><td>Body mass index, kg/m²</td><td>25.3 (4.1)</td><td>25.1 (4.1)</td><td>25.3 (4.3)</td></tr>
<tr><td>Female sex, n (%)</td><td>233 (84%)</td><td>229 (83%)</td><td>238 (84%)</td></tr>
<tr><td>Episodic migraine</td><td>112 (40%)</td><td>107 (39%)</td><td>110 (39%)</td></tr>
<tr><td>Chronic migraine</td><td>167 (60%)</td><td>169 (61%)</td><td>173 (61%)</td></tr>
<tr><td colspan="4">Number of previous preventive medication classes failed</td></tr>
<tr><td>2</td><td>142 (51%)</td><td>140 (51%)</td><td>133 (47%)</td></tr>
<tr><td>3</td><td>82 (29%)</td><td>85 (31%)</td><td>98 (35%)</td></tr>
<tr><td>4</td><td>54 (19%)</td><td>49 (18%)</td><td>50 (18%)</td></tr>
<tr><td>Monthly number of migraine days at baseline</td><td>14.3 (6.1)</td><td>14.1 (5.6)</td><td>14.1 (5.6)</td></tr>
<tr><td>Monthly number of headache days of at least moderate severity at baseline</td><td>12.8 (5.9)</td><td>12.4 (5.8)</td><td>12.7 (5.8)</td></tr>
</table>

	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 endpoint:* *Mean change from baseline in the monthly average number of migraine days during the double-blind period [Time Frame: Baseline (days -28 to 0), Treatment up to week 12]* *Secondary efficacy endpoint:* • *proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the double-blind period [Time Frame: Baseline, 12 weeks]* • *mean change from baseline in the monthly average number of headache days of at least moderate severity during the double-blind period [Time Frame: Baseline, 12 weeks]* • *mean change from baseline in the monthly average number of migraine days during the double-blind period [Time Frame: Baseline, 4 weeks]* • *proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the double-blind period [Time Frame: 4 weeks]* • *mean change from baseline in the monthly average number of days of use of any acute headache medications during the double-blind period [Time Frame: Baseline, 12 weeks]* • *mean change from baseline in the number of headache days of at least moderate severity during the double-blind period [Time Frame: Baseline, 4 weeks]* • *percentage of patients who did not complete study due to AEs [Time Frame: 12 weeks]* • *Percentage of Participants with Adverse Events [Time Frame: 12 weeks]*			
Method of analysis	*A sample size of 705 participants (235 per treatment group) completing the study was required for 90% power to show a difference of 1.8 in migraine days (assuming a common SD of 6 days) at an alpha level of 0.05. Assuming a 12% discontinuation rate, 268 participants per treatment group were planned for randomisation.* *The intention-to-treat analysis set comprised all randomly assigned participants. The safety analysis set comprised all randomly assigned participants who received at least one dose of study drug. Participants in the intention-to-treat analysis set who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessments for the primary outcome (modified intention-to-treat analysis set) were included in all efficacy analyses. The per-protocol analysis set was a subset of the modified intention-to-treat analysis set, including only participants who completed the study without important protocol deviations or any deviations or omissions in study drug administration.* *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 interaction, and treatment-bymigraine classification-by-month interaction 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. *Odds ratios (ORs), 95% CIs for ORs, and p values are presented for each fremanezumab dosing group (quarterly and monthly doses). Adverse events were summarised by counts and percentages. Changes in laboratory, electrocardiogram (ECG), and vital signs measurements data were summarized descriptively. All values were compared with predefined criteria to identify potentially clinically significant values or changes.*
Subgroup analyses	*As part of prespecified exploratory analyses, the primary efficacy outcome was evaluated in subgroups of participants who had previously not responded to topiramate, onabotulinumtoxinA, valproic acid, and valproic acid plus two to three classes of preventive medications.*

5.2 Topiramate

5.2.1 Storey et al, 2001

TABLE 34 MAIN CHARACTERISTICS FROM STOREY ET AL., 2001

Trial name	*Topiramate in migraine Prevention: A double blind placebo Controlled Study*
NCT number	*Not stated in publication*
Objective	*To evaluate the efficacy of Topiramate in the preventive treatment of episodic migraine*
Publications – title, author, journal, year	*Topiramate in migraine Prevention: A double blind placebo Controlled Study, Storey, Headache, 2001*
Study type and design	*Single center double blind, placebo-controlled randomized trial to evaluate the efficacy and safety of topiramate for the preventive treatment of migraine. The study consisted of a 4-week baseline phase, an 8-week titration phase and an 8 week maintenance phase.*
Follow-up time	*16 weeks double blind treatment*
Population (inclusion and exclusion criteria)	***Inclusion:*** • *men and women aged 18-65 years* • *diagnosed with migraine – with or without aura, based on IHD criteria* • *migraine throughout a period of 1 year, with a frequency of two or more/month* • *negative pregnancy test 72 hours prior study medication* • *two or more migraines per 28 days during the baseline phase* ***Exclusion Criteria:***

	• *Patients were excluded from the study if they required medication for the symptomatic relief of migraine within a 24 hours period, plus three times per week* • *If presented with a history of more than 12 tension type headaches pr. month and unable to distinguish between headache and migraine* • *If they met the DSM-IV, criteria for any substance related disorder within 12- month prior screening visit* • *Usage of any experimental drug 30 days prior study entry* • *History of renal calculi, Multiple Sclerosis, or a history of any medical condition, that would expose them to an increased risk of significant AE´s to interfere with the assessment of efficacy and safety of the trial*
Intervention	*At the end of the 4-week baseline phase, eligible patients were randomized 1:1 to topiramate (n=19) or placebo (n=20). Topiramate or matched placebo was given and Page 32 of 50 titrated weekly in 25 mg increments over 8 weeks, to 200 mg. pr. day or to the maximum tolerated doses.*

Baseline characteristics		*Topiramate N=19*	*Placebo N=21*
	Age, years (range)	*38.3 (19-62)*	*38.1 (24-56)*
	Female, n	*19*	*20*
	Male, n	*0*	*1*
	Migraine frequency per 28 days,n, (SD)	*5.14 (1.56)*	*4.37 (1.96)*
	Weight, lb (SD)	*170.8 (33,3)*	*181.0 (41.6)*

Primary and secondary endpoints	*Primary endpoint: The mean reduction in the 28 days migraine rate during the entire double blind phase (week5-20). The 28 day migraine rate was determined by dividing the number of migraines in the in the period and multiplying by 28.* *Secondary endpoint:* • *mean percent reduction in migraine rate* • *the percentage of responders in each group*
Method of analysis	*Statistical Analysis: Not applicable since the endpoints for this application are not the same as those analysed in the publication*
Subgroup analyses	*N/A*

5.2.2 Mei et al, 2004

TABLE 35 MAIN CHARACTERISTICS FROM MEI ET AL., 2004

Trial name	*Topiramate in migraine prophylaxis: A Randomized double blind versus placebo study*
NCT number	*Not stated in publication*
Objective	*To evaluate the efficacy and tolerability of topiramate, given at the dose of 100 mg/day in the prophylactic treatment of migraine*
Publications – title, author, journal, year	*Topiramate in migraine prophylaxis: a Randomized double blind versus placebo study, Mei et al., Neurol Sci, 2004*

Study type and design	*Randomized double blind versus placebo*		
Follow-up time	*16 weeks double blind treatment*		
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Diagnosed Migraine with/without aura* • *Frequency of crises ranging from 2 to 6 in a month* ***Exclusion Criteria:*** • *Renal pathologies* • *women taking oral contraceptives* • *potential fertile sexual active women not using contraceptives* • *those who presented episodes indistinguishable from migraine without aura in the interictal period* • *those who had commenced any form of prophylactic therapy in the 2 months preceding trial.*		
Intervention	*Patients were randomized using a computer-generated random number scheme to topiramate (n=58) or placebo (n=57). TPM started at a dose of 25 mg/day, increased by 25 mg weekly until 100 mg (first 4 weeks). Patients continued on 100 mg for 12 weeks, then decreased by 25 mg weekly.*		
Baseline characteristics	*Patients completing the study*	*Topiramate N=35*	*Placebo N=37*
	Age, years (SD)	*39.,74 (12.02)*	*38.70 (11.04)*
	Female, n	*19*	*20*
	Male, n	*16*	*17*
	Frequencies of crises, n (SD)	*5.26 (1.29)*	*5.76 (0.98)*
Primary and secondary endpoints	*Primary efficacy measures: reduction of mean migraine headache frequency compared to baseline and proportion of subjects responding to treatment (≥50% reduction in migraine headache frequency)* *Secondary efficacy measures:* • *Effect of the quantity of symptomatic drugs taken during the period of therapy* • *Numbers of days of disability*		
Method of analysis	*Not applicable since the endpoints for this application are not the same as those analysed in the publication*		
Subgroup analyses	*N/A*		

5.2.3 Diener et al, 2004

TABLE 36 MAIN CHARACTERISTICS FROM DIENER ET AL., 2004

Trial name	Topiramate in migraine prophylaxis Results from a placebo-controlled trial with propranolol as an active control
NCT number	*Not stated in publication*
Objective	To evaluate the efficacy and safety of two doses of topiramate (100 and 200 mg/d) vs placebo for migraine prophylaxis, with immediate-release propranolol (160 mg/d) as an active control.

Publications – title, author, journal, year	Topiramate in migraine prophylaxis - Results from a placebo-controlled trial with propranolol as an active control, Diener HC, et al. J Neurol 2004				
Study type and design	A randomized, double-blind, parallel-group, multicenter trial conducted in 13 countries. The trial included four phases: baseline, core double-blind, blinded extension, and taper/exit. The study is completed.				
Follow-up time	26-week core double blind phase, blinded extension phase for up to 12 months. Data from the core double blind phase are presented.				
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Age 12 and 65 years* • *Established history of migraine with or without aura for at least one year, according to International Headache Society (IHS) criteria* • *3 to 12 migraine headaches (periods)* • *No more than 15 headache days (including migraine days)* ***Exclusion Criteria:*** • *Patients must not have failed more than two previous adequate regimens of prophylactic medications for recurrent migraine episodes. Page 16 of 50* • *History of asthma, bradyarrhythmia, uncontrolled diabetes, and any other limitations to the use of beta-blockers*				
Intervention	*A total of 575 subjects were randomized; of these, 568 contributed efficacy data after randomization and were included in the intent-to-treat cohort for the efficacy analyses; 570 contributed to the safety analyses. The trial included four phases: baseline, core double-blind, blinded extension, and taper/exit. The baseline phase consisted of a 14-day washout period during which any prophylactic migraine medications were discontinued and a 28-day prospective baseline period during which subjects completed daily records of headache activity/symptoms and rescue medication usage. During the titration period, the initial daily dose of TPM (25 mg/d) or PROP (20 mg/d) was titrated upwards in weekly increments of 25 mg/d (TPM) or 20 mg/d (PROP) until achieving either the assigned dose or maximum tolerated dose, whichever was lower. After completing titration, subjects continued receiving the stable dose of study medication until the end of the maintenance period. Only subjects who completed the entire 26-week core double-blind phase were eligible to enter the blinded extension phase. All other subjects were discontinued from the trial. Subjects who were eligible to enter the blinded extension phase received the same dose of study medication that was achieved during the core double-blind phase. During this phase, subjects continued to receive study medication for up to 12 months after the last subject was randomized, or until they were withdrawn. At the end of treatment, regardless of the phase, study medication was tapered over period of up to 7 weeks.*				
Baseline characteristics	***Characteristic***	Placebo N=143	Topiramate 100 mg/d N=139	Topiramate 200 mg/d N=143	Propranolol 160 mg/d N=143
	Age, mean	*40.3*	*39.8*	*42.6*	*40.6*
	Male	*34*	*29*	*28*	*24*
	Female	*109*	*110*	*115*	*119*
	Mean body weight, kg	*71.2*	*70.8*	*70.2*	*68.9*
	MMD (mean monthly migraine days)	*6.1*	*5.8*	6.2	6.1

	Monthly days of rescue medication	*5.3*	*5.0*	*5.5*	5.4
	Migraine attack rate	*4.1*	*3.6*	*4.0*	3.9
Primary and secondary endpoints	The primary efficacy measure: • *The change in mean monthly migraine frequency from the baseline phase relative to the double-blind treatment phase.* • *Comparison of topiramate with placebo with respect to change in monthly (28-day) migraine frequency averaged over the entire core double-blind phase vs the frequency at baseline.* Secondary efficacy measures: • *Change in number of migraine days per month* • *Change in the average monthly rate of rescue medication use in days* • *Responder rate (response defined as at least a 50% reduction in average monthly migraine frequency) Page 17 of 50* • *Onset of action (defined as the earliest monthly time point when a statistically significant difference in the primary efficacy endpoint between the placebo and topiramate treatment groups was detected and consistently.*				
Method of analysis	*Efficacy analyses were conducted on the intent-to-treat cohort, which was defined as those randomized patients who had at least 1 post-baseline efficacy assessment. The primary efficacy endpoint is the change in average monthly migraine frequency (based on migraine periods). Efficacy endpoints were analyzed using a linear model with baseline value as a covariate and analysis center and treatment as factors. The least squares means, which are means adjusting for the variables in the statistical model, were used to compare treatment groups.*				
Subgroup analyses	*N/A*				

5.2.4 Brandes et al, 2004

TABLE 37 MAIN CHARACTERISTICS FROM BRANDES ET AL., 2004

Trial name	*Topiramate for migraine prevention a randomized controlled trial*
NCT number	*Not stated in publication*
Objective	*To assess the efficacy and safety of topiramate for migraine prevention in a large controlled trial*
Publications – title, author, journal, year	*Topiramate for migraine prevention a randomized controlled trial. Brandes JL, et al. JAMA 2004*
Study type and design	*A 26-week, multicenter, randomized, double blind, placebo-controlled study conducted during outpatient treatment. The study is completed.*
Follow-up time	*26 weeks (primary analysis)*
Population (inclusion and exclusion criteria)	*Inclusion:* • *Established history of migraine with or without aura for at least 6 months before screening.* • *Age 12 to 65 years*

<table>
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Between 3 and 12 migraines but not more than 15 headache days per 28 days during the prospective baseline phase. A headache day was defined as a Page 22 of 50 calendar day during which the patient experienced headache for at least 30 minutes.
Women were required to be post-menopausal, surgically incapable of bearing children, or practicing a medically acceptable method of birth control for at least 1 month before study entry.

Exclusion Criteria:

Headache other than migraine, episodic tension or sinus headache
Failed to respond to more than 2 adequate previous regimens of migraine preventive medications
Onset of migraine occurred after age 50 years
Overuse of analgesics or specific agents for acute treatments of migraine episodes
Continued use of following medication during the study: Beta blockers, tricyclic antidepressiva, antiepileptics,calcium channel blockers, monoamine oxidase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) daily, magnesium supplements at high doses (e.g., 600 mg/d), riboflavin at high doses (e.g., 100 mg/d), corticosteroids, local anesthetics, botulinum toxin, or herbal preparations such as feverfew or St John’s wort. Nonpharmacologic prophylactic approaches started at least 1 month before the prospective baseline phase could be continued throughout the study. • Patients with a history of nephrolithiasis
Patients who had participated in a topiramate study or had taken topiramate for more than 2 weeks.
Patients who had received an experimental drug or used an experimental device within 30 days of screening also were

</td></tr>
<tr><td>Intervention</td><td colspan="5">After evaluation for inclusion and exclusion criteria, eligible patients entered a washout period of up to 14 days, during which any migraine-preventive medications were tapered. This period was followed by a prospective baseline phase of 28 days, during which headache and medication record information completed by patients was reviewed. During the baseline phase, patients were permitted to take rescue medication. Patients who completed the prospective baseline phase and met all entry criteria were randomized to 1 of 4 treatment groups according to a computer- generated randomization schedule: placebo or topiramate at 50 mg/d, 100 mg/d, or 200 mg/d. Randomization was balanced by using permuted blocks of 4 and stratified by center. Patients and clinicians were blinded to study medication. Patients randomized to topiramate started at a dose of 25 mg/d; the daily dose was increased by 25 mg weekly (for a total of 8 weeks) until patients reached either their assigned dose or maximum tolerated dose, whichever was less. Patients then continued receiving that amount for 18 weeks in 2 divided doses (morning and evening). Patients who completed the 18-week maintenance period or who exited the double-blind phase for lack of efficacy were eligible to enter an open-label extension after a blinded transition period of 7 weeks. In the event of tolerability problems, patients were given the opportunity to reduce study medication by a maximum of 2 dose levels during the entire 26- week treatment phase</td></tr>
<tr><td rowspan="3">Baseline characteristics</td><td>Characteristic</td><td>Placebo N=114</td><td>Topiramate 50 mg/d N=117</td><td>Topiramate 100 mg/d N=120</td><td>Topiramate 200 mg/d N=117</td></tr>
<tr><td>Age, years</td><td>38.3</td><td>39.0</td><td>39.1</td><td>39.1</td></tr>
<tr><td>Men, n</td><td>20</td><td>20</td><td>11</td><td>11</td></tr>
</table>

	Women, n	*94*	*97*	*109*	*106*
	Monthly migraine frequency	*5.6*	*5.4*	*5.8*	*5.1*
	MMD, Monthly migraine days	*6.7*	*6.4*	6.9	6.1
	Monthly rescue medication used	*5.8*	*5.7*	*6.2*	5.8
	Migraine duration, days	*2.6*	*2.3*	*2.6*	2.1
	Monthly migraine severity	*2.2*	*2.3*	*2.2*	2.3
Primary and secondary endpoints	The primary efficacy measure: • *Change from baseline in mean monthly migraine frequency.* Secondary efficacy measures: • *Responder rate (proportion of patients with ≥50% reduction in monthly migraine frequency)* • *Reductions in mean number of monthly migraine days* • *Severity, duration, and days a month requiring rescue medication* • *Adverse events.* • *The month of onset of preventive treatment action was assessed*				
Method of analysis	*Efficacy analyses were conducted on the intent-to-treat population, which was defined as randomized patients who had at least 1 post baseline efficacy assessment. For patients discontinuing early, the mean monthly migraine frequency during the entire double-blind treatment phase and the cumulative monthly periods were computed according to the migraine periods observed before discontinuation. The primary and secondary continuous efficacy measure was assessed with a linear model, with treatment and analysis center as factors and the baseline value as a covariate. Estimates of treatment effects are based on the treatments' least squares mean, which are the means adjusted for the variables in the statistical model. Analyses were done with SAS (version 6.12; SAS Institute Inc, Cary, NC) at a significance level of .05.*				
Subgroup analyses	*None*				

5.2.5 Brandes et al, 2006

TABLE 38 MAIN CHARACTERISTICS FROM BRANDES ET AL., 2006

Trial name	*Assessing the Ability of Topiramate to Improve the Daily Activities of Patients With Migraine*
NCT number	*Not stated in the publication*
Objective	*To assess the impact of topiramate on the daily activities of patients with migraine.*
Publications – title, author, journal, year	*Assessing the Ability of Topiramate to Improve the Daily Activities of Patients With Migraine, Brandes et al., Mayo Clin Proc, 2006*
Study type and design	*Randomized, double-blind, placebo-controlled multicenter trial*
Follow-up time	*26 weeks.*

Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Patients included in the trial ranged from 12 to 65 years of age (patients between 12 and 17 years of age did not participate in the SF-36 and MSQ surveys)* • *had at least a 6-month history of migraine with or without aura based on International Headache Society criteria.* • *To be eligible for the trial, patients must have experienced between 3 and 12 migraine attacks but no more than 15 headache days during the 28-day prospective baseline phase.* • *Women were required to be postmenopausal, surgically incapable of bearing children, or on a medically acceptable birth control regimen for at least 1 month before study entry* ***Exclusion Criteria:*** • *Reasons for exclusion from the trial included:* • *the presence of headaches other than migraine (such as episodic tension headaches or sinus headaches) and previous failure of more than 2 adequately dosed migraine preventive medications.* • *Patients in whom more than 2 preventive measures had failed are not representative of the target population for which the study was designed.* • *Onset of migraine after the age of 50 years* • *patients with a history of overuse of analgesics or specific agents for the treatment of migraine attacks before trial entry were excluded.* *Examples of medication overuse included more than 8 treatment episodes per month with ergot-containing medication or triptans or more than 6 treatment episodes per month with potent opioids (e.g., fentanyl, buprenorphine, hydromorphone, oxycodone). This approach excludes patients who might be rebounding from medication-overuse headache with possible confounding by withdrawal of medications.*				
Intervention	*Patients were allowed to continue taking acute migraine medications for the treatment of breakthrough attacks during the trial, but any currently used migraine preventive medications were tapered off during an initial washout period of up to 14 days. Patients who then completed the 28-day prospective baseline phase and met all entry criteria were assigned with equal chance to 1 of 4 treatment groups (50 mg/d, 100 mg/d, or 200 mg/d of topiramate or placebo) based on a schedule prepared before the study started. The randomization was balanced using permutated blocks across the 4 treatment groups and stratified by study center. An interactive voice response system was used to assign randomization numbers to patients and to assign study drug based on the randomization schedule. The 26-week,* *double-blind phase consisted of an 8-week titration and an 18-week maintenance period. All dosages of topiramate were initiated at 25 mg/d and increased by 25 mg weekly until patients reached their assigned or maximum tolerated dose, whichever was lower*				
Baseline characteristics	***Intent-to-treat population***	***Placebo (n = 114)***	***Topiramate, 50 mg/d (n = 117)***	***Topiramate, 100 mg/d (n = 120)***	***Topiramate, 200 mg/d (n = 117)***

	No. with no MSQ or SF-36 data*	*8*	*7*	*9*	*10*
	No. with available MSQ and SF-36 data	*106*	*110*	*111*	*107*
	Mean ± SD age (y)	*38.3±12.0*	*39.0±12.1*	*39.1±12.6*	*39.1±12.7*
	No. (%) male	*20 (18)*	*20 (17)*	*11 (9)*	*11 (9)*
	No. (%) female	*94 (82)*	*97 (83)*	*109 (91)*	*106 (91)*
	No. (%) white	*101 (89)*	*99 (85)*	*108 (90)*	*103 (88)*
	Mean ± SD migraine frequency per month	*5.6±2.2*	*5.4±2.4*	*5.8±2.6*	*5.1±2.0*
	**All 34 patients who did not provide Migraine Specific Questionnaire (MSQ) or Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) data were minors. Patients between 12 and 17 years of age did not participate in the SF-36 and MSQ surveys.*				
Primary and secondary endpoints	*Primary efficacy outcome: change in mean monthly migraine frequency.* *The study reports a priori specified analyses of the MSQ (version 2.1) and SF-36 (version 1.0) questionnaire data collected as part of the aforementioned 6-month, randomized, double-blind, placebo-controlled, pivotal topiramate efficacy trial.*				
Method of analysis	*A mixed-effects model with piecewise linear regression, which took into account variations in the availability of MSQ and SF-36 data throughout the double-blind phase, was used to assess between-group differences in outcome scores for the prospectively designated MSQ and SF-36 domains. This model included 2 random effects and allowed changes in the slope at 8 and 16 weeks. This model assumed that the data were missing at random, conditional on treatment, and all observed. A series of sensitivity analyses tested different assumptions that related to missing MSQ and SF-36 data (ie, data missing at random or data missing not at random, conditional on either the time in the double-blind phase of the study or time to last MSQ and SF-36 assessment). Results of these tests were insensitive to these assumptions (data not shown). Multiple end points within each topiramate dosage vs placebo treatment analysis were controlled for across the 4 prospectively designated domains (MSQ-RR, MSQ-RP, SF36-RP, and SF36-VT) using a sequentially rejective Bonferroni adjustment procedure.22 All P values were adjusted using this step-up procedure, as outlined by Hochberg.22 No adjustment for multiple comparisons was performed for each treatment group within a given measure. Possible associations between changes in the level of daily activity (the prospectively designated MSQ and SF-36 domains) and mean monthly migraine frequency were examined using the Spearman rank correlation, pooling all study medication groups.*				
Subgroup analyses	*None*				

5.2.6 Silberstein et al, 2004

TABLE 39 MAIN CHARACTERISTICS FROM SILBERSTEIN ET AL., 2004

Trial name	*Topiramate in migraine Prevention*				
NCT number	*Not stated in publication*				
Objective	*To assess the efficacy and safety of Topiramate as a migraine-preventive therapy*				
Publications – title, author, journal, year	*Topiramate in migraine prevention. Results of a large controlled trial. Silberstein SD et al. Arch Neurol 2004*				
Study type and design	*A 26 weeks, randomized, double blind, placebo-controlled study. The study consisted of a 28-day prospective baseline phase. The double-blind phase was divided into titration (8 weeks) and maintenance (18 weeks).*				
Follow-up time	*Data from the 26 weeks double-blind treatment phase are presented.*				
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Patients age 12-65 years with 3-12 migraines during the prospective 28-day baseline phase.* • *Women needed to be post –menopausal, surgically incapable of childbearing or, or using contraceptives.* ***Exclusion Criteria:*** • *Headaches other than migraine* • *failed previously 2 migraine preventive drugs* • *had migraine onset after age 50.* • *>8 treatment days pr. month of ergots or triptans* • *used B-blockers, tricyclic anti-depressants, AED´s. ACE inhibitors etc.* • *patients with renal impairments* • *patients who had participated in previous topimarate study, • patients who had used topimarate for 2 weeks or longer* • *patients who had used an experimental drug or device within 30 days prior screening*				
Intervention	*469 patients composed the IIT population. Participants were randomized to placebo or topiramate, 50, 100 or 200 mg/WK to the assigned dose or as tolerated in 8 weeks; Maintenance therapy continued for 18 weeks.*				
Baseline characteristics	*Patients completing the study*	*Topiramate 50 mg N= 117*	*Topiramate 100 mg N=125*	*Topiramate 200 mg N=112*	*Placebo N=115*
	Age, years (SD)	*40.2 (11.5)*	*40.6 (11.0)*	*40.5 (11.4)*	*40.4 (11.5)*
	Female, n	*107*	*112*	*94*	*103*
	Male, n	*10*	*3*	*18*	*12*
	MMD	*6.4 (2.7)*	*6.4 (2.7)*	*6.6 (3.1)*	*6.4 (2.6)*
	Weight	*75.7 (18.9)*	*78.9 (19.3)*	*76.7 (20.1)*	*75.6 (18.5)*
	Days of acute headache medication use pr. 28 days	*5.8 (2.5)*	*6.4 (2.7)*	*6.1 (3.1)*	*6.1 (3.0)*

	Data shown are mean (SD), unless otherwise indicated.
Primary and secondary endpoints	*Primary endpoint:* • *Reduction in monthly migraine frequency across the 6 months treatment phase* *Secondary endpoint:* • *time to onset of action* • *the proportion of patients responding (≥50% reduction in monthly migraine frequency)* • *Mean change in migraine days per month* • *mean change in days with rescue medication per month*
Method of analysis	*The primary endpoint was analyzed using a linear model with treatment and analysis center as factors and baseline value as covariate. The least square means, which are means adjusted for the variables in the statistical model, were used to compare treatment groups. Efficacy analyses were conducted on the intent to treat population, which was defined as those randomized patients who had at least 1 post baseline efficacy assessment. For subjects discontinuing the study early, the average monthly migraine period rate was computed based on the migraine periods observed before discontinuation.*
Subgroup analyses	*N/A*

5.2.7 Silberstein et al, 2006

TABLE 40 MAIN CHARACTERISTICS FROM SILBERSTEIN ET AL., 2006

Trial name	*The impact of migraine on daily activities*
NCT number	*Not stated in publication*
Objective	*Assess the impact of migraine preventive therapy on patient-reported routine daily activities using the Migraine Specific Questionnaire (MSQ) and the Medical Outcomes Study Short Form-36 (SF-36) in patients with migraine who participated in a 26-week, randomized, double-blind, placebo-controlled trial of topiramate for migraine prevention*
Publications – title, author, journal, year	*The impact of migraine on daily activities: effect of topiramate compared with placebo. Silberstein SD et al. Current Medical Research and Opinion 2006*
Study type and design	*randomized, double-blind, placebo-controlled trial (MIGR-001)*
Follow-up time	*26 weeks*
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Patients age 12-65 years with 3-12 migraines during the prospective 28-day baseline phase.* • *Women needed to be post –menopausal, surgically incapable of childbearing or, or using contraceptives.* ***Exclusion Criteria:*** • *Headaches other than migraine* • *failed previously 2 migraine preventive drugs* • *had migraine onset after age 50.* • *>8 treatment days pr. month of ergots or triptans* • *used B-blockers, tricyclic anti-depressants, AED´s. ACE inhibitors etc.* • *patients with renal impairments*

	• *patients who had participated in previous topimarate study,* • *patients who had used topimarate for 2 weeks or longer* • *patients who had used an experimental drug or device within 30 days prior screening*				
Intervention	*469 patients composed the IIT population. Participants were randomized to placebo or topiramate, 50, 100 or 200 mg/WK to the assigned dose or as tolerated in 8 weeks; Maintenance therapy continued for 18 weeks.*				
Baseline characteristics	*ITT-population*	*Topiramate 50 mg N= 117*	*Topiramate 100 mg N=125*	*Topiramate 200 mg N=112*	*Placebo N=115*
	Age, years (SD)	*40.2 (11.5)*	*40.6 (11.0)*	*40.5 (11.4)*	*40.4 (11.5)*
	Female, n	*107*	*112*	*94*	*103*
	Male, n	*10*	*3*	*18*	*12*
	MMD	*6.4 (2.7)*	*6.4 (2.7)*	*6.6 (3.1)*	*6.4 (2.6)*
	Weight	*75.7 (18.9)*	*78.9 (19.3)*	*76.7 (20.1)*	*75.6 (18.5)*
	Days of acute headache medication use pr. 28 days	*5.8 (2.5)*	*6.4 (2.7)*	*6.1 (3.1)*	*6.1 (3.0)*
	Data shown are mean (SD), unless otherwise indicated.				
Primary and secondary endpoints	*Primary endpoint:* • *Reduction in monthly migraine frequency across the 6-month treatment phase* *Secondary endpoint:* • *time to onset of action* • *the proportion of patients responding (≥50% reduction in monthly migraine frequency)* • *Mean change in migraine days per month* • *mean change in days with rescue medication per month*				
Method of analysis	*A mixed-effects model with piecewise linear regression, which took into account variations in the availability of MSQ and SF-36 data throughout the double-blind phase, was used to assess between-group differences in the prospectively designated MSQ and SF-36 outcome scores. This model included two random effects and allowed changes in the slope at 8 and 16 weeks. The model allowed for a slope to describe the relationship from week 8 to week 16, and a slope to describe the relationship from week 16 to week 26. A sensitivity analysis, with different assumptions relating to missing MSQ and SF-36 data, was also performed jointly estimating the outcomes with time on the double-blind portion of the study and time to last MSQ or SF-36 assessment.*				
Subgroup analyses	*N/A*				

5.2.8 Silberstein et al, 2006 (pilot study)

TABLE 41 MAIN CHARACTERISTICS FROM SILBERSTEIN ET EL., 2006

Trial name	*Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults*
NCT number	*Not stated in publication*
Objective	*This paper evaluates efficacy and safety data from a pilot study of TPM 200 mg/d as preventive therapy in adult subjects with a history of migraine with or without aura*

Publications – title, author, journal, year	*Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. Silberstein et al., Clinical therapeutics, 2006*		
Study type and design	*The pilot study had a randomized, double-blind, placebo-controlled design. Subjects were randomized in a 2:1 ratio to receive TPM 200 mg/d or placebo. The double-blind treatment phase consisted of an 8-week titration period (25 mg/d for the first week, followed by weekly increases of 25 mg) and a 12-week maintenance period.*		
Follow-up time	*20 weeks*		
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Subjects between the ages of 18 and 65 years were required to have a history of migraine with or without aura, as assessed by International Headache Society criteria, 1° for at least 12 months before screening.* • *Subjects must have experienced an average of 3 to 8 migraine episodes per month (defined as 28 days) for 3 months (84 days) before screening.* *For the purposes of this study, a migraine episode was defined as the period from the onset of painful symptoms to the resolution of pain or 24 hours after onset, whichever was sooner. Migraine pain that recurred within 24 hours was considered part of the same episode.* ***Exclusion Criteria:*** • *Subjects were excluded from the study if they had previously failed to respond to TPM therapy or had taken preventive medication within 2 weeks (14 days) of the start of the prospective baseline period (defined in following section).* • *Also excluded were subjects who had >15 headache days per month during the 3 months before screening, during screening, or during the prospective baseline period.* • *Subjects with a diagnosis of cluster headache; basilar, ophthalmoplegic, hemiplegic, or transformed migraine; or migraine aura exclusively (without headache) were excluded.* • *Finally, subjects who had previously failed to respond to >2 adequately dosed migraine preventive medications, had migraine onset after the age of 50 years, or overused acute migraine treatment (e.g., triptan use on >8 days per month) also were excluded.* • *Receipt of injected corticosteroids, local anesthetics, or botulinum toxin within 60 days before screening was a cause for exclusion.* • *Women of childbearing age were required to be using an approved method of birth control or to abstain from sexual intercourse.* • *Pregnant or lactating women were excluded.* • *Subjects who had serum alanine and/or aspartate aminotransferase levels >2 times the upper limit of the normal range were excluded, as were subjects with active liver disease*		
Intervention	*The intent-to-treat (ITT) population*		
Baseline characteristics	*ITT-population*	*Topiramate (n= 138=*	*Placebo (n=73)*
	Age, years (SD)	*39.9 (11.8)*	*41.7 (9.4)*
	Female, n	*118 (85.5)*	*63 (86.3)*
	Weight, mean (SD), kg	*74.6 (17.5)*	*80.7 (20.3)*
	No. of migraine episodes per month (28 days)	*4.8 (1.5)*	*5.2 (1.7)*

	Migraine with aura, no. (%)	*46 (33.3)*	*29 (39.7)*
Primary and secondary endpoints	*The primary efficacy measure was the change in mean monthly migraine frequency.* *Additional measures were the median percent reduction in monthly migraine frequency and the proportion of responders (those with ≥50%, ≥75%, or 100% reduction in monthly migraine frequency).*		
Method of analysis	*A sample size of 195 subjects (130 TPM, 65 placebo) was calculated to provide 90% power to detect a 1.0 difference in the mean reduction in monthly migraine frequency, assuming a common SD of 2.0, at the 5% (2-sided) significance level. Statistical analyses were conducted in the ITT population. For subjects who withdrew prematurely from the double-blind phase, the last available efficacy evaluation after baseline was carried forward. The per-protocol, analysisof-covariance (ANCOVA) model was used to assess the significance of the data for the primary and secondary efficacy measures. Comparisons of responder rates were performed using logistic regression. For ANCOVA and logistic regression, the mean prospective baseline migraine frequency was treated as a covariate, and treatment and center were treated as qualitative independent factors.* *To provide proportional representation for each patient based on how long he or she remained in the study, a post hoc analysis of total migraine frequency during the entire double-blind phase was performed in the ITT population using an overdispersed Poisson regression model, in which the log of the duration of the double-blind phase was used as an offset. 11 In this regression model, the mean prospective baseline migraine frequency was treated as a covariate, and treatment and center were treated as qualitative independent factors. Correction for multiple comparisons was applied to the data derived from the prespecified analyses. This correction was not applied to the data derived from post hoc analyses, in which case nominal P values were provided*		
Subgroup analyses	*A post hoc analysis in the subgroup of ITT subjects having migraine with aura (46 TPM, 29 placebo) suggested that TPM was associated with a significant reduction in monthly migraine frequency compared with placebo (-2.43 vs -0.79; P = 0.02)*		

5.2.9 Silberstein et al, 2007

TABLE 42 MAIN CHARACTERISTICS FROM SILBERSTEIN ET AL., 2007

Trial name	*To evaluate the efficacy and safety of topiramate (100 mg/day) compared with placebo for the treatment of chronic migraine.*
NCT number	*NCT00210912*
Objective	*To evaluate the efficacy and safety of topiramate (100 mg/day) compared with placebo for the treatment of chronic migraine.*
Publications – title, author, journal, year	*Efficacy and Safety of Topiramate for the Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. Silberstein et al., Headache, 2007.*
Study type and design	*This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial (46 U.S. sites).*

	The study consisted of a pre-treatment phase lasting up to 56 days, a double-blind treatment phase lasting 16 weeks, and a taper/exit period that lasted up to 2 weeks. The pre-treatment phase consisted of 2 study periods: a screening and washout period (day −56 to day −29), and a prospective baseline period (day −28 to day 0). The screening and washout period commenced at visit 1 and occurred within 28 days of the start of the prospective baseline period (visit 2). Patients were instructed to discontinue all preventive migraine medications for 14 to 28 days prior to visit 2and for the duration of the study. The prospective baseline period began on day−28 (visit 2), as soon as the patient completed the screening and washout period. *The double-blind treatment phase consisted of a 4-week titration period and a 12-week maintenance period. During the titration period, subjects were given topiramate (or matching placebo) 25 mg/day once daily for 7 days, followed by weekly increases of 25 mg until either 100 mg/day of topiramate (or matching placebo) or a maximum tolerated dose was reached.*
Follow-up time	*12 weeks.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** *During the screening period, eligibility for participation in the study was determined. Adult subjects with a diagnosis of chronic migraine, defined according to Silberstein/ Lipton criteria for transformed migraine were identified. Subjects who met these criteria for chronic migraine during the screening period were required to meet additional criteria to proceed to randomization. Subjects were required to have at least 15 headache days per 28 days, defined as a calendar day during which they experienced head pain for at least 30 minutes. On at least half of these days, subjects were required to have experienced migraine with or without aura or migrainous headache[1]. Eligible subjects also were required to have a Migraine Disability Assessment (MIDAS) score of at least 11 at visit 1.* ***Exclusion Criteria:*** • *Previously failed more than 2 adequate trials of migraine preventive medications (adequate was defined as a trial of at least 3 months' duration at the recommended dose)* • *Previously failed an adequate trial of topiramate therapy due to lack of efficacy or adverse events* • *History of cluster headache or basilar, ophthalmoplegic, or hemiplegic migraines* • *Migraine onset after age 50* • *Overuse of acute migraine medication (defined in this trial as use in excess of 4 days per week during the prospective baseline period)* • *History of hepatic disorder or nephrolithiasis* • *Progressive neurologic disorder other than migraine* • *Pregnant or nursing*

[1] *Migrainous headache was defined as moderate to severe headache with 1 or more of the following migraine features: unilateral pain or pain worse on 1 side of the head, pulsatile pain, photophobia and/or phonophobia, nausea and/or vomiting, or pain made worse by physical activity.*

	Concomitant Headache medications: *All preventive migraine treatments were discontinued at least 14 to 28 days prior to the prospective baseline period and for the duration of the study. Use of acute headache pain medications such as analgesics, nonsteroidal anti-inflammatory drugs, triptans, opioids, and ergot derivatives was permitted for symptomatic relief of headache but could not exceed 4 days per week during the maintenance period. The specific acute headache pain medications used were recorded in the daily headache record along with migraine episode information. As much as possible, subjects were to utilize the same acute medications throughout the study as those they had employed prior to enrolment.*			
Intervention	*A total of 328 patients were randomized (topiramate, n = 165; placebo, n = 163), and 306 patients were included in the intent-to-treat population. Patients treated with topiramate has given a dose of 100 mg/day*			
Baseline characteristics	*Baseline characteristics (intent-to-treat population)*			
	Characteristic	***Topiramate***	***Placebo***	***Total***
	Age, years			
	n	*153*	*153*	*306*
	Mean	*37.8*	*38.6*	*38.2*
	SD	*12.38*	*11.80*	*12.08*
	Median	*37.0*	*40.0*	*39.0*
	Min, Max	*18, 64*	*18, 74*	*18, 74*
	Sex, n (%)			
	Male	*25 (16.3)*	*20 (13.1)*	*45 (14.7)*
	Female	*128 (83.7)*	*133 (86.9)*	*261 (85.3)*
	Race, n (%)			
	White	*126 (82.4)*	*120 (78.4)*	*246 (80.4)*
	Black	*19 (12.4)*	*26 (17.0)*	*45 (14.7)*
	Asian	*1 (0.7)*	*2 (1.3)*	*3 (1.0)*
	Other	*7 (4.6)*	*5 (3.3)*	*12 (3.9)*
	Weight (kg)			
	n	*153*	*152*	*305*
	Mean	*80.00*	*76.84*	*78.43*
	SD	*20.276*	*22.221*	*21.292*
	Median	*76.64*	*72.79*	*74.38*
	Min, Max	*39.9, 154.2*	*46.3, 190.5*	*39.9, 190.5*
	Body mass index (kg/m^2)			
	n	*152*	*150*	*302*
	Mean	*29.161*	*27.965*	*28.567*
	SD	*6.9659*	*7.2853*	*7.1396*
	Median	*28.007*	*26.614*	*27.427*
	Min, Max	*15.69, 54.87*	*16.60, 57.57*	*15.69,57.57*
	Headache Characteristics (mean ± SD)	***Topiramate***	***Placebo***	
	Age at migraine onset, years	*19.0 ± 10.1*	*20.4 ± 10.5*	
	Duration of chronic migraine, Years	*9.3 ± 10.5*	*9.1 ± 10.6*	

	Baseline monthly rate of migraine or migrainous days	*17.1 ± 5.4*	*17.0 ± 5.0*
	Baseline monthly rate of migraine Days	*15.2 ± 6.4*	*15.1 ± 5.8*
	Baseline monthly rate of total headache days	*20.4 ± 4.8*	*20.8 ± 4.6*
	Baseline number of days per month of acute medication use	*11.9 ± 7.0*	*11.4 ± 6.6*
Primary and secondary endpoints	*The primary endpoint was the change from baseline in the mean monthly (28 day) number of migraine/migrainous days. The change from baseline in the mean monthly number of migraine days also was analyzed in addition to the percent change from baseline for these 2 efficacy parameters.* *A Secondary prespecified efficacy measures that were derived but will be detailed in a subsequent publication include:* • *Categorical responder rates in the percent change from baseline in mean monthly number of migraine/migrainous, migraine, and total headache days* • *Change in the mean monthly rate of headache days* • *Change in monthly headache-free days* • *Reduction from baseline in the use of acute headache medications* • *Occurrence of associated symptoms of photophobia, phonophobia, and nausea* • *Absolute change in a Headache Index (which was defined as the sum of the product of daily average severity multiplied by headache duration for the day, divided by the number of days in the specified period. Severity was based on 5 categories: 1 = mild headache, easily ignored; 2= mild bothersome discomfort; 3 = moderate, painful; 4 = moderate, very painful; and 5 = severe, intensely painful) during the last 4 weeks of double-blind treatment compared with the prospective baseline period.* *Effects of study drug on MIDAS,22 Physician's Global Impression of Change, Subject's Global Impression of Change, and the Migraine-Specific Quality-of-Life Questionnaire were evaluated.* <u>*Safety and tolerability measures:*</u> *Safety measures included measurement of vital signs, serial physical and brief neurologic examinations, and clinical laboratory parameters (haematology, chemistry, and urinalysis). Women of childbearing potential had urine pregnancy tests. Spontaneously reported adverse events were collected and recorded at each visit. Treatment-emergent adverse events (TEAEs) were defined as those that were new in onset or aggravated in severity or frequency between the prospective baseline period and the conclusion of the double-blind treatment phase.* *The investigators recorded the date of onset, severity, and outcome of each adverse event, evaluated the possible relationship to treatment and recorded any action taken.*		

Method of analysis	*Analyses of treatment effectiveness were performed on the intent-to-treat population (full analysis set), which consisted of all randomized subjects who received at least 1 dose of study medication and provided at least 1 post-randomization efficacy evaluation.* *Safety analyses were performed on all randomized subjects who received at least 1 dose* *of study medication and for whom at least 1 posttreatment safety measurement was available.* *The mean monthly rate of migraine/migrainous headache days and migraine headache days were analyzed with analysis of covariance models using a fixed-sequence (i.e., a gatekeeper approach) to control the overall Type I error rate at the 2-sided 5% level. Treatment and treatment center were qualitative design factors, with baseline rate as a covariate. The first step involved an assessment of the change relative to baseline in the mean number of days per month with migraine/migrainous headache at the 2-sided 0.05 level of significance. If statistical significance was achieved, then the change in the mean monthly rate of migraine days could also be tested at the 2-sided 0.05 level. If significance again was achieved, then statistical significance would be declared at the* *2-sided 0.05 level for both measures. If significance on the migraine/migrainous parameter was not achieved, then the formal testing procedure ended. Analyses of additional efficacy variables were not adjusted for multiplicity.*
Subgroup analyses	*No subgroup was defined in this study.*

5.2.10 Silberstein et al, 2009

TABLE 43 MAIN CHARACTERISTICS FROM SILBERSTEIN 2009 ET AL., 2009

Trial name	*A Study of the Effectiveness and Safety of Topiramate Versus Placebo for Preventing Chronic Migraine Headaches*
NCT number	*NCT00210912*
Objective	*The purpose of this study is to assess the safety and effectiveness of topiramate as compared to placebo for the prevention of headaches in patients with chronic migraine. Topiramate has been approved to prevent migraine headaches as well as in the treatment of epilepsy.*
Publications – title, author, journal, year	*Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Silberstein et al., Headache, 2009*
Study type and design	*This is a multicenter, randomized, double-blind, placebo-controlled, parallel group study of patients with chronic migraine. The Pretreatment Phase for the study will last up to 56 days and will consist of 2 study periods: a Screening/Washout Period (Day -56 to Day -29) and a Prospective Baseline Period (28 days). Medications being used to prevent migraines will be stopped for 14 to 28 days prior to the Prospective Baseline Period and for the rest of the study. The Prospective Baseline Period will begin on study Day -28 (Visit 2), and patients will maintain a daily headache record during this period. Those who move forward in the study must have had at least 15 headache days during this period, half of which need to be migraine headache days. Patients who finish the Prospective Baseline Period, who have the required rates of headache, and who continue to meet the remainder of the entry criteria will be randomized*

	(like with the toss of a coin) to 1 of 2 treatment groups: topiramate 100 milligrams per day or placebo. *The Double-Blind Phase will last 16 weeks. During the first 4 weeks, patients will titrate up to the topiramate dose of 100 milligrams per day or to the maximum tolerated dose, whichever is less. The next 12 weeks is the maintenance phase where you will continue to take the dose that you were taking at the end of the 4-week titration period. The primary hypothesis of this study is that the mean decrease in the number of migraine/migrainous headache days per month is greater in the topiramate group than in the placebo group and topiramate is generally well-tolerated.*
Follow-up time	*16 weeks.*
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Diagnosis of chronic migraine* • *>=15 headache days per month in past 30 days* • *>= 15 headache days, half of which need to be migraine headaches during the prospective baseline period* • *MIDAS test score >= 11 at Visit 1* • *In generally good health* • *If female, using birth control* • *No abnormalities on neurological examination* ***Exclusion Criteria:*** • *Failed > 2 adequate trials of migraine prevention medications* • *Failed topiramate due to lack of effectiveness or adverse events* • *Daily headaches of severe intensity during past 30 days* • *Cluster, basilar, ophthalmoplegic, or hemiplegic migraines* • *Migraines started after age 50* • *Other pain greater than migraine pain* • *Use of drugs to treat migraines for > 4 days per week during the past month*
Intervention	*The intent-to-treat population consisted of 306 patients (topiramate, n = 153; placebo, n = 153)*
Baseline characteristics	*No baseline characteristics are presented in this study.*
Primary and secondary endpoints	*Primary efficacy measure: Change in the average number of days per month with migraine or migrainous headache by daily headache record.* *Secondary efficacy measure: Absolute change and % change from baseline in the headache index; change in the average daily and worst daily headache severity; quality of life assessments (MIDAS, MSQ, Physician's/Subject's global assessments of change.*
Method of analysis	*The proportions of subjects in the response categories for reductions of migraine, migraine/ migrainous and total headache days, and PGIC and SGIC were analyzed using the Cochran-MantelHaenszel test, stratified by center. The P values for the response rates, but not percent´s, were the result of a post hoc analysis. Changes from baseline to the final evaluations in scores on each MSQ domain (Role Function-Restrictive [RR], Role Function-Preventive [RP], and Emotional Function [EF]) were analyzed separately using the ANCOVA model, with treatment and center as qualitative independent factors and baseline value as a*

	covariate. Changes from baseline to the final evaluations in MIDAS scores were analyzed using the ANCOVA model, with treatment and center as qualitative independent factors and baseline value as a covariate. In addition, the changes were categorized as "Worse," "No Change," and "Improved" and analyzed using the Cochran-Mantel Haenszel test, stratified by center. All statistical tests were performed at the 2-sided 0.05 level. No adjustments were made for multiplicity.
Subgroup analyses	*N/A*

5.2.11 Diener et al, 2007

TABLE 44 MAIN CHARACTERISTICS FROM DIENER ET AL., 2007

Trial name	*Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study*
NCT number	*Not stated in publication*
Objective	*The aim of this study was to evaluate the efficacy and tolerability of topiramate for the prevention of chronic migraine in a randomized, double-blind, placebo-controlled trial.*
Publications – title, author, journal, year	*Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Diener et al., Cephalalgia, 2007.*
Study type and design	*Randomized, double-blind, placebo-controlled, parallel-group, multicentre trial of topiramate for the prevention of headache in patients with chronic migraine with and without medication overuse. The study is completed.*
Follow-up time	*A prospective, 4-week baseline phase was followed by a 16-week, double-blind treatment phase, which consisted of a 4-week titration and 12-week treatment period.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Patients (18–65 years of age) were required to have a diagnosis of chronic migraine that satisfied the second edition of The International Classification of Headache Disorders criteria of ≥15 migraine headache days per 4 weeks, at least during the last 3 months prior to trial entry, with an established migraine history for at least 1 year* • *Patients could be included if they had ≥ 12 migraine days in the prospective baseline period* • ***Exclusion Criteria:*** • *Primary chronic headache or any secondary headache except medication overuse headache (MOH)* • *Experienced onset of migraine after age 50* • *Severe depression [Beck Depression Inventory (BDI) scale score > 30]* • *Patients taking antidepressants (unless the antidepressant was used at a stable dose for at least 3 months prior to trial entry and the patient intended to continue the antidepressant throughout the trial* • *Patients taking any migraine prophylactic drug (unless the drug had been used for at least 3 months [at a stable dose for at least 1 month]) prior to trial entry and was continued throughout the trial*

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

- *Prior history of topiramate use, use of other anticonvulsants within 30 days of trial entry and use of a carbonic anhydrase inhibitor*

Concomitant therapies: Patients were allowed to take acute rescue medications such as analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, opioids and ergot derivatives during any phase in the trial as usual. The use of acute rescue medication had to be specified, next to the migraine attack information, in the trial-specific patient diary.</td></tr>
<tr><td>Intervention</td><td>*32 participants randomized to the topiramate arm, target dose of 100 mg/day (50 mg twice daily) at a rate of 25 mg/week. Study physicians could increase or decrease the target dose (within a range of 50–200 mg/day) during the first 12 weeks of the double-blind phase, depending on efficacy, tolerability, or both.*

27 participants randomized to the placebo arm</td></tr>
<tr><td>Baseline characteristics</td><td>*Baseline characteristics (intent-to-treat population)*
<table>
<tr><th>***Characteristic***</th><th>***Topiramate***</th><th>***Placebo***</th><th>***P-value***</th></tr>
<tr><td>***Age, year***</td><td>47.8 ± 9.4</td><td>44.4 ± 9.6</td><td>0.148</td></tr>
<tr><td>***Gender (F/M), %***</td><td>75/25</td><td>74/26</td><td>1.000</td></tr>
<tr><td>***Mean number of migraine days/month***</td><td>15.5 ± 4.6</td><td>16.4 ± 4.4</td><td>0.283</td></tr>
<tr><td>***Patients with and without medication overuse***</td><td>23/9</td><td>23/4</td><td>0.345</td></tr>
<tr><td>***Beck Depression Inventory***</td><td>9.0 ± 7.0</td><td>13.4 ± 8.8</td><td>0.064</td></tr>
</table></td></tr>
<tr><td>Primary and secondary endpoints</td><td>*The primary efficacy variable was the change in the mean number of monthly migraine days from baseline to the last 4 weeks of the double-blind phase. A migraine day was defined as a calendar day with symptoms of a migraine attack lasting at least 30 min.*

Secondary end points were:

- *Change in monthly migraine days from baseline to the entire double-blind phase*
- *The percentage of patients with ≥50% reduction in the mean number of monthly migraine days (categorical responder rates)*
- *Change from baseline in the mean number of days of acute medication intake*
- *Patient satisfaction ratings with the efficacy and tolerability of the treatment they received*
- *Mean changes from baseline on the Migraine-Specific Quality of Life Questionnaire (MSQ, Version 2.1), Headache Impact Test (HIT-6), and Migraine Disability Assessment (MIDAS) questionnaire scores*

All three questionnaires were administered at start and end of the double-blind treatment phase; the MSQ and HIT-6 were also administered at 4 and 8 weeks in the double-blind phase</td></tr>
</table>

	<u>Tolerability and safety measures</u> *Spontaneously reported treatment-emergent adverse events (TEAEs) were recorded. Vital signs, body weight changes and laboratory parameters, including bicarbonate, sodium, potassium and chloride, were measured at the start of the double-blind phase and at weeks 8 and 16. Fewer bicarbonate estimations were done compared with others since the bicarbonate measurement was added after the study had commenced.*
Method of analysis	*Since the effect size of topiramate is unknown in subjects with chronic migraine, the following assumptions were made based on the results obtained in subjects with episodic migraine:* • *First, the average number of migraine days would be between 15 and 28 at an average number of 20* • *Second, there would be a 45% reduction in the number of migraine days on topiramate.* • *Third, there would be a 25% reduction in the number of migraine days on placebo, so the estimated effect size over placebo was four migraine days per month* • *Fourth, the SD was estimated of the change in the number of migraine days per month to be 5* *Under these assumptions two treatment groups of 29 subjects each would be needed to show a statistically significant difference between topiramate and placebo with a power of 0.80 and a = 0.05 (two-sided).* *Efficacy analyses were performed on the intent-to-treat (ITT) population, which consisted of all randomized patients who received at least one post baseline efficacy evaluation. Differences between treatment groups (topiramate vs. placebo) were compared using the Wilcoxon two-sample test for ordinal/continuous data and interpreted at the 5% significance level (two-tailed comparison). Differences within a treatment group were tested using the Wilcoxon signed rank test (ordinal/continuous data). Fisher's exact test was used to assess differences between nominal data.* *For patients who dropped out, data from the last visit available were carried forward only for the end-point visit. Data have not been corrected for multiple comparisons.*
Subgroup analyses	*The subgroup of patients who were overusing acute medication (n = 46) consisted of 23 patients receiving topiramate and 23 receiving placebo There were no significant differences in demographics and baseline characteristics between the topiramate-treated and placebo-treated patients.* *It appeared, however, that triptans were the most commonly overused acute medications in the placebo group (96%, vs. 61% in the topiramate group), whereas the topiramate group had a higher rate of analgesic overuse (30%, vs. 9% in the placebo group). The modal dose of topiramate was assessed for each individual in this treatment subgroup. From these values, the calculated mean modal dose was 102 ± 17 (mg/day±SD).*

5.2.12 Lipton et al, 2011 (INTREPID)

TABLE 45 MAIN CHARACTERISTICS OF INTERPID

Trial name	*INTREPID*
NCT number	*NCT00212810*
Objective	*The purpose of this study is to determine whether Topiramate is effective in preventing the development of chronic daily headache among patients with episodic migraine headaches.*
Publications – title, author, journal, year	*Topiramate intervention to prevent transformation of episodic migraine: The topiramate INTREPID study. Lipton et al., Cephalalgia, 2011*
Study type and design	*This is a randomized, double-blind, placebo-controlled multicenter study that will enrol patients 18-65 years old with an established history of migraine headaches who, in the 28 days prior to the study should have a migraine frequency of at least 10 but less than 15 migraine headache days per month, and less than 15 total headache days (migraine plus non migraine headaches) per month. The study duration will be approximately 26 weeks. The study is divided into 4 phases as follows: A Screening/Washout Phase that may last between 2-6 weeks, depending on whether you need to stop taking a medication that is not allowed in the study; A Baseline Phase lasting 4 weeks, at which time information will be collected on the migraine and non-migraine headaches you experience during this period; A double-blind Titration Phase lasting 4-6 weeks where all patients will be randomized to treatment with either Topiramate or placebo. If you are randomized to Topiramate, your dose will be gradually increased up to a dose of either 75 or 100 mg a day; A Maintenance Period lasting 20 weeks at which time you will continue on the dose you were taking at the completion of the Titration period; and a Taper/Exit phase, lasting 2 weeks, where you will gradually reduce the dose of study medication you were taking during the study.* *The study hypothesis is that the study drug will be more effective than placebo in preventing patients from transforming from episodic migraines to chronic daily headaches. Each patient will be asked to record their headache pain information and medication use on paper headache diaries. Patients will receive either Topiramate or placebo. The number of tablets of topiramate or placebo, will be gradually increased to either a minimum of 3 tablets/day or a maximum of 4 tablets/day. For those on Topiramate, 3 tablets would represent 75 mg and 4 tablets would represent 100 mg/day.*
Follow-up time	*26 weeks*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *To qualify for this study, you must be 18-65 years old* • *have a history of migraine headaches for at least 1 year* • *experience at least 10 but less than 15 migraine headache days and less than 15 total headache days/month* • *able to take oral medication* • *able to understand and sign the informed consent and to complete headache diaries.*

<table>
<tr><td></td><td colspan="3">Exclusion Criteria:
• You will not be able to participate in the study if you previously discontinued Topiramate because it did not make you feel better or it made you feel different
• have migraine aura without headache
• have a positive urine drug screen
• have a history of kidney stones
• have a history of suicide attempt
• pregnant females
• already on a migraine preventive medicine.</td></tr>
<tr><td>Intervention</td><td colspan="3">A total of 385 patients were randomized. A total of 159 topiramate 100 mg/day subjects and 171 placebo subjects were efficacy-evaluable.</td></tr>
<tr><td>Baseline characteristics</td><td colspan="3">Baseline characteristics</td></tr>
<tr><td></td><td>Characteristic</td><td>Topiramate (n=159)</td><td>Placebo (n=171)</td></tr>
<tr><td></td><td>Females (%)</td><td>138 (86.8)</td><td>156 (91.2)</td></tr>
<tr><td></td><td>Age (years ± SD)</td><td>39.6 (10.6)</td><td>40.9 (11.2)</td></tr>
<tr><td></td><td>BMI (kg/m^2)</td><td>30.2 (8.5) (N (n=158)</td><td>30.4 (8.4)</td></tr>
<tr><td></td><td>Age at migraine onset (years)</td><td>19.8 (10.0)</td><td>20.8 (10.8)</td></tr>
<tr><td></td><td>Number of headache days per 28 days</td><td>13.0 (2.5)</td><td>13.1 (2.6)</td></tr>
<tr><td></td><td>Number of migraine headache days per 28 days</td><td>11.6 (2.0)</td><td>11.8 (2.2)</td></tr>
<tr><td></td><td>Days of acute headache medication use per 28 days</td><td>8.6 (3.2)</td><td>8.6 (3.5)</td></tr>
<tr><td></td><td>Usual migraine headache pain intensity per 28 days (N, %)
- Mild
- Moderate
- Severe</td><td>
2 (1.3)
88 (55.3)
69 (43.4)</td><td>
2 (1.2)
90 (52.6)
79 (46.2)</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The primary efficacy parameter will be whether or not a patient experiences 15 or more headache days (migraine and non-migraine) during the last 28 days of the study.

Secondary end point: time to development of transformed migraine; occurrence of transformation as function of baseline headache days; change in the average rate of migraine days; percentage change in the average rate of migraine days;50%,75%, and 100% reduction in migraine days</td></tr>
<tr><td>Method of analysis</td><td colspan="3">The primary analysis of the primary efficacy measure, whether a subject reported 15 headache days per 28-day period at month 6, was analyzed based on the EE analysis set. Six 28-day periods during the double-blind phase were designated as months 1 through 6. For each subject, a binary outcome of whether 15 headache days/28 days was experienced or not experienced was determined for each month. A generalized linear mixed model (GLMM) using a logit link function was used to analyze this repeated binary outcome data. The standard assumption of local independence of repeated measures within a subject given the subject effect was made. Baseline monthly headache day rate was included as a covariate in the model. The null</td></tr>
</table>

	hypothesis tested was that the difference between treatment groups at month 6 as measured by the log odds ratio was 0. The marginal probability of reporting 15 headache days at each month was estimated by generating random normal deviates from the estimated normal distribution of the subject effect. A plot of the observed monthly probabilities of reporting 15 headache days against those predicted by the GLMM was generated. *The primary efficacy data variable was also analyzed using another statistical approach, the generalized estimating equation model for the EE analysis set. Secondary efficacy variables involving change from baseline and percent change in the mean 28-day rate during the double-blind phase were analyzed using analysis of covariance (ANCOVA) methodology with treatment and center as independent factors and baseline value (of the dependent) variable as a covariate. Categorical secondary variables were analyzed using the Cochran-Mantel-Haenszel test with modified ridit score, stratified by center. Analysis of time to the first reporting of 15 headache days per 28-day period, and time to the first reporting of 15 or more headache days, of which at least half were migraine, were analyzed using Kaplan-Meier (with a log rang test for treatment group difference) methodology and Cox's proportional hazards model, with baseline headache days or migraine headache days as a covariate.*
Subgroup analyses	*No subgroup was defined in this study.*

5.3 Candesartan

5.3.1 Tronvik et al, 2003

TABLE 46 MAIN CHARACTERISTICS FROM TRONVIK ET AL., 2003

Trial name	*Prophylactic treatment of Migraine with an Angiotensin II Receptor blocker*
NCT number	*Not stated in publication*
Objective	*To determine whether treatment with the angiotensin II receptor blocker Candesartan is effective as a migraine-prophylactic drug*
Publications – title, author, journal, year	*Prophylactic treatment of Migraine with an Angiotensin II Receptor blocker. A Randomized Controlled Trial. Tronvik E, et al. JAMA 2003*
Study type and design	*Randomized double blind, placebo-controlled cross-over study*
Follow-up time	*12 weeks*
Population (inclusion and exclusion criteria)	***Inclusion criteria:*** • *Age 18-65* • *migraine occurrence with/without aura according to IHS criteria.at a rate of 2-6 attacks pr. Month* • *Debut 1-year prior randomization, before age 50* ***Exclusion:*** • *Headache not distinguishable from migraine Page 21 of 50* • *Pregnancy/nursing* • *Hepatic impairment*

	• *History of angioneurotic edema, psychiatric illness* • *Use of daily migraine prophylactic 12 weeks prior to study.*	
Intervention	*Placebo runs in a period of 4 weeks, followed by two 12-week treatment periods separated by 4 weeks of placebo washout. 30 patients were randomized to assign to receive 16 mg candesartan/day in the first treatment period, followed by 1 placebo tablet/day in the second period. Remaining 30 received placebo followed by candesartan.*	
Baseline characteristics		***IIT population N=57***
	Women, n	*45*
	Age, women. Years (SD)	*42 (11)*
	Age, men. Years (SD)	*48 (13)*
	Migraine days per 4 weeks (SD)	*5.7 (2.9)*
	Headache days per 4 weeks (SD)	*8.4 (3.9)*
Primary and secondary endpoints	*Primary: Number of days with headache per 4 weeks* *Secondary:* • *Hours with headache per 4 weeks* • *days with migraine per 4 weeks* • *hours with migraine per 4 weeks* *headache severity index, level of disability, dosis of triptans, doses of analgetics, acceptability of treatment, days of sick leave, and QOL in the SF 36 questionnaire*	
Method of analysis	*All statistical tests were between treatment periods, and did not include baseline data. MMD was tested with Wilcoxon's paired signed rank test. The analysis was based on the ITT analysis set.*	
Subgroup analyses	*N/A*	

5.3.2 Stovner et al, 2014

TABLE 47 MAIN CHARACTERISTICS OF STOVNER ET AL., 2014

Trial name	*Candesartan Versus Propranolol for Migraine Prevention*
NCT number	*NCT00884663*
Objective	*The main aim of the present study is to compare candesartan with propranolol for migraine prophylaxis.*
Publications – title, author, journal, year	*A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Stovner et al., Cephalalgia, 2014*
Study type and design	*randomized double-blind cross-over study*
Follow-up time	*12 weeks*

Population (inclusion and exclusion criteria)	***Inclusion criteria:*** • *age 18 to 65 years* • *retrospectively have ≥ 2 migraine attacks per month during the last 3 months* • *during the baseline period have ≥ 2 migraine attacks* • *debut of migraine at least one year prior to inclusion* • *start of migraine before age 50 years.* ***Exclusion:*** • *interval headache not distinguishable from migraine* • *chronic tension-type headache or other headache occurring on ≥ 15 days/month* • *pregnancy, nursing or inability to use contraceptives* • *heart conduction block on ECG or significant ECG abnormality on inclusion* • *heart rate < 54 after 3 minutes rest* • *previous or present asthma, diabetes; decreased hepatic or renal function* • *hypersensitivity to active substance* • *history of angioneurotic edema* • *significant psychiatric illness* • *use of daily migraine prophylactics less than 4 weeks prior to start of study* • *having tried ≥ 3 prophylactic drugs against migraine during the last 10 years* • *previous use of propranolol or candesartan in adequate doses* • *previous discontinuation of either Atacand or Inderal Retard (or another beta blocker) due to adverse events* • *current use of antihypertensive medication* • *require use of rizatriptan (Maxalt) 10 mg tabl.* • *subjects requiring detoxification from acute medication (ergotamine¨s, opioids)* • *patients who consistently fail to respond to any acute migraine medication* • *patients with alcohol or illicit drug dependence*			
Intervention	*72 adult patients with episodic or chronic migraine went through three 12-week treatment periods on either candesartan 16 mg, propranolol slow-release 160 mg, or placebo.*			
Baseline characteristics		***Whole***	***mITT***	***PP***
	Women, n (%)	59 (82)	51 (84)	45 (83)
	Mean age, years (SD)	37 (11)	38 (11)	37 (11)
	Mean duration of headache history in years (SD)	19 (11)	20 (11)	19 (11)
	Mean number of attacks per month (SD)	4.8 (3.6)	4.8 (3.3)	4.7 (3.0)
	Mean number of migraine days per four weeks (SD)	4.9 (3.0)	4.8 (3.4)	4.5 (2.6)
	Migraine without aura, n (%)	38 (53)	32 (52)	29 (54)
	Migraine with aura, n (%)	6 (8)	4 (7)	4 (7)
	Migraine with and without aura, n (%)	27 (38)	24 (39)	21 (39)

	Chronic migraine, n (%)	1 (1)	1 (2)	0 (0)
Primary and secondary endpoints	*Primary: The number of days per 4 weeks with moderate or severe headache lasting ≥ 4 hours or is treated with the patient's usual headache medication [Time Frame: One year]* *Secondary:* • *Days with headache [Time Frame: One year]* • *Hours with headache [Time Frame: One year]* • *Headache intensity (0-3 scale) on days with headache [Time Frame: one year]* • *Doses of analgesics [Time Frame: one year]* • *Doses of triptans [Time Frame: One year]* • *Days with sick leave [Time Frame: one year]* • *Number of responders (≥ 50% decrease in migraine days compared with baseline) [Time Frame: one year]* • *Number of reported adverse events [Time Frame: one year]* • *Number of predefined retrospective adverse events [Time Frame: one year]*			
Method of analysis	*All statistical tests were between treatment periods and did not include baseline data (except for analyses of responder rate). In accordance with the predetermined statistical protocol, H1 (CAN-PLA-difference) was tested with Wilcoxon's paired signed rank test, and likewise the secondary comparisons (CAN-PRO and PLA– PRO). The differences in responder rate and AE proportions were tested with a standardised normal deviate. SYSTATv11 (Systat Software Inc, Chicago, IL, USA) was used with two-sided level of significance 0.05 and subjects fulfilling mITT-requirements were included in the main analysis. H2 was tested in accordance with CONSORT recommendations for non-inferiority analysis (12%), including only PP completers (n = 54). A mean difference of 1.2 days per four weeks was chosen as the cutoff delta value. This was deemed to be a clinically relevant improvement corresponding to an expected standardised difference of 0.35 SD, but clearly less than the effect (0.5 SD) considered in the power calculation for the main superiority hypothesis. In order to select an a priori reasonable delta, we calculated the probability of reaching an inconclusive result, i.e. we calculated power for detecting true inferiority as a function of both delta and the 'true active comparator difference'. For a reasonably small true active comparator difference = 0.1 SD (or even 0 SD) and delta = 0.35 SD, the power for detecting true non-inferiority was deemed acceptable = 58% (or 83% for 0 SD, i.e. true equality). The expected treatment effect difference between the active drugs was estimated from a previous migraine trial*			
Subgroup analyses	*N/A*			

5.4 Lisinopril

5.4.1 Schrader et al, 2001

TABLE 48 MAIN CHARACTERISTICS FROM SCHRADER ET AL., 2001

Trial name	*Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study*
NCT number	*Not stated in the publication*

Objective	*To determine the efficacy of an angiotensin converting enzyme inhibitor in the prophylaxis of migraine.*
Publications – title, author, journal, year	*Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo-controlled crossover study. Schrader et al., BMJ (Clinical research ed.), 2001*
Study type and design	*Double blind, placebo-controlled crossover study. After a four-week placebo run-in period to verify the frequency of attacks, patients were randomly allocated to take one tablet daily containing either 10 mg lisinopril (active) or placebo (inactive). The participants kept a daily diary in which they recorded the presence, severity, and, if appropriate, duration of symptoms in hours. Quality of life was assessed with a standardised questionnaire (SF-36). After each treatment period participants were also asked about the acceptability of the treatment ("If you could receive this treatment on prescription, would you like to continue with the treatment that you have used in the past 12 weeks?"). Participants were defined as compliant with treatment if they had adhered to the drug regimen (>80% of the tablets taken as determined by a tablet count at the end of the treatment period) and had given complete data in the diary.*
Follow-up time	*12 weeks*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Diagnosis of migraine with and without aura according to the criteria of the International Headache Society* • *Men and women aged between 18 and 60 year* • *Presence of migraine for more than a year* • *Onset of migraine before the age of 50 years* • *Attacks of migraine occurring two to six times a month.* ***Exclusion Criteria:*** • *Interval headache that the patient was unable to differentiate from migraine* • *Use of prophylactic drugs for migraine in the four weeks before randomization* • *Pregnancy or inability to use contraceptives* • *Decreased renal or hepatic function* • *Hypersensitivity to angiotensin converting enzyme inhibitors* • *History of angio neurotic oedema, and psychiatric disorder.*
Intervention	*Treatment period of 12 weeks with one 10 mg lisinopril tablet once daily for one week then two 10 mg lisinopril tablets once daily for 11 weeks, followed by a two week wash out period. Second treatment period of one placebo tablet once daily for one week and then two placebo tablets for 11 weeks. Thirty participants followed this schedule, and 30 received placebo followed by lisinopril.*
Baseline characteristics	*No baseline characteristics stated in the publication.*
Primary and secondary endpoints	*Primary end points: number of hours with headache, number of days with headache, number of days with migraine. Secondary end points: headache severity index, use of drugs for symptomatic relief, quality of life and number of days taken as sick leave, acceptability of treatment*

Method of analysis	*A Wilcoxon signed rank test was used to compare end point variables. For comparison of adverse events and acceptability we used a McNemar's matched pairs test A two-sided P<0.05 was considered significant A paired study including 55 subjects will have about 80% power to detect a group mean difference of 0.5 SD (with Student's t test).*
Subgroup analyses	*None*

5.5 Propranolol

5.5.1 Diener et al, 1996

TABLE 49 MAIN CHARACTERISTICS FROM DIENER ET AL., 1996

Trial name	*Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol*
NCT number	*Not stated in publication*
Objective	*To test the hypothesis that cyclandelate is more effective than placebo in the prophylaxis of migraine using the minimal effective dosage of 1200 mg/day, and as a secondary hypothesis, investigate the comparative efficacy with propranolol (120 mg/day).*
Publications – title, author, journal, year	*Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group. Diener et al., Cephalalgia, 1996*
Study type and design	*A randomized, parallel-group, double-blind multicenter study. The study is completed.* *Patients who fulfilled the entry criteria entered a 4-week baseline period without any prophylactic treatment. Those who recorded 2-10 attacks on their migraine headache diaries during the baseline period qualified for randomization (randomization ratio =3 : 2 : 3) to cyclandelate, placebo or propranolol. To avoid early withdrawals due to initial adverse events, treatment started with a 2-week run-in period at a dosage of 400 mg tid cyclandelate placebo or 40 mg tid propranolol. This was followed by a 12-week period of active prophylaxis at a dosage of 400 mg tid cyclandelate, placebo or 40 mg tid propranolol. At the end of the study and prior to breaking the code, the attending physician evaluated all migraine headache diaries, blinded to the number and total duration of migraine attacks at baseline and in the last 4 weeks of prophylaxis. This diary database was used for primary analysis*
Follow-up time	*20 weeks (primary analysis)*
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Patients between the age 18 and 60 years* • *Male or female* • *Migraine with and/or without aura according to the IHS criteria* • *Migraine history of at least 12 months' duration* • *A mean number of 2-10 migraine attacks per month within the last 3 months prior to the study)* ***Exclusion Criteria:*** • *Pregnant or lactating women* • *Psychiatric disorders Page 18 of 50* • *Concomitant non-migraine headaches 23 times per month within the last 3 months*

<table>
<tr><td></td><td colspan="4">

- *Intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks preceding the tria*
- *Specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder)*
- *Intake of drugs to treat migraine attacks>12 days/month. Prior to study entry and at the end of the treatment*

</td></tr>
<tr><td>Intervention</td><td colspan="4">A total of 214 ITT patients in 17 centres were randomized after completing the baseline period, 81 patients (37.9%) were treated with cyclandelate, 55 (25.7%) with placebo and 78 (36.4%) with propranolol. Forty patients had to be excluded from the ITT analysis for various reasons and 174 patients (cyclandelate n=67, placebo n =39, propranolol n =68) remained for the PI' analysis. The study had a 2-week run-in period at a dosage of 400 mg tid cyclandelate placebo or 40 mg tid propranolol.

This was followed by a 12-week period of active prophylaxis at a dosage of 400 mg tid cyclandelate, placebo or 40 mg tid propranolol. The study ended with a 2-week run-out period to avoid early recurrence of migraine, using the same dosages as in the run-in period. Additional medication to treat acute migraine attacks was allowed for up to 12 days/month for the duration of the study, including the baseline period. Patients were required to come for a check-up visit at the end of the baseline period and at weeks 10, 14, 18 and 20.</td></tr>
<tr><td rowspan="8">Baseline characteristics</td><td>Characteristic</td><td>Cyclandelate N=81</td><td>Propranolol N=78</td><td>Placebo N=55</td></tr>
<tr><td>Age, mean</td><td>39</td><td>40</td><td>39</td></tr>
<tr><td>Male</td><td>15</td><td>18</td><td>14</td></tr>
<tr><td>No of patients with acute migraine medication
- Analgesics/antirheumatics
- Specific migraine drugs</td><td>
55
46</td><td>
51
49</td><td>
36
32</td></tr>
<tr><td>Mean number of attacks/4 weeks ≤ 4 attacks</td><td>4
3</td><td>4
3</td><td>4
3</td></tr>
<tr><td>Additional medication under attacks
- Never
- Sometimes
- Every Day</td><td>
6
23
52</td><td>
3
24
51</td><td>
2
15
38</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="4">The primary efficacy measure:
- "Rate of responders", i.e. patients with ≥50% reduction in the number of migraine attacks
- Mean "migraine duration" in hours.

Secondary efficacy measures:
- The efficacy of propranolol versus placebo and equivalent efficacy of cylandelate compared to propranolol
- change in intensity of headache
- Intake of analgesics or migraine drugs
- Number of working days lost due to migraine
- frequency and severity of adverse events.</td></tr>
</table>

Method of analysis	*Not applicable since the endpoints for this application are not the same as those analyzed in the publication*
Subgroup analyses	*N/A*

5.5.2 Diener et al, 2004

TABLE 50 MAIN CHARACTERISTICS FROM DIENER ET AL., 2004

Trial name	Topiramate in migraine prophylaxis Results from a placebo-controlled trial with propranolol as an active control
NCT number	*Not stated in publication*
Objective	To evaluate the efficacy and safety of two doses of topiramate (100 and 200 mg/d) vs placebo for migraine prophylaxis, with immediate-release propranolol (160 mg/d) as an active control.
Publications – title, author, journal, year	Topiramate in migraine prophylaxis - Results from a placebo-controlled trial with propranolol as an active control, Diener HC, et al. J Neurol 2004
Please see description in Table 36	

5.5.3 Stovner et al, 2014

TABLE 51 MAIN CHARACTERISTICS FROM STOVNER ET AL., 2014

Trial name	*Candesartan Versus Propranolol for Migraine Prevention*
NCT number	*NCT00884663*
Objective	*The main aim of the present study is to compare candesartan with propranolol for migraine prophylaxis.*
Publications – title, author, journal, year	*A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Stovner et al., Cephalalgia, 2014*
Please see description in Table 47	

5.6 Valproate

5.6.1 Jensen et al, 1994

TABLE 52 MAIN CHARACTERISTICS FROM JENSEN ET AL., 1994

Trial name	*Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study*
NCT number	*Not stated in publication*
Objective	*To evaluate if sodium valproate has a prophylactic effect in migraine without aura.*
Publications – title, author, journal, year	*Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study. Jensen R, et al. Neurology 1994*
Study type and design	*A triple-blind, dose-controlled, crossover study in patients with migraine without aura. After a 4-week medication-free run-in period, patients eligible for inclusion were*

<table>
<tr><td></td><td colspan="3">randomized to sodium valproate or placebo. After randomization, all patients were given three apparently identical tablets per day during the entire trial. The treatment periods were separated by a 4-week wash-out period with three placebo tablets per day. Thereafter, the patients were shifted to either placebo or sodium valproate in a similar 12-week treatment period</td></tr>
<tr><td>Follow-up time</td><td colspan="3">Data from the 12-week triple-blind treatment phases is presented.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td colspan="3">Inclusion Criteria:
• a diagnosis of migraine without aura, a history of migraine for at least 1 year
• 2 to 10 days with migraine per month
• age between 18 and 70 years
• women of childbearing potential had to use adequate contraceptive measures throughout the study.
Exclusion Criteria:
• daily headache
• more than six attacks per year of migraine with aura
• cluster headache or trigeminal neuralgia
• other neurologic, somatic, or psychiatric diseases
• other migraine prophylaxis
• any form of drug abuse or dependency, including daily ergotamine or large amounts of plain analgesics
• previous participation in more than two migraine drug trials.</td></tr>
<tr><td>Intervention</td><td colspan="3">Randomization assigned 22 patients to the sodium valproate-placebo sequence (group A) and 21 patients to the placebo-sodium valproate sequence (group B). Doses of valproate were 1000-1500 mg based on serum valproate level.</td></tr>
<tr><td rowspan="4">Baseline characteristics</td><td></td><td>Group A ValproatePlacebo
N=22</td><td>Group B PlaceboValproate
N=21</td></tr>
<tr><td>Age, mean (years)
Range</td><td>45
28-58</td><td>47
27-62</td></tr>
<tr><td>Male/Female</td><td>4/18</td><td>2/19</td></tr>
<tr><td>Frequency of migraine/4 weeks
Mean
Range</td><td>
6.3
(3-10)</td><td>
6.8
(4-10)</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">Primary endpoints: The mean number of days with migraine during sodium valproate as compared with the placebo period.

Secondary endpoints: Frequency of tension-type headache, headache intensity, headache duration, and drug consumption. Responders defined as those patients for whom the</td></tr>
</table>

	frequency of migraine days was reduced to 50% or less when compared with the baseline period.
Method of analysis	*Patients who dropped out of the trial after randomization were excluded from the statistical analysis, but reasons for dropping out were recorded. The primary efficacy variable was the treatment effect, i.e., the mean number of days with migraine during sodium valproate as compared with the placebo period. Other variables were considered secondary. A nonparametric statistical test, Wilcoxon's rank sum test, was used to test the treatment effect. A 5% level of significance was used.*
Subgroup analyses	None

5.6.2 Mathew et al, 1995

TABLE 53 MAIN CHARACTERISTICS FROM MATHEW ET AL., 1995

Trial name	*Migraine Prophylaxis With Divalproex*
NCT number	*Not stated in publication*
Objective	*To compare the effectiveness and safety of divalproex sodium (Depakote) and placebo in the prophylaxis of migraine headache*
Publications – title, author, journal, year	*Migraine prophylaxis with Divalproex. Mathew NT, et al. Arch Neurol. 1995*
Study type and design	*The investigation was conducted as a randomized, placebo controlled, double-blind, parallel-group, multicenter study, designed to compare the efficacy and safety of divalproex with that of placebo in the prophylaxis of migraine headache. The study was divided into two phases: a baseline phase (4 weeks) and treatment phase (12 weeks with 4-week dose adjustment and 8-week maintenance). Patients were randomized to groups receiving divalproex or placebo in a 2:1 ratio of divalproex to placebo within each center. Total duration of the study was 16 weeks*
Follow-up time	*Data from the 12 week double-blind treatment phase is presented.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *16 to 75 years of age* • *have suffered migraine episodes with or without aura per International Headache Society criteria for 6 or more months previously;* • *migraine frequency was required to be two or more episodes per month for the previous 3 months Page 41 of 50* • *the patient had not received prophylactic treatment previously or had failed no more than two adequate trials, in the investigator's opinion, of established prophylactic antimigraine regimens*. ***Exclusion Criteria:*** • *only migraine episodes unassociated with headache* • *chronic daily headaches or tension-type headaches occurring more than 15 days per month* • *cluster headaches*

<table>
<tr><td></td><td colspan="3">

- *a history of any significant medical or psychiatric disorder (particularly one that would confound data interpretation or required medication whose known effects included antimigraine prophylaxis*
- *a history of poor compliance with previous medication regimens*
- *a history of previous valproate use*
- *women of child bearing potential*

</td></tr>
<tr><td>Intervention</td><td colspan="3">Patients were randomized to groups receiving divalproex or placebo in a 2:1 ratio of divalproex (n=70) to placebo (n=37). Treatment with divalproex sodium was started at a dose of 250 mg/d; doses were then titrated upward at recommended increments of 250 mg every other day (or 250 mg every third day for patients weighing</td></tr>
<tr><td rowspan="4">Baseline characteristics</td><td></td><td>Placebo N=37</td><td>Valproate N=70</td></tr>
<tr><td>Age (years)</td><td>43</td><td>47</td></tr>
<tr><td>Female %</td><td>73</td><td>80</td></tr>
<tr><td>Duration of migraine diagnosis</td><td colspan="2">25</td></tr>
<tr><td></td><td>Previous prophylactic treatments</td><td colspan="2">1.3</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The primary outcome measure was the 4-week migraine headache frequency (i.e., the number of migraine headaches, with or without aura, per 4 weeks) during the treatment phase.

Secondary outcomes:

• proportion of patients with a reduction of 50% or more in 4-week migraine headache frequencies compared with the baseline phase
• the average duration of episodes
• the average severity of episodes at peak intensity (peak severity)
• the average severity related to functional ability (assessment of functional restriction)
• the average symptomatic medication usage (measuring usage days of each medication summed across medications) per episode
• the 4-week frequencies of migraine headaches with associated nausea, vomiting, aura, photophobia, and phonophobia
• the number of days per 4 weeks with migraine headaches</td></tr>
<tr><td>Method of analysis</td><td colspan="3">Analyses were performed using all data from randomized patients. The nonparametric Van Elteren method of linearly combining Wilcoxon test results from individual investigators, using weights recommended by Lehmann, was the method used to compare treatment groups with respect to the primary efficacy outcome measure. The Cochran-Mantel-Haenszel statistic was used to compare treatment groups with respect to the proportion of patients with a 50% or greater reduction in 4-week migraine headache frequencies. All hypothesis tests were two tailed, and values of .05 or less were considered significant.</td></tr>
<tr><td>Subgroup analyses</td><td colspan="3">None</td></tr>
</table>

5.6.3 Klapper et al, 1997

TABLE 54 MAIN CHARACTERISTICS FROM KLAPPER ET AL., 1997

Trial name	*Divalproex sodium in migraine prophylaxis: a dose-controlled study*
NCT number	*Not stated in publication*
Objective	*To evaluate the efficacy and safety of divalproex sodium (DVPX) when used as prophylactic monotherapy in patients with migraine.*
Publications – title, author, journal, year	*Divalproex sodium in migraine prophylaxis: a dose-controlled study. Klapper J et al. Cephalalgia 1997*
Study type and design	*Design: Multicenter, double-blind, placebo-controlled, parallel group. During a 4-week (single-blind) baseline phase (BP), patients received placebo and completed a headache diary. Patients completing the BP who had experienced at least two migraine attacks during this period were randomized to one of four treatment groups (placebo, or either 500 mg, 1000 mg, or 1500 mg DVPX) in a 1: 1 : 1 : 1 ratio within each study center. The experimental phase (EP) lasted 12 weeks, the first 4 weeks for dose escalation to randomized dose, and the remaining 8 weeks for maintenance at that dose.*
Follow-up time	*Data from the 12-week double-blind experimental phase are presented.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** *Patients 16 years or older were eligible to enrol in the study if they had suffered migraine attacks with or without aura (as defined by the International Headache Society criteria) for at least 6 months prior to the study and had averaged at least two migraine attacks per month during the previous 3 months. Page 39 of 50 Patients previously untreated for migraine or patients who, in the opinion of the investigator, had previously failed no more than two adequate trials (e.g. at least 1 month of treatment at a full therapeutic dose) of prophylactic therapy were eligible. Patients already receiving prophylactic treatment were required to discontinue these medications and complete a washout period of a length equivalent to at least five half-lives of the medication prior to enrolment.* ***Exclusion Criteria:*** *Patients were excluded from the study if they experienced other headache types (i.e. interval headaches) on more than 15 days per month, had migraines which were always unassociated with headache, or had cluster headaches. Also excluded were pregnant women, women of child-bearing potential not practicing effective birth control, patients previously treated with valproate, and patients with a significant medical or psychiatric disorder, particularly one requiring medication that could have confounded data interpretation. Disallowed concomitant medications included beta-adrenergic blocking agents, tricyclic antidepressants, calcium channel blockers, monoamine oxidase inhibitors, methysergide maleate, lithium carbonate, phenobarbital, phenytoin, arbamazepine, warfarin, and any of the following used on a daily basis: ergotamine preparations, non-steroidal anti-inflammatory agents, analgesics, benzodiazepines, or cyproheptadine hydrochloride. Treatment with symptomatic medications was allowed on an as-needed*

<table>
<tr><td></td><td colspan="5">basis for treatment of individual headaches during the study but was to average less than 3 days per week.</td></tr>
<tr><td>Intervention</td><td colspan="5">Patients were randomized to receive a valproate daily dose of 500 (n=45), 1000 (n=43), or 1500 (n=44) mg, or to placebo (n=44). The EP began with a 4-week dose titration period and was followed by an 8-week dose maintenance period. The initial daily dose for DVPX-treated patients was 250 mg. The daily dose was then increased by 250 mg every 4 days (every 8 days for the 500 mg group) until the assigned randomized dose was achieved, at which time study medication was taken twice daily in equal, divided doses, morning and evening. The dose then remained fixed at the randomized dose throughout the remainder of the study.</td></tr>
<tr><td rowspan="15">Baseline characteristics</td><td></td><td>Placebo N=44</td><td>Divalproex sodium 500 mg N=45</td><td>Divalproex sodium 1000 mg N = 43</td><td>Divalproex sodium 1500 mg N = 44</td></tr>
<tr><td colspan="5">Age (years)</td></tr>
<tr><td>Mean</td><td>40.2</td><td>40.8</td><td>41.5</td><td>40.7</td></tr>
<tr><td>Range</td><td>(19-67)</td><td>(17-65)</td><td>(21-70)</td><td>(23-76)</td></tr>
<tr><td>Gender</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Female</td><td>91%</td><td>93%</td><td>88%</td><td>84%</td></tr>
<tr><td colspan="5">Race</td></tr>
<tr><td>Caucasian</td><td>89%</td><td>93%</td><td>86%</td><td>93%</td></tr>
<tr><td>Black</td><td>7%</td><td>0%</td><td>12%</td><td>2%</td></tr>
<tr><td>Other</td><td>5%</td><td>7%</td><td>2%</td><td>5%</td></tr>
<tr><td colspan="5">Weight</td></tr>
<tr><td>Mean (kg)</td><td>68.4</td><td>66.8</td><td>71.6</td><td>69.6</td></tr>
<tr><td>Range</td><td>(37.2-109.5)</td><td>(46-129.7)</td><td>(46.7-117.5)</td><td>(53.2-128.6)</td></tr>
<tr><td>Years with migraine</td><td>21</td><td>20,6</td><td>23,7</td><td>21,3</td></tr>
<tr><td>Previously used other prophylactic antimigraine medications</td><td>55%</td><td>56%</td><td>56%</td><td>45%</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="5">The primary efficacy variable was the 4-week migraine attack frequency (i.e. the number of migraine attacks, with or without aura, during the EP' multiplied by the ratio of 28 days to the actual number of days the patient was treated).

- The proportional reduction from baseline in migraine attack frequencies was also evaluated.</td></tr>
</table>

	Other headache characteristics evaluated included *• the duration and peak severity of migraine attacks that continued to occur* *• the numbers of days per 4 weeks with migraine attacks that impair usual activities or necessitating symptomatic medication, and* *• the 4-week attack frequencies of migraines with nausea, vomiting, photophobia and/or phonophobia and of all non-migraine headache types combined.*
Method of analysis	*Not applicable since the endpoints for this application are not the same as those analysed in the publication*
Subgroup analyses	None

5.6.4 Freitag et al, 2002

TABLE 55 MAIN CHARACTERISTICS FROM FREITAG ET AL., 2002

Trial name	*A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis*
NCT number	*Not stated in publication*
Objective	*To evaluate the efficacy and safety of extended-release divalproex sodium compared with placebo in prophylactic monotherapy treatment of migraine headache.*
Publications – title, author, journal, year	*A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Freitag FG, et al. Neurology 2002.*
Study type and design	*This was a 17-week multicenter, double-blind, randomized, placebo-controlled, parallel-group study consisting of three phases: a 4-week baseline phase; a 12-week double-blind experimental phase; and a 1-week double-blind termination phase. During the baseline phase, subjects maintained a headache diary in which headache activity was recorded. Subjects compliant in maintaining a headache diary and who had at least two migraine headache attacks (separated by a headache-free interval of at least 24 hours) during the 4-week baseline phase were eligible to be randomized.* *Following the 4-week baseline phase, eligible subjects were randomly assigned in a 1:1 ratio at each center to receive either extended-release divalproex sodium or identical gray ovaloid placebo tablets, and entered into the 12-week experimental phase. The experimental phase consisted of a 2-week dose titration/adjustment period followed by a 10-week fixed-dose treatment period. Headache diaries were used to collect information regarding the start and end times, characteristics, and symptomatic medication usage associated with each headache attack. Headache attacks separated by any headache-free interval were to be reported separately. Based on review of the diaries, the headache type of each attack was determined by the investigator per the IHS diagnostic criteria. The tolerability and safety of study medication were monitored through adverse event reporting and assessments of prior and concurrent medication, physical and brief*

<table>
<tr><td></td><td colspan="3">neurologic examinations, routine laboratory evaluations, and serum pregnancy tests for women of childbearing potential.</td></tr>
<tr><td>Follow-up time</td><td colspan="3">Data from the 12-week double-blind experimental phase are presented.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td colspan="3">Inclusion Criteria:
• Men or woman more 12 years or older
• More than two migraine headache attacks during a 4-week baseline period
Exclusion Criteria:
• Women who were lactating or pregnant
• subjects who had headaches an average of >15 days per month; had ever experienced cluster headaches;
• had previously received an adequate course of treatment with valproate or divalproex sodium for migraine headaches
• had a CNS neoplasm or infection, demyelinating disease, degenerative neurologic disease, or progressive CNS disease
• had failed more than two adequate trials of prophylactic antimigraine regimens
• or who had received prophylactic antimigraine medication within five half-lives of that medication before entering the baseline phase.</td></tr>
<tr><td>Intervention</td><td colspan="3">Subjects initiated treatment on 500 mg once daily for 1 week, and the dose was then increased to 1,000 mg once daily with an option, if intolerance occurred, to permanently decrease the dose to 500 mg during the second week. 122 patients was randomized to active treatment and 101 patients completed</td></tr>
<tr><td rowspan="5">Baseline characteristics</td><td></td><td>Placebo N=115</td><td>Treatment 1 N=122</td></tr>
<tr><td>Age (years)</td><td>41.3</td><td>39.8</td></tr>
<tr><td>Female, n</td><td>90 (78%)</td><td>97 (80%)</td></tr>
<tr><td>Weight (kg)</td><td>74.5</td><td>74.39</td></tr>
<tr><td>Height (cm)</td><td>166.88</td><td>166.88</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The primary efficacy variable was the experimental phase reduction from baseline (i.e., the baseline phase) in 4-week migraine headache rate. The 4-week rates for the experimental and baseline phases were calculated for each subject as the number of migraine headaches during the study phase multiplied by the ratio of 28 days to the actual number of days in the phase. The principal secondary variables were the experimental phase percent reduction from baseline in 4-week migraine headache rate, assessing both actual percentages and the proportion of subjects achieving at least a 50% reduction, and the experimental phase reduction from baseline in the number of migraine headache days per 4 weeks.

Other secondary variables included the experimental phase changes from baseline in the proportions of migraine headaches treated with particular classes of symptomatic medications (e.g., triptans).</td></tr>
</table>

Method of analysis	*The primary and secondary efficacy variables chosen for the current study were specified in the protocol and were based on (or were slight modifications of) variables included in the IHS committee guidelines for controlled trials of drugs in migraine,14 including the committee's recommended use of the 4-week migraine headache rate as the primary efficacy variable and the 24-hour headache free rule in calculating the migraine headache rates. Per this rule, migraine headache attacks separated by a _24- hour headache-free interval were combined and considered as a single migraine headache in calculations of 4-week migraine headache rates. The efficacy data set was an intent-to-treat data set that included all data from randomized subjects who received study drug and provided at least one headache evaluation during the experimental phase.* *The primary efficacy variable was the experimental phase reduction from baseline (i.e., the baseline phase) in 4-week migraine headache rate. The 4-week rates for the experimental and baseline phases were calculated for each subject as the number of migraine headaches during the study phase multiplied by the ratio of 28 days to the actual number of days in the phase.* *The principal secondary variables were the experimental phase percent reduction from baseline in 4-week migraine headache rate, assessing both actual percentages Page 37 of 50 and the proportion of subjects achieving at least a 50% reduction, and the experimental phase reduction from baseline in the number of migraine headache days per 4 weeks* *The nonparametric van Elteren method of linearly combining Wilcoxon test results from individual investigators, using weights recommended by Lehmann, was the protocol-specified primary analysis method for the continuous variables. Ninety-five percent CI of weighted treatment differences in means for these variables were derived using the analogous protocol-specified alternative analysis method, an analysis of variance (ANOVA) model that weighted treatment differences at each investigator site inversely proportional to the variance of the estimated treatment group difference.*
Subgroup analyses	None

5.7 Amitriptyline

5.7.1 Couch et al, 2011

TABLE 56 MAIN CHARACTERISTICS FROM COUCH ET AL., 2011

Trial name	*Amitriptyline in the Prophylactic Treatment of Migraine and Chronic Daily Headache*
NCT number	*Not stated in publication*
Objective	*To compare amitriptyline with placebo in the treatment of intermittent migraine and chronic daily headache*

<table>
<tr><td>Publications – title, author, journal, year</td><td colspan="3">Amitriptyline in the Prophylactic Treatment of Migraine and Chronic Daily Headache. Couch JR, el al. Headache 2011</td></tr>
<tr><td>Study type and design</td><td colspan="3">This study was a double-blind, placebo controlled, study comparing amitriptyline in doses of 25-100 mg/day, depending on the tolerance of the patient, with a matched placebo. Patients received placebo for 4 weeks (Period A – baseline period). After 4 weeks patients with at least 2 moderate or worse migraine headaches during Period A could be randomized into the double-blind period of 5-20 weeks (Periods B and C). Patients were randomized to either amitriptyline or placebo therapy on a 1:1 basis in blocks of 4 subjects. During Periods B and C the patient received pills that were identical to each other and identical to those dispensed in Period A, which contained either amitriptyline 25 mg or placebo. The first 4 weeks (Phase B) was a dose titration phase, and the following 12 weeks (Phase C) was a dose maintenance phase.</td></tr>
<tr><td>Follow-up time</td><td colspan="3">Data from the 20-week double-blind treatment phase is presented.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td colspan="3">Inclusion criteria

Patients between 18 and 70 years of age with at least two moderate or worse migraine headaches per month

Exclusion criteria

• absence of migraine headache
• secondary headache
• pregnant females or nursing mother
• known allergy to amitriptyline
• urinary retention, glaucoma, any cardiac disease, sustained hypertension
• subjects taking guanethidine or monoamine oxidase inhibitors
• prostatic hypertrophy
• thyroid disease or taking thyroid medication
• seizure disorder
• patients taking any known preventative antimigraine agent including methysergide, propranolol, cyproheptadine, antianxiety agents, or other tricyclic antidepressants</td></tr>
<tr><td>Intervention</td><td colspan="3">Placebo or amitriptyline in doses of 25-100 mg/day, depending on the tolerance of the patient. 194 patients received amitriptyline and 197 received placebo</td></tr>
<tr><td rowspan="4">Baseline characteristics</td><td></td><td>Placebo N=197</td><td>Amitriptyline N=194</td></tr>
<tr><td>Age (years)</td><td>35.7</td><td>34.1</td></tr>
<tr><td>Male (n)</td><td>34 (17%)</td><td>40 (21%)</td></tr>
<tr><td>Female (n)</td><td>163 (83%)</td><td>154 (79%)</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The major efficacy measures for this study are the frequency, duration, and severity of headaches</td></tr>
</table>

	Headache frequency was measured as number of days per 4 weeks with a headache of any degree of severity. *Duration was measured in hours.* *Headache severity was measured on a 5-point scale as follows: disabling (4) – a headache so severe the patient must lie down; severe (3) – a headache severe enough that usual activity is diminished by 50% or more; however, some activity is possible; moderate (2) – a headache that limits usual activity by less than 50%; mild (1) – a headache that is present but does not limit activity; no headache (0).*
Method of analysis	*Not applicable since the endpoints for this application are not the same as those analysed in the publication*
Subgroup analyses	*None*

5.7.2 Gonçalves et al, 2016

TABLE 57 MAIN CHARACTERISTICS FROM GONCALVES ET AL., 2016

Trial name	*EDUMAP*
NCT number	*NCT01357031*
Objective	*The purpose of this study was to determine the effectiveness of melatonin 3 mg compared to placebo and amitriptyline 25 mg in the preventive treatment of migraine*
Publications – title, author, journal, year	*Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. Gonçalves AL, et al. J Neurol Neurosurg Psychiatry 2016*
Study type and design	*The study was a randomized, multicenter, parallel-group study. Melatonin 3 mg was compared with amitriptyline 25 mg and placebo. The study consisted of a 4-week period to established baseline measures followed by a 12-week treatment period. Randomization was performed centrally with the use of Page 34 of 50 randomization lists with randomly permuted block lengths stratified according to center. Patients, treating clinicians and the outcome assessor were blinded.*
Follow-up time	*Data from the 12-week double-blind treatment period is presented*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *age of 18–65 years;* • *migraine with or without aura criteria according to the International Classification of Headache Disorders, third edition, β-version12 for at least 1 year* • *age of onset before 50 years,* • *at least three migraine headache attacks or four migraine headache days (defined as any occurrence of migraine headache pain of at least 30 min in duration with acute treatment) per month,* • *presents with migraine or non-migraine headache attacks*

<table>
<tr><td></td><td colspan="3">

- *Migraine diagnosis was performed by a trained neurologist headache specialist.*
- *Women were eligible if they were unable to bear children or if they were not pregnant and using adequate contraception.*

Exclusion criteria

- *history of psychiatric disorder (in the past or present);*
- *ergotamine, triptan, opioid, or combination medication intake for >10 days per month, or simple analgesic intake for >15 days per month for >3 months;*
- *in use of preventive medications such as β-blockers, tricyclic antidepressants, calcium channel blockers, antiepileptic drugs, bupropion, serotonergic norepinephrine reuptake inhibitors; and were unable to discontinue the treatment*
- *had previously taken melatonin, amitriptyline or agomelatine;*
- *had uncontrolled hypertension (i.e., sitting systolic blood pressure >160 mm Hg or sitting diastolic blood pressure >90 mm Hg) at the screening visit or at randomization.*

</td></tr>
<tr><td>Intervention</td><td colspan="3">Patients were randomized 1:1:1 to amitriptyline 25 mg/day (n=59), melatonin 3 mg/day (n=60) and placebo (n=59)</td></tr>
<tr><td rowspan="4">Baseline characteristics</td><td></td><td>Placebo N=59</td><td>Amitriptyline N=59</td></tr>
<tr><td>Age (years)</td><td>36.6</td><td>37.2</td></tr>
<tr><td>Female (n)</td><td>45 (76.3%)</td><td>44 (74.6%)</td></tr>
<tr><td>BMI Kg/m^2</td><td>24.6</td><td>41.1</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The primary efficacy outcome measure was frequency in number of migraine headache days per month comparing baseline with the past 4 weeks of treatment. Secondary end points included:

- *reduction in migraine intensity, attack duration,*
- *number of analgesics used and*
- *percentages of patients with greater than 50% reductions in migraine headache days.*

</td></tr>
<tr><td>Method of analysis</td><td colspan="3">Efficacy data were analyzed for the intention-to-treat population, defined as randomized patients who received at least one dose of the study medication and provided at least one post-baseline efficacy assessment. Missing days as non-migraine headache days. An analysis of covariance (ANCOVA) model was used to test the null Page 35 of 50 hypothesis of no difference between placebo and the average of the values for the three groups. Results were summarized using the adjusted mean and SE for each treatment group, a 95% CI for the change from baseline for each treatment group, a model estimate of the difference between each active treatment group and placebo, a 95% CI for the difference, and an associated p value and adjusted p value for the difference. Analysis of the primary end point was carried out using a combination of a sequential method and a Hochberg procedure to maintain the experiment-wise α level of 0.05.</td></tr>
<tr><td>Subgroup analyses</td><td colspan="3">None</td></tr>
</table>

5.8 Botox

5.8.1 Aurora et al, 2010 (PREEMPT I)

TABLE 58 MAIN CHARACTERISTICS FROM AURORA ET AL., 2010

Trial name	*PREEMPT I*
NCT number	*NCT00156910*
Objective	*This is the first of a pair of studies designed to assess efficacy, safety and tolerability of onabotulinumtoxinA (BOTOX®) as headache prophylaxis in adults with chronic migraine.*
Publications – title, author, journal, year	*OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT I trial, Aurora SK. et al. Cephalalgia, 2010.* *Pooled analyses:* • *OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Aurora SK, et al. Headache 2011 Page 44 of 50* • *Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. Silberstein SD, et al. J Neurol Neurosurg Psychiatry 2015 OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Dodick DW, et al. Headache. 2010* • *OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Aurora SK et al. Acta Neurol Scand 2014* • *Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine. Diener H et al. European Journal of Neurology 2014* • *OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine, Lipton R.B. et al. Neurology, 2011* • *OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: Pooled results from the PREEMPT randomized clinical trial program Lipton RB et al. Cephalalgia 2016* • *The impact of onabotulinumtoxinA on severe headache days: PREEMPT 56-week pooled analysis. Matharu M et al. The Journal of Headache and Pain 2017*
Study type and design	*Phase III with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Enrolled patients were randomly assigned 1:1, Randomization was stratified based on the frequency of acute headache pain medication intake during the 28-day baseline as yes/no overuse of acute headache pain medications, where medication overuse–yes was defined as intake during baseline of simple analgesics on 15 days, or other medication types or combination of types for 10 days, with intake 2 days/week from the category of overuse. The randomization sequence was generated using SAS programming language (SAS Institute, Cary, NC, USA). Randomization programmers had access to the central server, where the randomization sequence was kept. The study is Completed.*
Follow-up time	*Primary analysis after 24 weeks*

<table>
<tr><td>Population (inclusion and exclusion criteria)</td><td colspan="3">Inclusion Criteria:

• Frequent migraine (≥15 headache days per month)
• ≥4 distinct headache episodes lasting ≥4 hours
• ≥50% of baseline headache days migraine/probable migraine days
Exclusion Criteria:
• Previous use of botulinum toxin of any serotype or immunization to any botulinum toxin serotype
• Any medical condition that puts the patient at increased risk with exposure to BOTOX • Diagnosis of complicated migraine, chronic tension-type headache, hypnic headache, hemicrania continua, new daily persistent headache
• Use of prophylactic headache medication within 28 days prior to week -4
• Unremitting headache lasting continuously throughout the 4-week baseline period
• Known or suspected Temporomandibular Disorders (TMD)
• Diagnosis of fibromyalgia
• Beck depression inventory score >24 at week-4
• Psychiatric problems that may have interfered with study participation</td></tr>
<tr><td>Intervention</td><td colspan="3">• Biological: Botulinum Toxin Type A
Two treatment sessions in the double-blind phase and three treatment sessions in the open-label extension phase. Total minimum dose is 155 U with 31 fixed-site, Page 45 of 50 fixed dose injections across seven specific head/neck muscle areas with the total maximum dose of 195 U with 39 head/neck injections. Other Name: BOTOX®

• Other: Placebo (saline)
Two treatment sessions in the double-blind phase. Total minimum dose in 155 U with 31 fixed-site, fixed dose injections across seven specific head/neck muscle areas and the total maximum dose is 195 U with 39 head/neck injections</td></tr>
<tr><td rowspan="6">Baseline characteristics</td><td></td><td>Placebo N= 338</td><td>Botulinum Toxin Type A N= 341</td></tr>
<tr><td>Age</td><td>42.1</td><td>41.2</td></tr>
<tr><td>Female, %</td><td>85.8</td><td>89.1</td></tr>
<tr><td>Monthly migraine days</td><td>19.1 (4.1)</td><td>19.1 (4.0)</td></tr>
<tr><td>% patients with 1 or more prophylaxis</td><td>64.2</td><td>59.5</td></tr>
<tr><td>Mean BMI</td><td>27.3</td><td>26.7</td></tr>
<tr><td>% patients with medication overuse</td><td>69.8</td><td>66.3</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The primary endpoint in PREEMPT 1 was mean change from baseline in frequency of headache episodes for the 28-day period ending with week 24.

Secondary:</td></tr>
</table>

	• *Frequency of headache days (defined as a calendar day [00:00 to 23:59] when the patient reported 4 continuous hours of headache diary episode)* • *Migraine days (defined as a calendar day with 4 continuous hours of headache meeting ICHD-II criteria for migraine 1.1, 1.2, or 1.6)* • *Migraine episodes (defined as patient-reported headache with a start and stop time indicating that the pain lasted 4 continuous hours and met ICHD-II criteria for migraine 1.1, 1.2, or 1.6)* • *Overall acute headache pain medication use (all categories; referred to hereafter as acute pain medication intakes)*
Method of analysis	All efficacy analyses used the intent-to-treat population, which included all randomized patients. Analysis of covariance (ANCOVA) of the change from baseline, with the same variable's baseline values as covariate, with main effects of treatment group and medication overuse strata. Scores for months with ≥20 days of diary data were prorated to 28-day equivalents. Scores for months with <10 days of diary data were estimated using a modified last observation carried forward (mLOCF) methodology. This involved the substitution of the patient's previous 28-day period score multiplied by the ratio of the mean across all patients in the 28-day period of interest divided by the mean across all patients in the previous 28-day period. Scores for months with 10–19 days of diary data were estimated using an average of the prorated and mLOCF estimates. The mLOCF method of imputation of missing data was prespecified, but sensitivity analyses were also done (e.g., using observed data without imputation). For binomial variables, the between-group comparisons were done with Pearson's Chi-square or Fisher's exact tests, except that logistic regression with the same variable's baseline as covariate was used for variables with baseline imbalance. A two-sided test with $p \leq .05$ was considered to be statistically significant. No control of the type-1 error rate for multiple secondary endpoints was prespecified in PREEMPT 1. Therefore, a highly conservative Bonferroni adjustment was applied to compare the week 24 p values to a critical level of .01, which adjusted the prespecified type-1 error rate of .05 for the five variables that were prespecified as primary or secondary.
Subgroup analyses	None

5.8.2 Diener et al, 2010 (PREEMPT II)

TABLE 59 MAIN CHARACTERISTICS FROM DIENER ET AL., 2010

Trial name	*PREEMPT II*
NCT number	*NCT00168428*
Objective	*This is the second of a pair of studies designed to assess efficacy and safety of onabotulinumtoxinA (BOTOX®) for prophylaxis of headaches in adults with chronic migraine.*
Publications – title, author, journal, year	*OnabotulinumtoxinA for treatment of chronic migraine: Results from the doubleblind, randomized, placebo-controlled phase of the PREEMPT 2 trial, Diener H.C. et al. Cephalalgia, 2010*

	Pooled analysis: • *OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Aurora SK, et al. Headache 2011* • *Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. Silberstein SD, et al. J Neurol Neurosurg Psychiatry 2015* • *OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Dodick DW, et al. Headache. 2010* • *OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Aurora SK et al. Acta Neurol Scand 2014* • *Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine. Diener H et al. European Journal of Neurology 2014* • *OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine, Lipton R.B. et al. Neurology, 2011* • *OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: Pooled results from the PREEMPT randomized clinical trial program Lipton RB et al. Cephalalgia 2016* • *The impact of onabotulinumtoxinA on severe headache days: PREEMPT 56- week pooled analysis. Matharu M et al. The Journal of Headache and Pain 2017*
Study type and design	*Phase III with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase.* *Qualified subjects were randomized (1:1) in a double-blind fashion to onabotulinumtoxinA or placebo. Randomization was stratified based on the frequency of acute headache pain medication use during baseline (designated as ''medication overuse–yes'' or ''medication overuse–no''), with treatments balanced in blocks of four within each medication-overuse stratum for each investigator site. The randomization sequence was generated using SAS programming language (SAS Institute, Cary, NC, USA) and was stored in a central server with access granted to the randomization programmers. The study is completed.*
Follow-up time	*Primary analysis after 24 weeks*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Frequent migraine (≥15 headache days per month)* • *≥4 distinct headache episodes lasting ≥4 hours* • *≥50% of baseline headache days migraine/probable migraine days* ***Exclusion Criteria:*** • *Previous use of botulinum toxin of any serotype or immunization to any botulinum toxin serotype* • *Any medical condition that puts the patient at increased risk with exposure to BOTOX* • *Diagnosis of complicated migraine, chronic tension-type headache, hypnic headache, hemicrania continua, new daily persistent headache* • *Use of prophylactic headache medication within 28 days prior to week -4* • *Unremitting headache lasting continuously throughout the 4-week baseline period* • *Known or suspected TMD* • *Diagnosis of fibromyalgia*

<table>
<tr><td></td><td colspan="3">• Beck depression inventory score >24 at week-4
• Psychiatric problems that may have interfered with study participation</td></tr>
<tr><td>Intervention</td><td colspan="3">• Biological: Botulinum Toxin Type A
Two treatment sessions in the double-blind phase and three treatment sessions in the open-label extension phase. Total minimum dose is 155 U with 31 fixed-site, fixed dose injections across seven specific head/neck muscle areas with the total maximum dose of 195 U with 39 head/neck injections.
Other Name: BOTOX®
• Other: Placebo (saline)
Two treatment sessions in the double-blind phase. Total minimum dose in 155 U with 31 fixed-site, fixed dose injections across seven specific head/neck muscle areas and the total maximum dose is 195 U with 39 head/neck injections.</td></tr>
<tr><td rowspan="7">Baseline characteristics</td><td></td><td>Placebo N= 358</td><td>Botulinum Toxin Type A N= 347</td></tr>
<tr><td>Age</td><td>41.0</td><td>40.9</td></tr>
<tr><td>Female, %</td><td>84.6</td><td>86.2</td></tr>
<tr><td>MMD (SD)</td><td>18.7 (4.1)</td><td>19.2 (3.9)</td></tr>
<tr><td>% patients with 1 or more prophylaxis</td><td>66.2</td><td>64.0</td></tr>
<tr><td>Mean BMI</td><td>27.1</td><td>26.7</td></tr>
<tr><td>% patients with medication overuse</td><td>69.8</td><td>66.3</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The primary efficacy endpoint was mean change from baseline in frequency of headache days for the 28-day period ending with week 24.
Secondary:
• Frequency of migraine days (defined as a calendar day with ≥4 continuous hours of headache meeting ICHD-II criteria for migraine 1.1, 1.2 or 1.6)
• Frequency of moderate/severe headache days (defined as a calendar day with 4 continuous hours of headache and a maximum severity of moderate or severe, per the patient diary among all headache episodes reported on that day regardless of duration)
• Monthly cumulative headache hours on headache days
• Proportion of patients with severe (≥60) Headache Impact Test (HIT)-6 score Page 48 of 50
• Frequency of headache episodes (defined as patient-reported headache with a start and stop time indicating that the pain lasted ≥4 continuous hours).</td></tr>
<tr><td>Method of analysis</td><td colspan="3">All efficacy analyses used the intent-to-treat population, which included all randomized patients. For each primary and secondary variable, prespecified comparisons between treatment groups were done by analysis of covariance of the change from baseline, with the same variable’s baseline value as a covariate, with main effects of treatment group and medication overuse strata. The baseline covariate adjustment was prespecified as the</td></tr>
</table>

	primary analysis; sensitivity analyses (e.g., rank-sum test on changes from baseline without a baseline covariate) were also performed. Scores for months with at least 20 days of diary data were prorated to 28- day equivalents. Scores for months with less than 10 days of diary data were estimated using a modified last observation carried forward (mLOCF) methodology. This involved the substitution of the patient's previous 28-day period score multiplied by the ratio of the mean across all patients in the 28-day period of interest divided by the mean across all patients in the previous 28-day period. Scores for months with 10– 19 days of diary data were estimated using an average of the prorated and the mLOCF estimates. The mLOCF method of imputation of missing data was prespecified, but sensitivity analyses were also done (e.g., using observed data, without imputation). For binomial variables, the between-group comparisons were done with Pearson's Chi-square or Fisher's exact tests, except that logistic regression, with the same variable's baseline as covariate, was used for variables with baseline imbalance. A two-sided test with $p \leq .05$ was considered statistically significant. To control the type 1 error rate for multiple secondary endpoints in the amended PREEMPT 2 protocol and analysis plan, a fixed-sequence gate-keeping approach was used for the five ranked secondary variables at the week 24 primary visit. If the p value of a secondary endpoint was not ≤.05, the tests of any lower-ranked secondary endpoints were not considered statistically significant, regardless of individual p value.
Subgroup analyses	*None*

APPENDIX C. Results per study

Fremanezumab

5.8.3 Dodick et al., 2018 (HALO EM) + EPAR

TABLE 60 RESULTS OF DODICK ET AL, 2018

Trial name:	*HALO EM + EPAR*									
NCT number:	*NCT02629861*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Fremanezumab monthly dosing	287	-3.7 (-4.15 to -3.18)	-1.5	-2.01 to -0.93	0.00				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Fremanezumab quarterly dosing	288	-3.4 (-3.94 to -2.96)	-1.3	-1.79 to -0.72	0.00				
	Placebo	290	-2.2 (-2.68 to -1.71)							
≥50% reduction in migraine days	Fremanezumab monthly dosing	287	0.48	0.2	0.12 to 0.28	0.00	1.71	1.37 to 2.13	0.00	
	Fremanezumab quarterly dosing	288	0.44	0.17	0.09 to 0.24	0.00	1.59	1.27 to 1.99	0.00	
	Placebo	290	0.28							
MIDAS score	Fremanezumab monthly dosing	287	-24.6 (-27.68 to -21.45)	-7.10	-11.48 to -2.72	0.00				
	Fremanezumab quarterly dosing	288	-23 (-26.1 to -19.82)	-5.5	-9.89 to -1.11.	0.01				
	Placebo	290	-17.5 (-20.62 to -14.47)							
Use of acute headache medication	Fremanezumab monthly dosing	287	-3 (-3.41 to -2.56)	-1.4	-1.84 to -0.89	0.00				
	Fremanezumab quarterly dosing	288	-2.9 (-3.34 to -2.48)	-1.3	-1.76 to -0.82	0.00				
	Placebo	290	-1.6 (-2.04 to -1.2)							
Discontinuation	Fremanezumab monthly dosing	290	0.02	0.00	-0.02 to 0.02	0.99	1.01	0.30 to 3.45	0.99	
	Fremanezumab quarterly dosing	291	0.02	0.00	-0.02 to 0.02	0.99	1.01	0.29 to 3.44	0.99	
	Placebo	293	0.02							

5.8.4 Bigal et al., 2015 (EM)

TABLE 61 RESULTS OF BIGAL ET AL, 2015 (EM)

Trial name:	*Bigal et al, 2015 (EM)*									
NCT number:	*NCT0205556*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	P value	
Change in monthly migraine days	Fremanezumab monthly dosing	95		-2.81	-4.07 to -1.55	0.00				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	104								
≥50% reduction in migraine days	Fremanezumab monthly dosing	85	0.53	0.25	0.11 to 0.39	0.00	1.89	1.30 to 2.74	0.00	
	Placebo	100	0.28							
MIDAS score	Fremanezumab monthly dosing	95		-14.5	-26.79 to -2.2	0.02				
	Placebo	104								
Use of acute medication	Fremanezumab monthly dosing	95		-1.76	-2.86 to -0.66	0.00				
	Placebo	104								

5.8.5 Silberstein et al., 2017 (HALO CM)

TABLE 62 RESULTS OF SILBERSTEIN ET AL, 2017 (HALO CM)

Trial name:	*HALO CM + EPAR*									
NCT number:	*NCT02631931*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Fremanezumab monthly dosing	375	-5 (-5.7 to -4.33)	-1.8	-2.61 to -1.09	0.00				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Fremanezumab quarterly dosing	375	-4.9 (-5.59 to -4.2)	-1.7	-2.48 to -0.97	0.00				
	Placebo	371	-3.2 (-3.86 to -2.47)							
HIT-6 score	Fremanezumab monthly dosing	375	-6.8 (-7.58 to -6.02)	-2.30	-3.56 to -1.04	0.00				
	Fremanezumab quarterly dosing	375	-6.4 (-7.38 to -5.42)	-1.90	-3.29 to -0.51	0.01				
	Placebo	371	-4.5 (-5.48 to -3.52)							
Use of acute headache medication	Fremanezumab monthly dosing	375	-4.2 (-4.49 to -3.61)	-1.8	-2.43 to -1.12	0.00				
	Fremanezumab quarterly dosing	375	-3.7 (-4.25 to -3.06)	-2.3	-2.97 to -1.67	0.00				
	Placebo	371	-1.9 (-2.48 to -1.28)							
Discontinuation	Fremanezumab monthly dosing	379	0.02	0.00	-0.02 to 0.02	0.78	0.87	0.32 to 2.36	0.78	
	Fremanezumab quarterly dosing	376	0.01	-0.01	-0.03 to 0.01	0.40	0.62	0.21 to 1.89	0.40	
	Placebo	375	0.02							
Change in monthly headache days	Fremanezumab monthly dosing	375	-4.6 (-5.16 to -3.97)	-2.1	-2.76 to -1.45	0.00				
	Fremanezumab quarterly dosing	375	-4.3 (-4.87 to -3.66)	-1.8	-2.46 to -1.15	0.00				
	Placebo	371	-2.5 (-3.06 to -1.85)							

5.8.6 Bigal et al., 2015 (CM)

TABLE 63 RESULTS OF BIGAL 2015 (CM)

Trial name:	*Bigal et al, 2015 (CM)*									
NCT number:	*NCT02021773*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Fremanezumab monthly dosing	87	NA	-1.72	-3.7 to 0.2	0.08				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	89	NA							
Use of acute headache medication	Fremanezumab monthly dosing	87	NA	-2.15	-4 to 0.3	0.02				
	Placebo	89	NA							
Change in monthly headache days	Fremanezumab monthly dosing	87	NA	-1.74	-3.6 to 0.1	0.07				
	Placebo	89	NA							

*Note that the dose of 900 mg of fremanezumab is excluded in the analysis in this application according to the dosages of fremanezumab provided in the protocol by Medicinrådet.

5.8.7 Ferrari et al, 2019 (FOCUS)

TABLE 64 RESULTS OF FOCUS

Trial name:	*An Efficacy and Safety Study of Fremanezumab in Adults With Migraine (FOCUS)*									
NCT number:	*NCT03308968*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Fremanezumab monthly dosing	283	-4.1 (-4.73 to -3.41)	-3.5	-4.19 to -2.78	0.00				See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods
	Fremanezumab quarterly dosing	276	-3.7 (-4.38 to -3.05)	-3.1	-3.84 to -2.42	0.00				
	Placebo	279	-0.6 (-1.25 to 0.07)							
≥50% reduction in migraine days	Fremanezumab monthly dosing	283	0.34	0.26	0.19 to 0.32	0.00	3.97	2.62 to 6.01	0.00	
	Fremanezumab quarterly dosing	276	0.34	0.26	0.19 to 0.32	0.00	3.99	2.63 to 6.04	0.00	
	Placebo	278	0.09							
HIT-6 score	Fremanezumab monthly dosing	283	-6.1 (-7.12 to -4.99)	-3.90	-5.40 to -2.40	0.00				
	Fremanezumab quarterly dosing	276	-5.2 (-6.29 to -4.13)	-3.00	-4.51 to -1.49	0.00				
	Placebo	279	-2.2 (-3.31 to -1.17)							
Use of acute headache medication	*Fremanezumab monthly dosing*	*283*	-3.9 (-4.58 to -3.32)	-3.4	-4.03 to -2.69	0.00				
	Fremanezumab quarterly dosing	*276*	-3.7 (-4.3 to -3.03)	-3.1	-3.75 to -2.41	0.00				
	Placebo	*279*	-0.6 (-1.21 to 0.04)							
Discontinuation	*Fremanezumab monthly dosing*	*285*	0.01	0.00	-0.02 to 0.02	0.73	1.30	0.29 to 5.74	0.73	
	Fremanezumab quarterly dosing	*276*	0	-0.01	-0.02 to 0.01	0.32	0.33	0.04 to 3.20	0.34	
	Placebo	*277*	0,01							

Topiramate

5.8.8 Storey et al., 2001

TABLE 65 RESULTS OF STOREY ET AL, 2001

Trial name:	*Topiramate in migraine Prevention: A double blind placebo Controlled Study*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Discontinuation	Topiramate	19	0.11	0.11	-0.05 to 0.26	0.13	5.51	0.28 to 107.88	0.26	*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	21	0							

5.8.9 Mei et al., 2004

TABLE 66 RESULTS OF MEI ET AL, 2004

Trial name:	*Topiramate in migraine prophylaxis: A Randomized double blind versus placebo study*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Discontinuation	Topiramate	58	0.29	0.26	0.13 to 0.38	0.00	8.35	2.02 to 34.52	0.00	*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	57	0.04							

5.8.10 Diener et al., 2004

TABLE 67 RESULTS OF DIENER ET AL, 2004

Trial name:	*Topiramate in migraine prophylaxis Results from a placebo-controlled trial with propranolol as an active control*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Topiramate 100 mg/day	139	-1.8 (-2.29 to -1.31)	-0.70	-1.38 to -0.02	0.04				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Topiramate 200 mg/day	143	-1.3 (-1.79 to -0.81)	-0.20	-0.88 to 0.48	0.56				
	Topiramate	282	-1.55 (-1.89 to -1.2)	-0.45	-1.03 to 0.14	0.13				
	Placebo	143	-1.1 (-1.57 to -0.63)							
Use of acute headache medication	Topiramate 100 mg/day	139	-1.5 (-1.91 to -1.09)	-0.70	-1.27 to -0.13	0.02				
	Topiramate 200 mg/day	143	-0.9 (-1.31 to -0.49)	-0.10	-0.67 to 0.47	0.73				
	Topiramate	282	-1.2 (-1.49 to -0.9)	-0.40	-0.88 to 0.09	0.11				
	Placebo	143	-0.8 (-1.19 to -0.41)							
Discontinuation	*Topiramate 100 mg/day*	*139*	0.27	0.16	0.07 to 0.25	0.00	2.54	1.46 to 4.41	0.00	
	Topiramate 200 mg/day	*143*	0.44	0.34	0.24 to 0.43	0.00	4.20	2.51 to 7.02	0.00	
	Topiramate	*282*	0.35	0.25	0.17 to 0.32	0.00	3.38	2.04 to 5.60	0.00	
	Placebo	*143*	0.1							

5.8.11 Brandes et al., 2004

TABLE 68 RESULTS OF BRANDES ET AL, 2004

Trial name:	*Topiramate for migraine prevention a randomized controlled trial*									
NCT number:	*NA*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Topiramate 50mg/d	116	NA	NA						*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Topiramate 100mg/d	120	-2.6 (-3.21 to -1.99)	-1.3	-2.17 to -0.43	0.00				
	Topiramate 200mg/d	117	-2.9 (-3.53 to -2.27)	-1.6	-2.49 to -0.71	0.00				
	Topiramate	237	-2.75 (-3.18 to -2.31)	-1.45	-2.21 to -0.68	0.00				
	Placebo	114	-1.3 (-1.93 to -0.67)							
Use of acute headache medication	Topiramate 50mg/d	116	NA	NA						
	Topiramate 100mg/d	120	-2.1 (-2.67 to -1.53)	-1.10	-1.90 to -0.30	0.01				
	Topiramate 200mg/d	117	-2.2 (-2.77 to -1.63)	-1.20	-2.00 to -0.40	0.00				
	Topiramate	237	-2.15 (-2.55 to -1.75)	-1.15	-1.85 to -0.45	0.00				
	Placebo	114	-1 (-1.57 to -0.43)							
Discontinuation	Topiramate 50mg/d	117	0.15	0.11	0.04 to 0.18	0.00	4.10	1.42 to 11.83	0.01	
	Topiramate 100mg/d	119	0.3	0.27	0.18 to 0.36	0.00	8.55	3.14 to 23.24	0.00	
	Topiramate 200mg/d	117	0.17	0.14	0.06 to 0.21	0.00	4.83	1.70 to 13.69	0.00	
	Topiramate	353	0.21	0.17	0.12 to 0.23	0.00	5.84	2.18 to 15.63	0.00	
	Placebo	113	0.04							

5.8.12 Brandes et al., 2006

TABLE 69 RESULTS OF BRANDES ET AL, 2006

Trial name:	*Assessing the Ability of Topiramate to Improve the Daily Activities of Patients With Migraine*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
MSQ score (RR domain)	Topiramate 50 mg/day	110	71.9 (68.18 to 75.62)	4.70	-0.43 to 9.83	0.07				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Topiramate 100 mg/day	111	75.8 (72.08 to 79.52)	8.60	3.47 to 13.73	0.00				
	Topiramate 200 mg/day	107	77.9 (74.18 to 81.62)	10.70	5.57 to 15.83	0.00				
	Topiramate	328	75.18 (73.03 to 77.33)	7.98	3.85 to 12.11	0.00				
	Placebo	106	67.2 (63.67 to 70.73)							
MSQ score (RP domain)	Topiramate 50 mg/day	110	82.6 (79.27 to 85.93)	1.80	-2.78 to 6.38	0.44				
	Topiramate 100 mg/day	111	85.5 (82.17 to 88.83)	4.70	0.12 to 9.28	0.04				
	Topiramate 200 mg/day	107	87.2 (83.87 to 90.53)	6.40	1.82 to 10.98	0.01				
	Topiramate	328	85.08 (83.16 to 87.01)	4.28	0.60 to 7.96	0.02				
	Placebo	106	80.8 (77.66 to 83.94)							
MSQ score (EF domain)	Topiramate 50 mg/day	110	77.6 (73.48 to 81.72)	3.50	-2.18 to 9.18	0.23				
	Topiramate 100 mg/day	111	82.9 (78.78 to 87.02)	8.80	3.12 to 14.48	0.00				
	Topiramate 200 mg/day	107	82.7 (78.58 to 86.82)	8.60	2.92 to 14.28	0.00				
	Topiramate	328	81.06 (78.68 to 83.43)	6.96	2.37 to 11.54	0.00				
	Placebo	106	74.1 (70.18 to 78.02)							

5.8.13 Silberstein et al., 2004

TABLE 70 RESULTS OF SILBERSTEIN ET AL, 2004

Trial name:	*Topiramate in migraine Prevention*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Topiramate 50mg/day	117	-1.6 (-2.47 to -0.73)	-0.50	-1.69 to 0.69	0.41				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Topiramate 100 mg/day	125	-2.7 (-3.45 to -1.95)	-1.60	-2.70 to -0.50	0.00				
	Topiramate 200 mg/day	112	-2.7 (-3.55 to -1.85)	-1.60	-2.78 to -0.42	0.01				
	Topiramate	354	-2.34 (-2.81 to -1.86)	-1.24	-2.18 to -0.30	0.01				
	Placebo	115	-1.1 (-1.91 to -0.29)							
Use of acute headache medication	Topiramate 50mg/day	117	-1.3 (-2.02 to -0.58)	-0.40	-1.49 to 0.69	0.47				
	Topiramate 100 mg/day	125	-1.9 (-2.64 to -1.16)	-1.00	-2.10 to 0.10	0.07				
	Topiramate 200 mg/day	112	-2.1 (-2.81 to -1.39)	-1.20	-2.28 to -0.12	0.03				
	Topiramate	354	-1.76 (-2.18 to -1.35)	-0.86	-1.78 to 0.05	0.06				
	Placebo	115	-0.9 (-1.72 to -0.08)							
Discontinuation	Topiramate 50mg/day	117	0.18	0.08	0.00 to 0.17	0.06	1.88	0.95 to 3.71	0.07	
	Topiramate 100 mg/day	125	0.19	0.10	0.01 to 0.18	0.03	2.01	1.03 to 3.91	0.04	
	Topiramate 200 mg/day	112	0.34	0.24	0.14 to 0.35	0.00	3.55	1.91 to 6.58	0.00	
	Topiramate	354	0.23	0.14	0.07 to 0.21	0.00	2.45	1.36 to 4.43	0.00	
	Placebo	115	0.1							

5.8.14 Silberstein et al., 2006

TABLE 71 RESULTS OF SILBERSTEIN ET AL, 2006

Trial name:	*The impact of migraine on daily activities*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
MSQ score (RR domain)	Topiramate 50 mg/day	117	72.2 (68.67 to 75.73)	6.40	1.41 to 11.39	0.01				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Topiramate 100 mg/day	125	72.2 (68.87 to 75.53)	6.40	1.55 to 11.25	0.01				
	Topiramate 200 mg/day	112	75.8 (71.88 to 79.72)	10.00	4.73 to 15.27	0.00				
	Topiramate	354	73.34 (71.27 to 75.41)	7.54	3.45 to 11.63	0.00				
	Placebo	115	65.8 (62.27 to 69.33)							
MSQ score (RP domain)	Topiramate 50 mg/day	117	84.3 (81.36 to 87.24)	3.70	-0.46 to 7.86	0.08				
	Topiramate 100 mg/day	125	88.3 (85.56 to 91.04)	7.70	3.68 to 11.72	0.00				
	Topiramate 200 mg/day	112	84.4 (81.07 to 87.73)	3.80	-0.64 to 8.24	0.09				
	Topiramate	354	85.74 (84.01 to 87.47)	5.14	1.73 to 8.56	0.00				
	Placebo	115	80.6 (77.66 to 83.54)							
MSQ score (EF domain)	Topiramate 50 mg/day	117	78.5 (74.58 to 82.42)	5.60	0.06 to 11.14	0.05				
	Topiramate 100 mg/day	125	84.4 (80.68 to 88.12)	11.50	6.09 to 16.91	0.00				
	Topiramate 200 mg/day	112	81.2 (76.89 to 85.51)	8.30	2.47 to 14.13	0.01				
	Topiramate	354	81.44 (79.14 to 83.73)	8.54	3.99 to 13.08	0.00				
	Placebo	115	72.9 (68.98 to 76.82)							

5.8.15 Silberstein et al., 2006 (pilot study)

TABLE 72 RESULTS OF SILBERSTEIN ET AL, 2006

Trial name:	*Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Discontinuation	Topiramate	138	0.15	0.10	0.02 to 0.18	0.04	2.78	0.99 to 7.79	0.05	*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	73	0.05							

5.8.16 Silberstein et al., 2007

TABLE 73 RESULTS OF SILBERSTEIN ET AL, 2007

Trial name:	*To evaluate the efficacy and safety of topiramate (100 mg/day) compared with placebo for the treatment of chronic migraine.*									
NCT number:	*NCT00210912*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Topiramate	153	-5.6 (-6.55 to -4.65)	-1.5	-2.86 to -0.14	0.03				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with*
	Placebo	153	-4.1 (-5.07 to -3.13)							
Discontinuation	Topiramate	165	0.11	0.05	-0.01 to 0.11	0.12	1.78	0.85 to 3.73	0.13	
	Placebo	163	0.06							

5.8.17 Silberstein et al., 2009

TABLE 74 RESULTS OF SILBERSTEIN ET AL, 2009

Trial name:	*A Study of the Effectiveness and Safety of Topiramate Versus Placebo for Preventing Chronic Migraine Headaches*									
NCT number:	*NCT00210912*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
≥50% reduction in migraine days	Topiramate	153	0.39	0.08	-0.03 to 0.19	0.15	1.26	0.92 to 1.71	0.15	*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	153	0.31							
MSQ score (RR domain)	Topiramate	153	23.7 (20.04 to 27.36)	4.90	-0.22 ti 10.02	0.06				
	Placebo	153	18.8 (15.22 to 22.38)							
MSQ score (RP domain)	Topiramate	153	16.1 (12.69 to 19.51)	3.50	-1.26 to 8.26	0.15				
	Placebo	153	12.6 (9.27 to 15.93)							
MSQ score (EF domain)	Topiramate	153	26.3 (21.89 to 30.71)	5.30	-1.20 to 11.80	0.11				
	Placebo	153	21 (16.21 to 25.79)							
MIDAS score	Topiramate	153	-31.4 (-39.92 to -22.88)	- 10.40	-22.28 to 1.48	0.09				
	Placebo	153	-21 (-29.27 to -12.73)							
Use of acute headache	Topiramate	153	-4.4 (-5.32 to -3.48)	- 1.00	-2.24 to 0.24	0.12				
	Placebo	153	-3.4 (-4.24 to -2.56)							
Change in monthly headache days	Topiramate	153	-5.8 (-6.69 to -4.91)	-1.10	-2.35 to 0.15	0.09				
	Placebo	153	-4.7 (-5.59 to -3.81)							

5.8.18 Diener et al., 2007

TABLE 75 RESULTS OF DIENER ET AL, 2007

Trial name:	*Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Topiramate	32	-3.5 (-5.68 to -1.32)	-3.70	-6.51 to -0.89	0.01				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	27	0.2 (-1.57 to 1.97)							
≥50% reduction in migraine days	Topiramate	32	0.22	0.22	0.07 to 0.37	0.01	12.69	0.76 to 212.38	0.08	
	Placebo	27	0							
MIDAS score	Topiramate	25	-26 (-49.91 to -2.09)	-29	-55.32 to -2.68	0.03				
	Placebo	14	3 (-8 to 14)							
Use of acute headache	Topiramate	32	-3 (-5.04 to -0.96)	-2.30	-5.41 to 0.81	0.15				
	Placebo	27	-0.7 (-3.04 to 1.64)							
Discontinuation	Topiramate	32	0.19	0.08	-0.10 to 0.26	0.42	1.69	0.47 to 6.12	0.43	
	Placebo	27	0.11							

5.8.19 Lipton et al., 2011 (INTREPID)

TABLE 76 RESULTS OF LIPTON ET AL, 2011

Trial name:	*Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study (INTERPID)*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Topiramate	159	-6.6 (-7.14 to -6.06)	-1.30	-2.07 to -0.53	0				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	171	-5.3 (-5.84 to -4.76)							
Use of acute headache	Topiramate	159	-4.8 (-5.34 to -4.26)	-1.00	-1.78 to -0.22	0.01				
	Placebo	171	-3.8 (-4.35 to -3.25)							
Discontinuation	Topiramate	188	0.11	0.02	-0.04 to 0.08	0.51	1.22	0.67 to 2.22	0.51	
	Placebo	197	0.09							

Candesartan

5.8.20 Tronvik et al., 2003

TABLE 77 RESULTS OF TRONVIK AL, 2003

Trial name:	*Prophylactic treatment of Migraine with an Angiotensin II Receptor blocker*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Candesartan	28	-2.7 (-4.22 to -1.18)	-1.20	-3.31 to 0.91	0.27				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	29	-1.5 (-2.97 to -0.03)							
≥50% reduction in migraine days	Candesartan	57	0.4	0.37	0.23 to 0.50	0.00	11.50	2.84 to 46.52	0.00	
	Placebo	57	0.04							

5.8.21 Stovner et al., 2014

TABLE 78 RESULTS OF STOVNER ET AL, 2014

Trial name:	*Candesartan Versus Propranolol for Migraine Prevention*									
NCT number:	*NCT00884663*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Candesartan	56	-1.87 (-2.76 to -0.98)	-0.58	-1.81 to 0.65	0.36				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	60	-1.29 (-2.15 to -0.43)							
≥50% reduction in migraine days	Candesartan	56	0.43	0.20	0.03 to 0.36	0.03	1.84	1.06 to 3.18	0.03	
	Placebo	60	0.23							
Change in monthly headache days	Candesartan	56	-2.91 (-4.39 to -1.43)	-0.67	-2.74 to 1.40	0.53				
	Placebo	60	-2.24 (-3.69 to -0.79)							

Lisinopril

5.8.22 Schrader et al., 2001

TABLE 79 RESULTS OF SCHRADER ET AL, 2001

Trial name:	*Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Lisinopril	47	-2 (-3.21 to -0.79)	-1.40	-3.12 to 0.32	0.11				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	47	-0.6 (-1.81 to 0.61)							
≥50% reduction in migraine days	Lisinopril	47	0.3	0.23	0.09 to 0.38	0.00	4.67	1.43 to 15.18	0.01	
	Placebo	47	0.06							
Change in monthly headache days	Lisinopril	47	-2.8 (-4.42 to -1.18)	-1.30	-3.46 to 0.86	0.24				
	Placebo	47	-1.5 (-2.93 to -0.07)							

Propranolol

5.8.23 Diener et al., 1996

TABLE 80 RESULTS OF DIENER ET AL, 1996

Trial name:	*Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Discontinuation	Propranolol	78	0.08	0.06	-0.01 to 0.13	0.14	4.23	0.52 to 34.16	0.18	*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	55	0.02							

5.8.24 Diener et al., 2004

TABLE 81 RESULTS OF DIENER ET AL, 2004

Trial name:	*Topiramate in migraine prophylaxis Results from a placebo-controlled trial with propranolol as an active control*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Propranolol	143	-1.9 (-2.39 to -1.41)	-0.80	-1.48 to -0.12	0.02				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	143	-1.1 (-1.57 to -0.63)							
Use of acute headache	Propranolol	143	-1.6 (-2.01 to -1.19)	-0.80	-1.37 to -0.23	0.01				
	Placebo	143	-0.8 (-1.19 to -0.41)							
Discontinuation	Propranolol	144	0.2	0.1	0.02 to 0.18	0.02	1.96	1.10 to 3.50	0.02	
	Placebo	146	0.1							

5.8.25 Stovner et al., 2014

TABLE 82 RESULTS OF STOVNER ET AL, 2014

Trial name:	*Candesartan Versus Propranolol for Migraine Prevention*									
NCT number:	*NCT00884663*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Propranolol	60	-1.91 (-2.76 to -1.06)	-0.62	-1.83 to 0.59	0.31				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	60	-1.29 (-2.15 to -0.43)							
≥50% reduction in migraine days	Propranolol	60	0.4	0.17	0.00 to 0.33	0.05	1.71	0.99 to 2.89	0.06	
	Placebo	60	0.23							
Change in monthly headache days	Propranolol	60	-2.46 (-4.15 to -0.77)	-0.22	-2.45 to 2.01	0.85				
	Placebo	60	-2.24 (-3.69 to -0.79)							

Valproate

5.8.26 Jensen et al., 1994

TABLE 83 RESULTS OF JENSEN ET AL,1994

Trial name:	*Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Valproate	34	-2.6	-2.6						*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	34	0							
Discontinuation	Valproate	34	0.12	0.06	-0.08 to 0.19	0.39	2.00	0.39 to 10.20	0.40	
	Placebo	34	0.06							

5.8.27 Mathew et al., 1995

TABLE 84 RESULTS OF MATHEW ET AL, 1995

Trial name:	*Migraine Prophylaxis With Divalproex*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Valproate	69	-3	-2						*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	36	-1							
≥50% reduction in migraine days	Valproate	69	0.48	0.34	0.18 to 0.50	0.00	3.44	1.47 to 8.06	0.00	
	Placebo	36	0.14							
Discontinuation	Valproate	70	0.13	0.07	-0.03 to 0.18	0.23	2.38	0.54 to 10.44	0.25	
	Placebo	37	0.05							

5.8.28 Klapper et al., 1997

TABLE 85 RESULTS OF KLAPPER ET AL, 1997

Trial name:	*Divalproex sodium in migraine prophylaxis: a dose-controlled study*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Discontinuation	Valproate 500 mg	45	0.16	0.11	-0.01 to 0.23	0.08	3.42	0.75 to 15.58	0.11	*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Valproate 1000 mg	43	0.14	0.09	-0.03 to 0.21	0.13	3.07	0.66 to 14.38	0.15	
	Valproate 1500 mg	44	0.27	0.23	0.08 to 0.37	0.00	6.00	1.43 to 25.26	0.01	
	Valproate	132	0.19	0.14	0.05 to 0.23	0.02	4.17	1.03 to 16.88	0.05	
	Placebo	44	0.05							

5.8.29 Freitag et al., 2002

TABLE 86 RESULTS OF FREITAG ET AL, 2002

Trial name:	*A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Valproate	122	-1.7	-1.00						*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	115	-0.7							
Discontinuation	Valproate	122	0.08	0.00	-0.08 to 0.07	0.89	0.94	0.41 to 2.18	0.89	
	Placebo	115	0.09							

Amitriptyline

5.8.30 Couch et al., 2011

TABLE 87 RESULTS OF COUCH ET AL, 2011

Trial name:	*Amitriptyline in the Prophylactic Treatment of Migraine and Chronic Daily Headache*									
NCT number:	*N/A*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Discontinuation	Amitriptyline 25-100 mg	194	0.12	0.05	0.00 to 0.11	0.07	1.80	0.94 to 3.44	0.08	*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	197	0.07							

5.8.31 Gonçalves et al., 2016

TABLE 88 RESULTS OF GONÇALVES ET AL, 2016

Trial name:	*EDUMAP*									
NCT number:	*NCT01357031*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Amitriptyline 25 mg	59	-2.2 (-3.1 to -1.3)	-1.10	-2.46 to 0.26	0.11				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	59	-1.1 (-2.12 to -0.08)							
≥50% reduction in migraine days	Amitriptyline 25 mg	59	0.39	0.19	0.03 to 0.35	0.03	1.92	1.05 to 3.48	0.03	
	Placebo	59	0.2							

5.8.32 Aurora et al., 2011 (PREEMPT I+II)

TABLE 89 RESULTS OF AURORA ET AL, 2011

Trial name:	*PREEMPT I + PREEMT II*									
NCT number:	*NCT00156910 + NCT00168428*									
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Relative Risk	95% CI	*P* value	
Change in monthly migraine days	Botox	688	-8.2 (-8.69 to -7.7)	-2.00	-2.71 to -1.29	0.00				*See following description: Method of analysis in main characteristics, Presentation of relevant studies and section 2 with data and methods*
	Placebo	696	-6.2 (-6.69 to -5.68)							
≥50% reduction in migraine days	Botox	688	0.48	0.12	0.07 to 0.17	0.00	1.33	1.17 to 1.50	0.00	
	Placebo	696	0.36							
HIT-6 score	Botox	688	-4.8 (-5.34 to -4.29)	-2.40	-3.09 to -1.71	0.00				
	Placebo	696	-2.4 (-2.84 to -1.95)							
Use of acute headache	Botox	688	-6.1 (-6.58 to -5.54)	-0.80	-1.53 to -0.07	0.03				
	Placebo	696	-5.3 (-5.77 to -4.75)							
Discontinuation	Botox	687	0.04	0.03	0.01 to 0.04	0.00	3.27	1.49 to 7.18	0.00	
	Placebo	692	0.01							
Change in monthly headache days	Botox	688	-8.4 (-8.9 to 7.92)	-1.80	-10.22 to 6.62	0.68				
	Placebo	696	-6.6 (-7.07 to -6.08)							

APPENDIX D: Results per PICO

THE HETEROGENEITY RESULTS FOR CLINICAL QUESTION 1 AND 2 IS GIVEN IN FEJL! HENVISNINGSKILDE IKKE FUNDET. TO

Figure 35. Following the Cochrane handbook, the I^2 statistic can be roughly interpreted as follows [85]:

I^2 statistic	Degree of heterogeneity
0% - 40%	Possibly important
30% - 60%	Moderate
50% - 90%	Substantial
75% - 100%	Considerable

5.9 Clinical Question 1

RDs were derived from RR estimates using the ACR approach. Consequently, since the RD results are not independent, but simply a restatement of RR analyses, statements about statistical significance or evaluation of statistical properties on the RD scale would be duplication of information, and potentially give a misleading impression of the strength of evidence. To avoid this risk, we did not produce heterogeneity plots for RD outcomes, and did not produce separate p-values for the RD results.

5.9.1 Heterogeneity plots

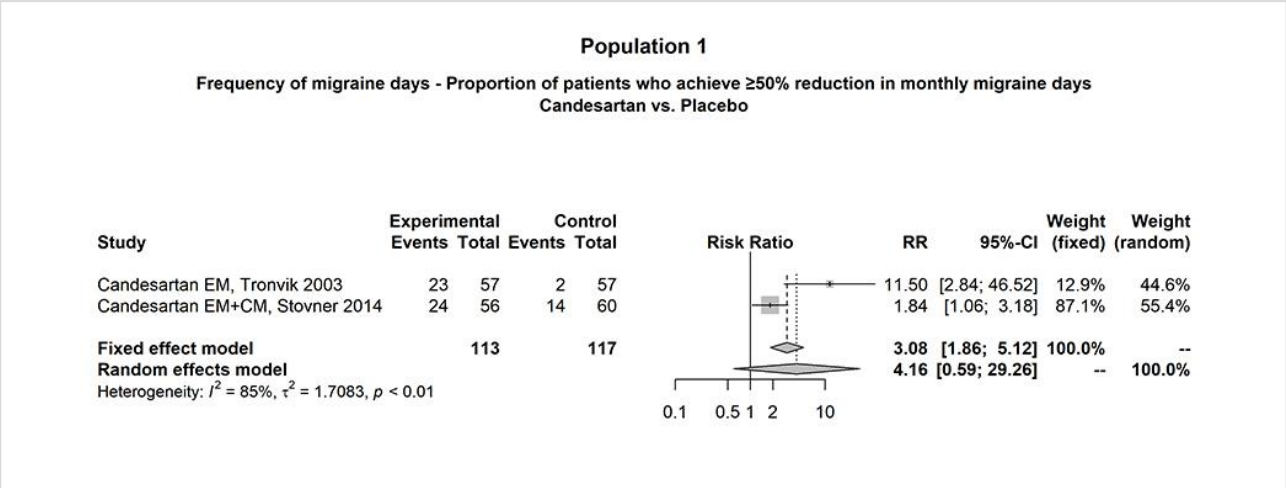

FIGURE 16 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, RISK RATIO (RR) FOR THE PROPORTION OF PATIENTS WHO ACHIEVE ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS, CANDESARTAN VS. PLACEBO.

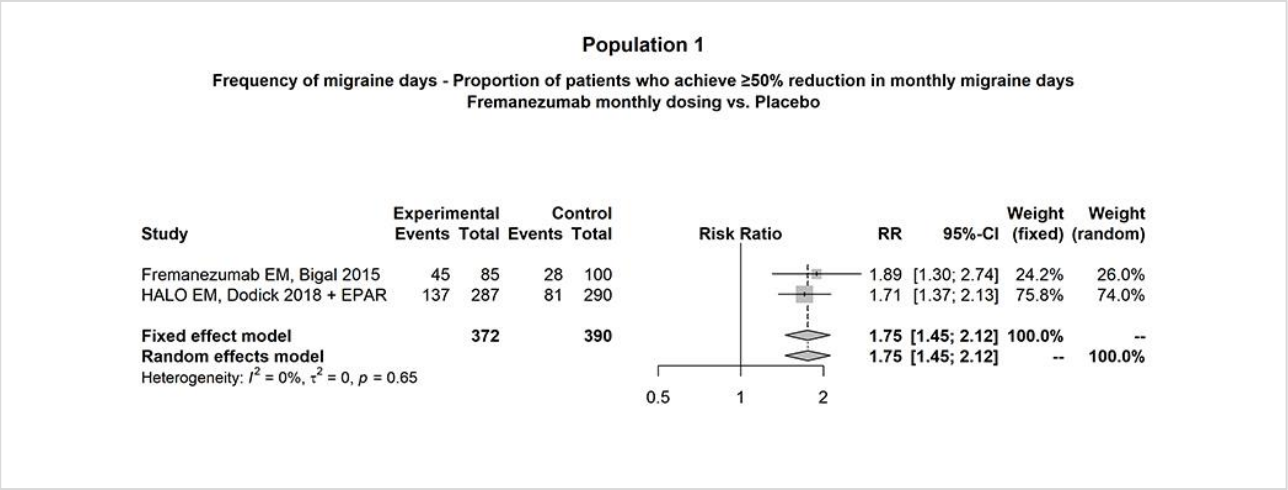

FIGURE 17 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, RISK RATIO (RR) FOR THE PROPORTION OF PATIENTS WHO ACHIEVE ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS, FREMANEZUMAB MONTHLY DOSING VS. PLACEBO

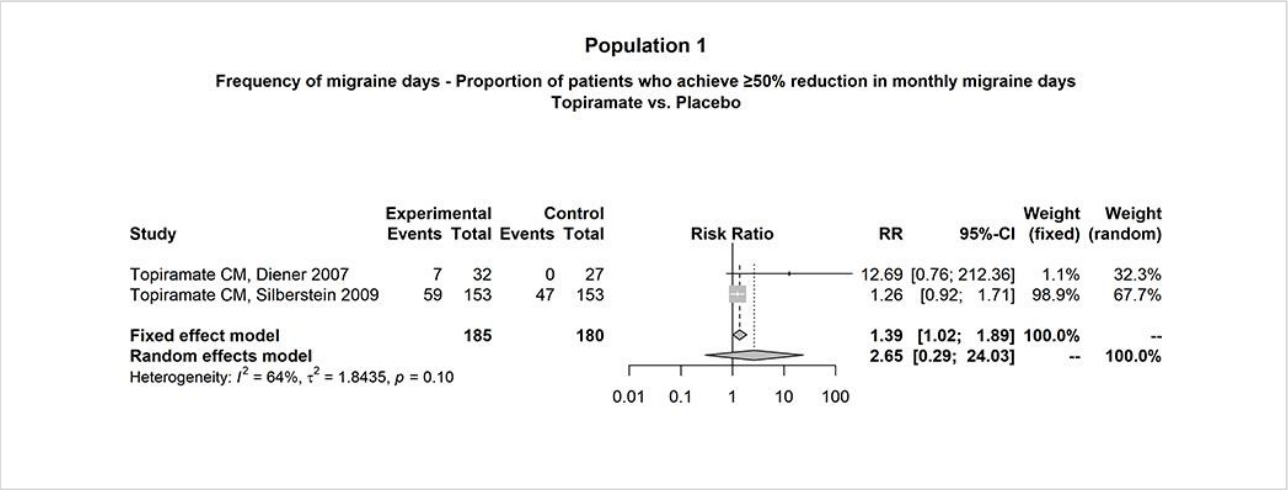

FIGURE 18 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, RISK RATIO (RR) FOR THE PROPORTION OF PATIENTS WHO ACHIEVE ≥50% REDUCTION IN MONTHLY MIGRAINE DAYS, TOPIRAMATE VS. PLACEBO

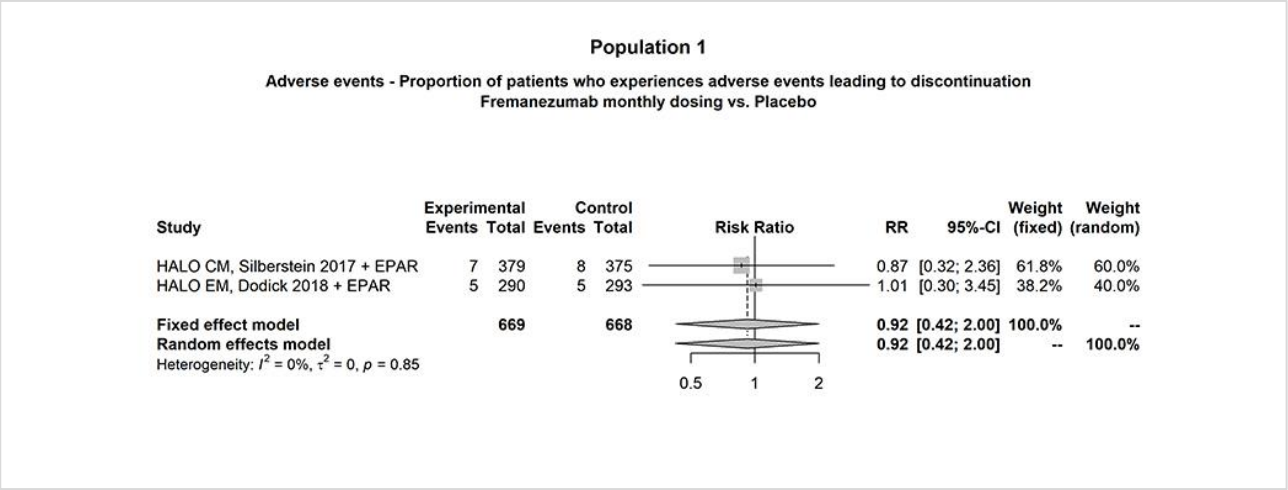

FIGURE 19 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, RISK RATIO (RR) FOR THE PROPORTION OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS LEADING TO DISCONTINUATION, FREMANEZUMAB MONTHLY DOSING VS. PLACEBO

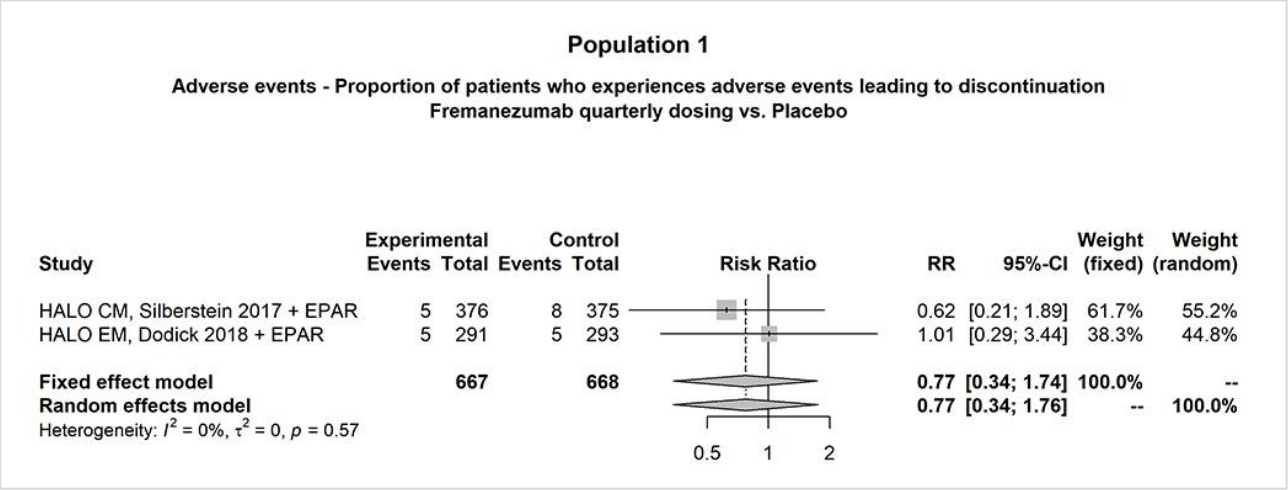

FIGURE 20 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, RISK RATIO (RR) FOR THE PROPORTION OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS LEADING TO DISCONTINUATION, FREMANEZUMAB QUARTERLY DOSING VS. PLACEBO.

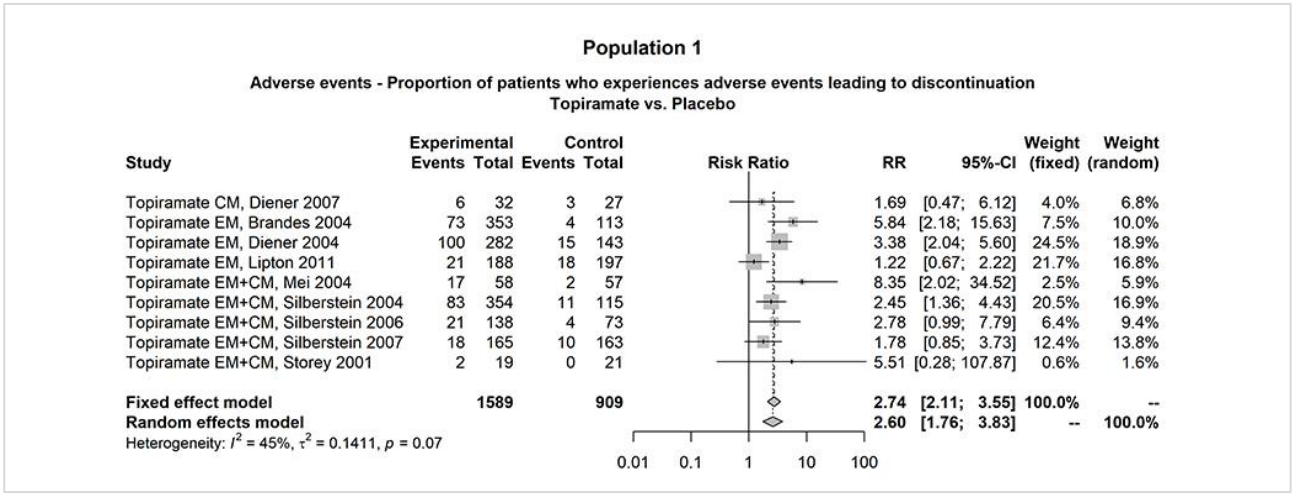

FIGURE 21 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, RISK RATIO (RR) FOR THE PROPORTION OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS LEADING TO DISCONTINUATION, TOPIRAMATE VS. PLACEBO

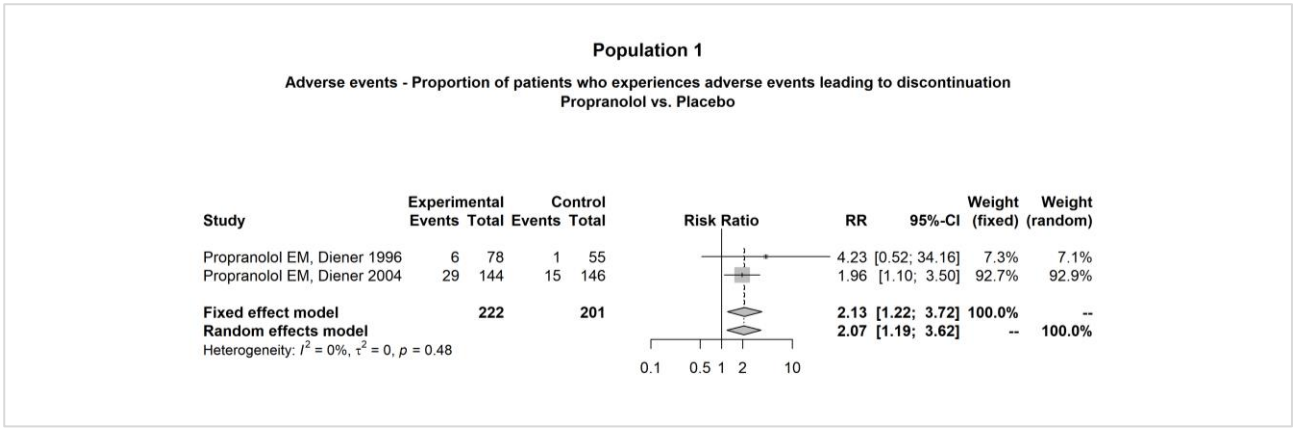

FIGURE 22 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, RISK RATIO (RR) FOR THE PROPORTION OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS LEADING TO DISCONTINUATION, PROPRANOLOL VS. PLACEBO

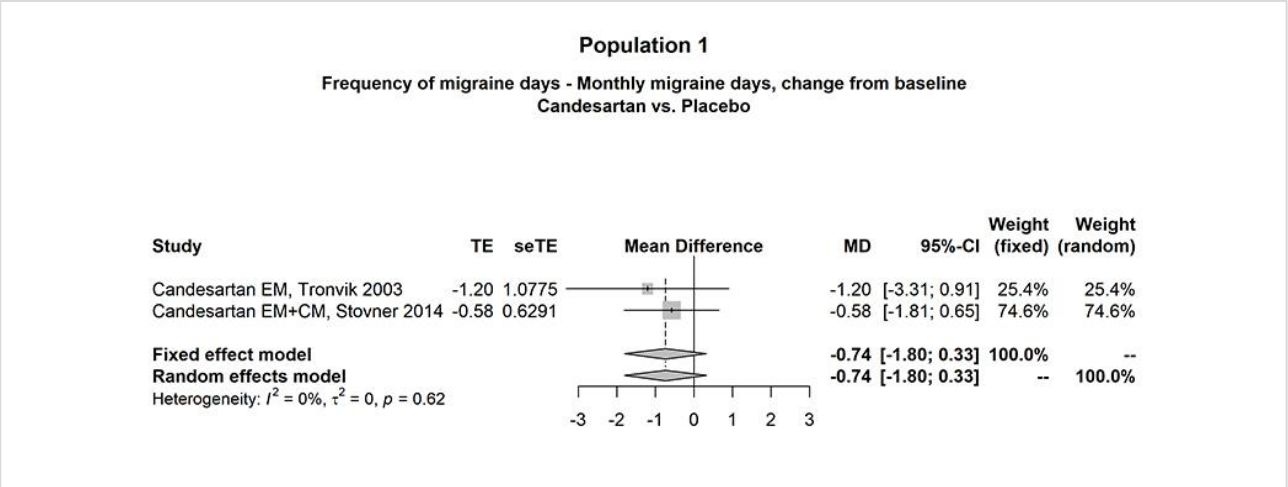

FIGURE 23 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY MIGRAINE DAYS, CHANGE FROM BASELINE, CANDESARTAN VS. PLACEBO

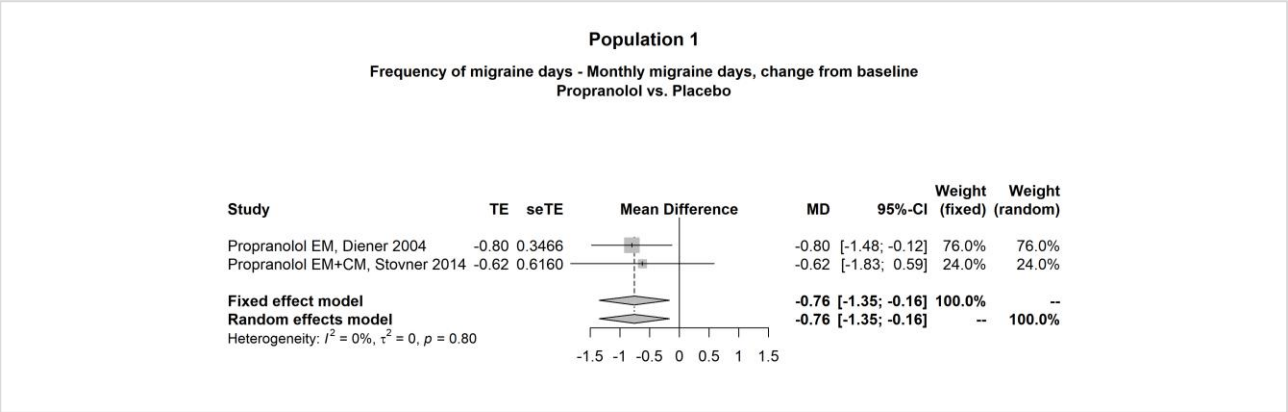

FIGURE 24 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY MIGRAINE DAYS, CHANGE FROM BASELINE, PROPRANOLOL VS. PLACEBO

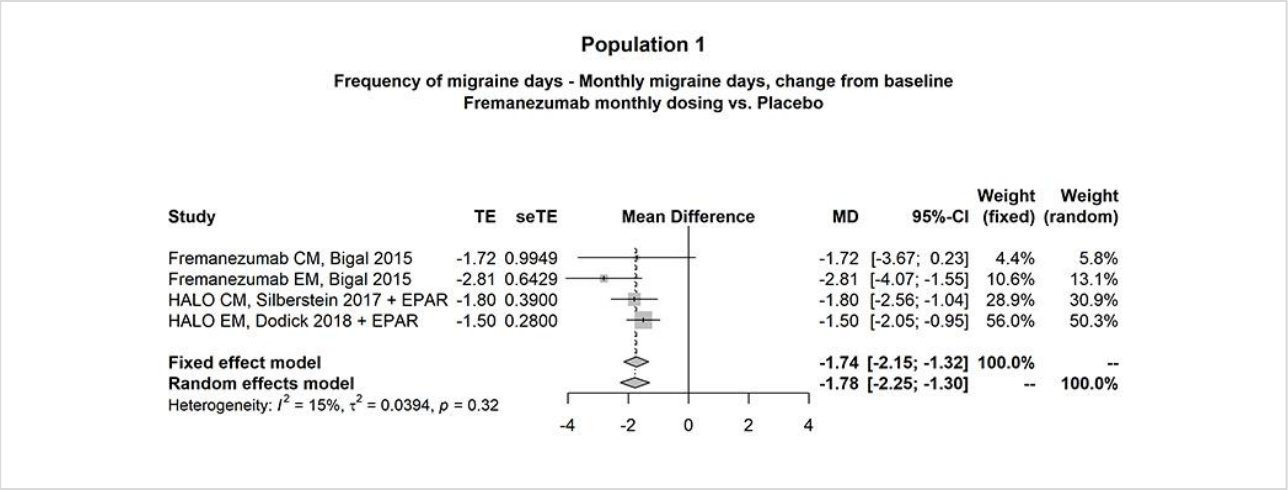

FIGURE 25 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY MIGRAINE DAYS, CHANGE FROM BASELINE, FREMANEZUMAB MONTHLY DOSING VS. PLACEBO

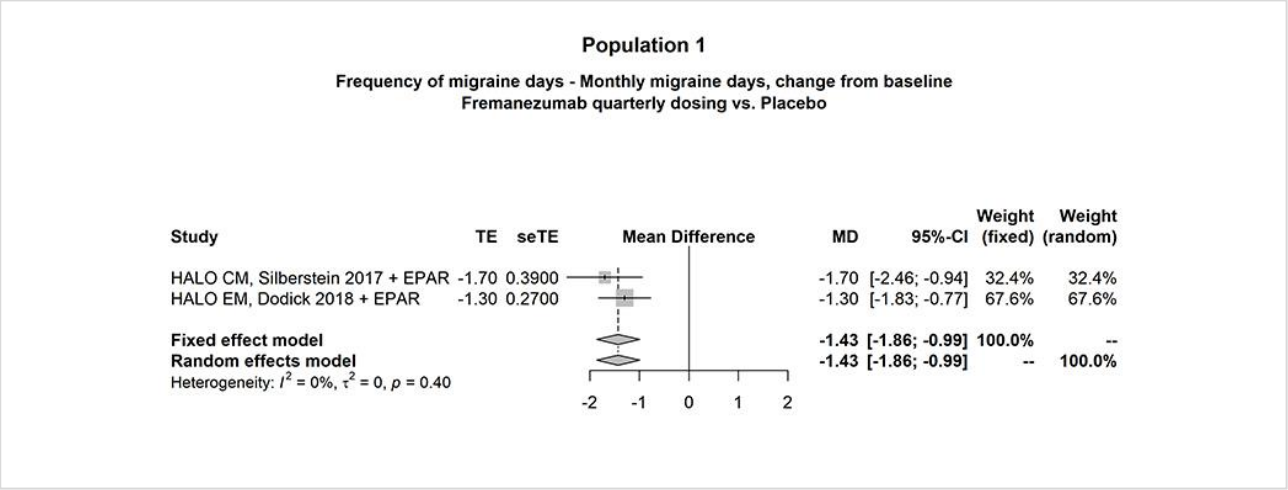

FIGURE 26 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY MIGRAINE DAYS, CHANGE FROM BASELINE, FREMANEZUMAB QUARTERLY DOSING VS. PLACEBO

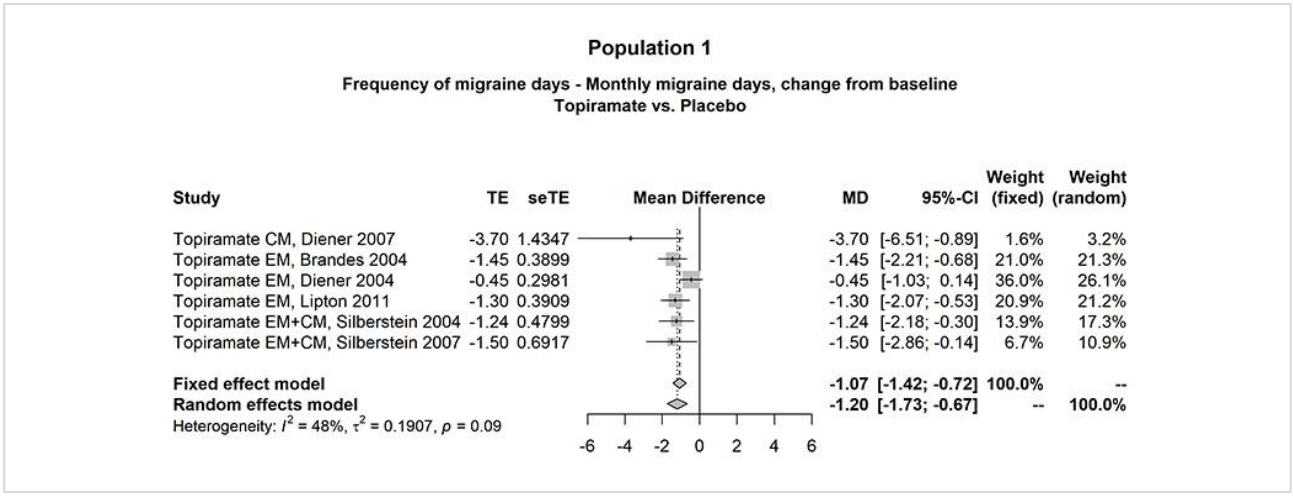

FIGURE 27 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY MIGRAINE DAYS, CHANGE FROM BASELINE, TOPIRAMATE VS. PLACEBO

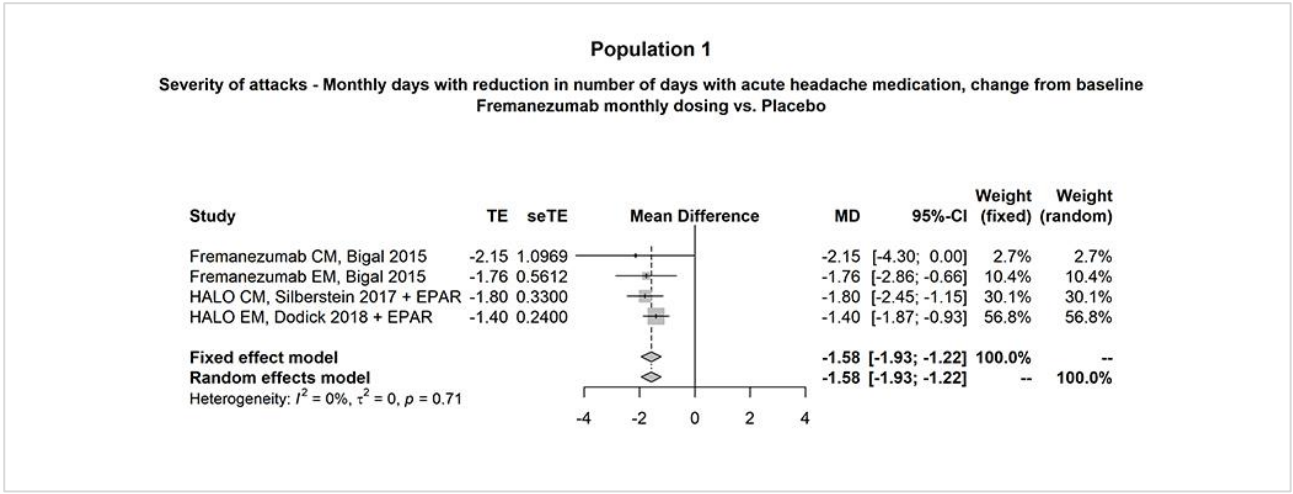

FIGURE 28 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY DAYS WITH REDUCTION IN NUMBER OF DAYS WITH ACUTE HEADACHE MEDICATION, CHANGE FROM BASELINE, FREMANEZUMAB MONTHLY DOSING VS. PLACEBO

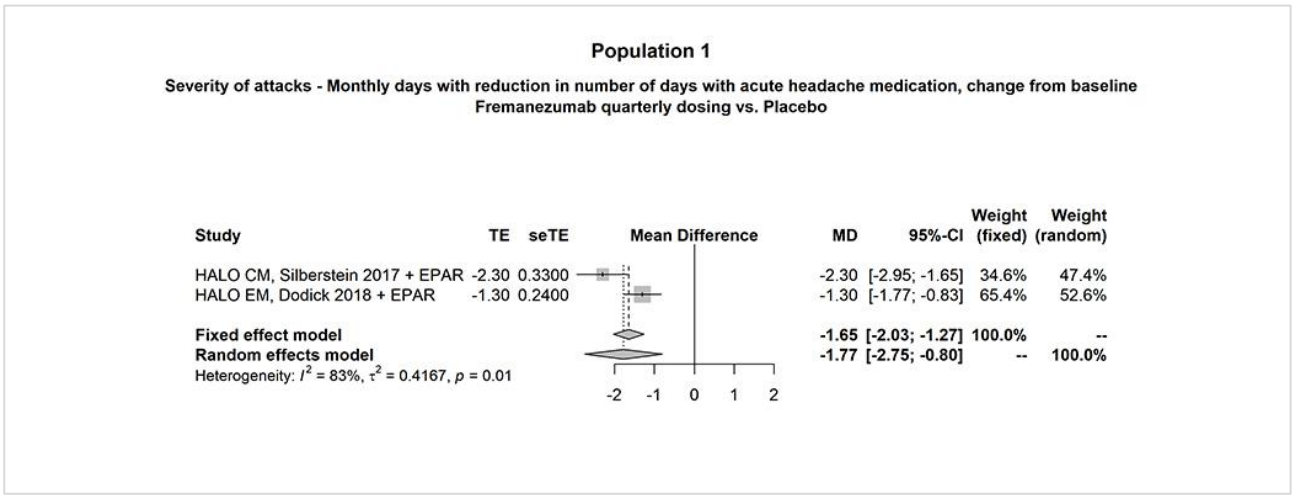

FIGURE 29 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY DAYS WITH REDUCTION IN NUMBER OF DAYS WITH ACUTE HEADACHE MEDICATION, CHANGE FROM BASELINE, FREMANEZUMAB QUARTERLY DOSING VS. PLACEBO

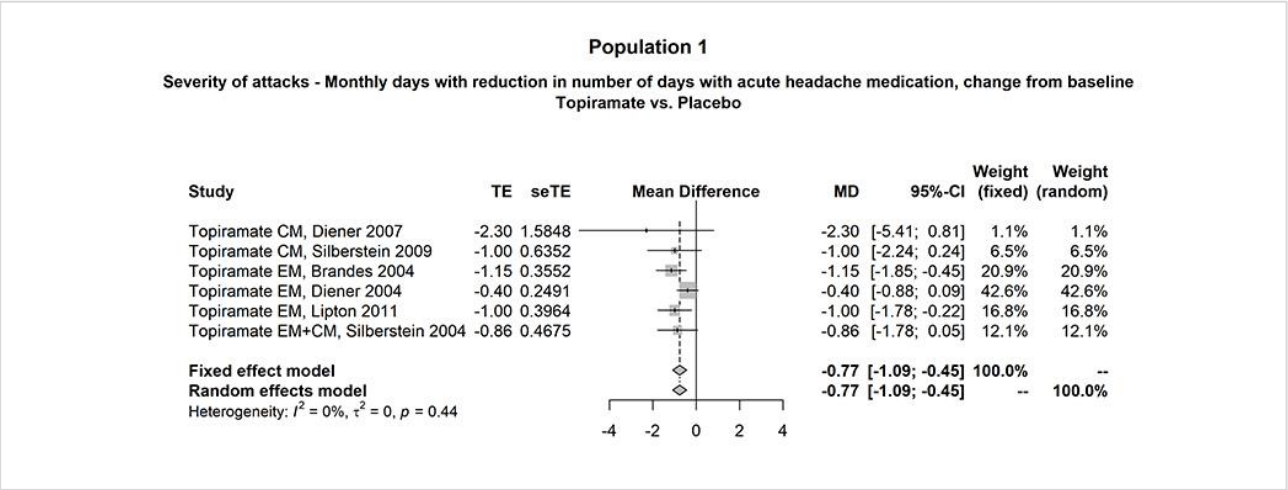

FIGURE 30 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY DAYS WITH REDUCTION IN NUMBER OF DAYS WITH ACUTE HEADACHE MEDICATION, CHANGE FROM BASELINE, TOPIRAMATE VS. PLACEBO

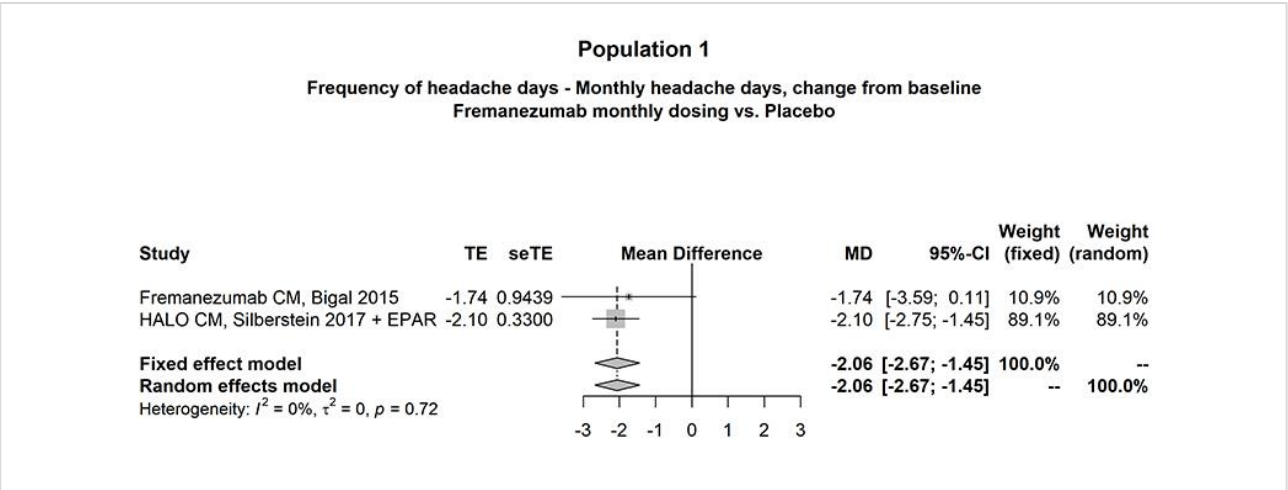

FIGURE 31 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, MEAN DIFFERENCE (MD) FOR MONTHLY HEADACHE DAYS, CHANGE FROM BASELINE, FREMANEZUMAB MONTHLY DOSING VS. PLACEBO

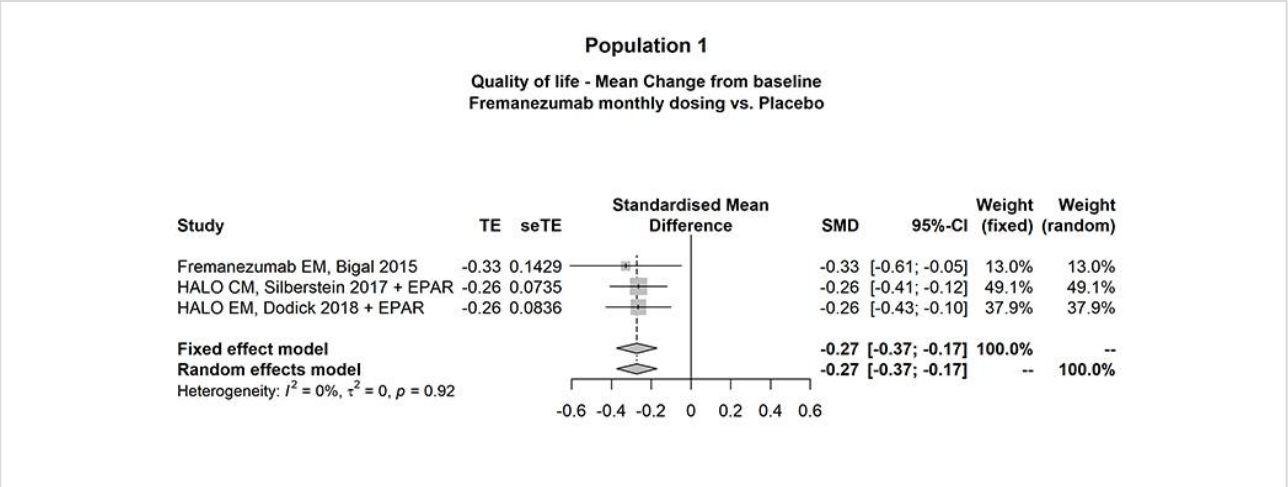

FIGURE 32 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, STANDARDISED MEAN DIFFERENCE (SMD) FOR QUALITY OF LIFE, MEAN CHANGE FROM BASELINE, FREMANEZUMAB MONTHLY DOSING VS. PLACEBO

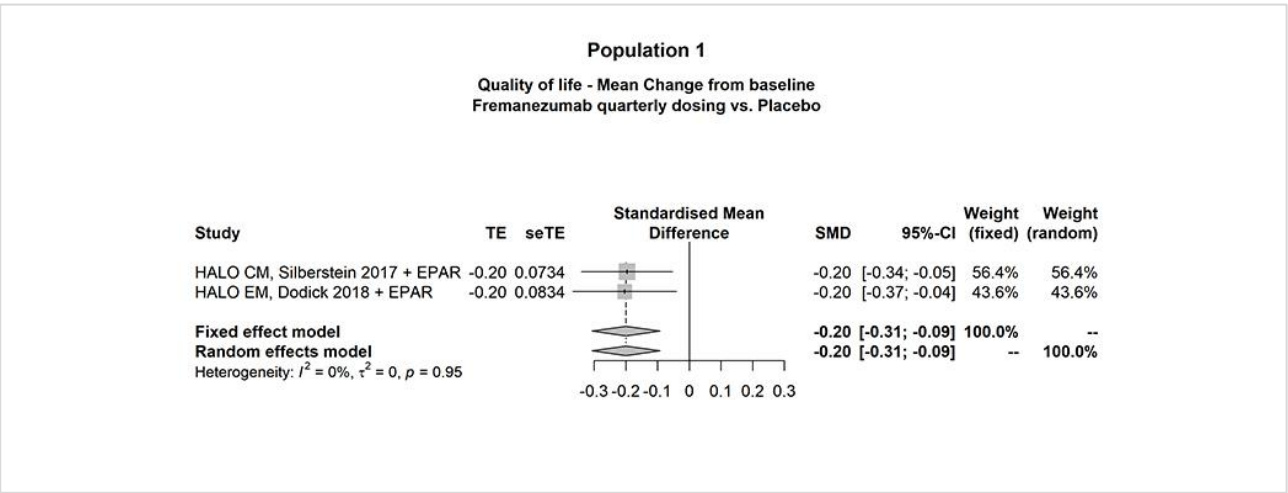

FIGURE 33 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, STANDARDISED MEAN DIFFERENCE (SMD) FOR QUALITY OF LIFE, MEAN CHANGE FROM BASELINE, FREMANEZUMAB QUARTERLY DOSING VS. PLACEBO

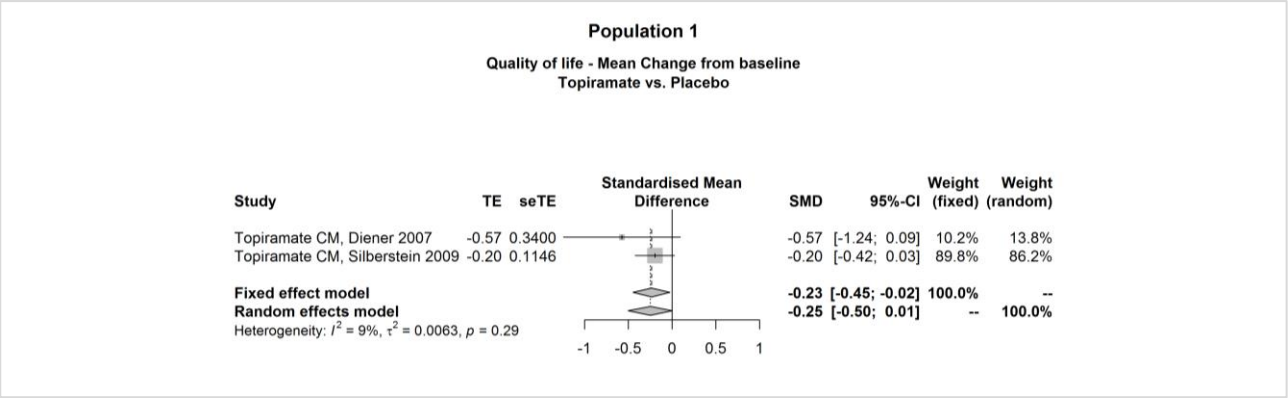

FIGURE 34 HETEROGENEITY PLOT FOR CLINICAL QUESTION 1, STANDARDISED MEAN DIFFERENCE (SMD) FOR QUALITY OF LIFE, MEAN CHANGE FROM BASELINE, TOPIRAMATE VS. PLACEBO

5.9.2 Results per PICO (Indirect treatment comparison)

The four fremanezumab studies were included in the analysis for clinical question 1 [22,23,29,34].

TABLE 90 RESULTS PER OUTCOME. FREMANEZUMAB MONTHLY VS. TOPIRAMATE (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	Fremanezumab CM, Bigal 2015 Fremanezumab EM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate EM, Brandes 2004 Topiramate EM, Diener 2004 Topiramate EM, Lipton 2011 Topiramate EM+CM, Silberstein 2004 Topiramate EM+CM, Silberstein 2007	4.73	-12.25	-27.32 to 2.82	0.11100				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab EM, Bigal 2015 HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate CM, Silberstein 2009	0.28	-9.47	-25.94 to 140.99		0.66	0.07 to 6.04	0.71416	
Point reduction quality of life (MIDAS & HIT-6)	Fremanezumab EM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate CM, Silberstein 2009	37.00	-0.21	-2.60 to 2.17	0.86124				
Monthly days with reduction in number of days with acute headache medication, change from baseline	Fremanezumab CM, Bigal 2015 Fremanezumab EM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate CM, Silberstein 2009 Topiramate EM, Brandes 2004 Topiramate EM, Diener 2004 Topiramate EM, Lipton 2011 Topiramate EM+CM, Silberstein 2004	4.06	-19.88	-31.63 to -8.13	0.00091				
Proportion of patients who experiences adverse events leading to discontinuation	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate EM, Brandes 2004 Topiramate EM, Diener 2004 Topiramate EM, Lipton 2011 Topiramate EM+CM, Mei 2004 Topiramate EM+CM, Silberstein 2004 Topiramate EM+CM, Silberstein 2006 Topiramate EM+CM, Silberstein 2007 Topiramate EM+CM, Storey 2001	0.05	-3.54	-4.66 to -0.85		0.35	0.15 to 0.85	0.01936	
Percent reduction of mean monthly headache days	Fremanezumab CM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR Topiramate CM, Silberstein 2009	14.60	-6.58	-16.14 to 2.98	0.17721				

TABLE 91 RESULTS PER OUTCOME. FREMANEZUMAB QUARTERLY VS. TOPIRAMATE (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**ACR**	**Difference**	**CI**	***P* value**	**Risk Ratio**	**CI**	***P* value**	
Percent reduction of mean monthly migraine days	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate EM, Brandes 2004 Topiramate EM, Diener 2004 Topiramate EM, Lipton 2011 Topiramate EM+CM, Silberstein 2004 Topiramate EM+CM, Silberstein 2007	4.73	-4.91	-19.40 to 9.58	0.50670				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate CM, Silberstein 2009	0.28	-11.18	-26.10 to 125.61		0.60	0.07 to 5.50	0.65115	
Point reduction quality of life (MIDAS & HIT-6)	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate CM, Silberstein 2009	37.00	0.46	-2.20 to 3.13	0.73320				
Monthly days with reduction in number of days with acute headache medication, change from baseline	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate CM, Silberstein 2009 Topiramate EM, Brandes 2004 Topiramate EM, Diener 2004 Topiramate EM, Lipton 2011 Topiramate EM+CM, Silberstein 2004	4.06	-24.72	-50.08 to 0.65	0.05614				
Proportion of patients who experiences adverse events leading to discontinuation	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Topiramate CM, Diener 2007 Topiramate EM, Brandes 2004 Topiramate EM, Diener 2004 Topiramate EM, Lipton 2011 Topiramate EM+CM, Mei 2004 Topiramate EM+CM, Silberstein 2004 Topiramate EM+CM, Silberstein 2006 Topiramate EM+CM, Silberstein 2007 Topiramate EM+CM, Storey 2001	0.05	-3.85	-4.82 to -1.43		0.30	0.12 to 0.74	0.00902	
Percent reduction of mean monthly headache days	HALO CM, Silberstein 2017 + EPAR Topiramate CM, Silberstein 2009	14.60	-4.79	-14.46 to 4.88	0.33113				

TABLE 92 RESULTS PER OUTCOME. FREMANEZUMAB MONTHLY VS. CANDESARTAN (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	Fremanezumab CM, Bigal 2015 Fremanezumab EM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Candesartan EM, Tronvik 2003 Candesartan EM+CM, Stovner 2014	2.98	-34.93	-74.15 to 4.29	0.08089				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab EM, Bigal 2015 HALO EM, Dodick 2018 + EPAR Candesartan EM, Tronvik 2003 Candesartan EM+CM, Stovner 2014	0.26	-14.83	-24.11 to 50.93		0.42	0.06 to 2.99	0.38701	
Percent reduction of mean monthly headache days	Fremanezumab CM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR Candesartan EM+CM, Stovner 2014	5.30	-26.24	-66.92 to 14.44	0.20610				

TABLE 93 RESULTS PER OUTCOME. FREMANEZUMAB QUARTERLY VS. CANDESARTAN (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Candesartan EM, Tronvik 2003 Candesartan EM+CM, Stovner 2014	2.98	-23.26	-61.93 to 15.41	0.23838				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	HALO EM, Dodick 2018 + EPAR Candesartan EM, Tronvik 2003 Candesartan EM+CM, Stovner 2014	0.23	-14.42	-22.08 to 40.11		0.38	0.05 to 2.72	0.33656	
Percent reduction of mean monthly headache days	HALO CM, Silberstein 2017 + EPAR Candesartan EM+CM, Stovner 2014	5.30	-21.32	-62.20 to 19.56	0.30665				

TABLE 94 RESULTS PER OUTCOME. FREMANEZUMAB MONTHLY VS. LISINOPRIL (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	Fremanezumab CM, Bigal 2015 Fremanezumab EM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Lisinopril EM+CM, Schrader 2001	4.80	-7.85	-44.94 to 29.24	0.67833				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab EM, Bigal 2015 HALO EM, Dodick 2018 + EPAR Lisinopril EM+CM, Schrader 2001	0.28	-17.43	-24.75 to 6.75		0.38	0.11 to 1.24	0.10855	
Percent reduction of mean monthly headache days	Fremanezumab CM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR Lisinopril EM+CM, Schrader 2001	6.60	-11.53	-45.51 to 22.46	0.50620				

TABLE 95 RESULTS PER OUTCOME. FREMANEZUMAB QUARTERLY VS. LISINOPRIL (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Lisinopril EM+CM, Schrader 2001	4.80	-0.62	-37.48 to 36.25	0.97385				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	HALO EM, Dodick 2018 + EPAR Lisinopril EM+CM, Schrader 2001	0.17	-11.31	-15.40 to 2.28		0.34	0.10 to 1.13	0.07909	
Percent reduction of mean monthly headache days	HALO CM, Silberstein 2017 + EPAR Lisinopril EM+CM, Schrader 2001	6.60	-7.58	-41.72 to 26.56	0.66361				

TABLE 96 RESULTS PER OUTCOME. FREMANEZUMAB MONTHLY VS. PROPRANOLOL (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	Fremanezumab CM, Bigal 2015 Fremanezumab EM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Propranolol EM, Diener 2004 Propranolol EM+CM, Stovner 2014	3.56	-28.69	-50.08 to -7.31	0.00854				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	Fremanezumab EM, Bigal 2015 HALO EM, Dodick 2018 + EPAR Propranolol EM+CM, Stovner 2014	0.28	0.66	-12.01 to 23.40		1.02	0.57 to 1.84	0.93804	
Monthly days with reduction in number of days with acute headache medication, change from baseline	Fremanezumab CM, Bigal 2015 Fremanezumab EM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Propranolol EM, Diener 2004	3.80	-20.47	-38.10 to -2.85	0.02283				
Proportion of patients who experiences adverse events leading to discontinuation	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Propranolol EM, Diener 1996 Propranolol EM, Diener 2004	0.02	-1.10	-1.64 to 0.31		0.44	0.17 to 1.16	0.09710	
Percent reduction of mean monthly headache days	Fremanezumab CM, Bigal 2015 HALO CM, Silberstein 2017 + EPAR Propranolol EM+CM, Stovner 2014	5.75	-32.01	-72.18 to 8.15	0.11823				

TABLE 97 RESULTS PER OUTCOME. FREMANEZUMAB QUARTERLY VS. PROPRANOLOL (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Propranolol EM, Diener 2004 Propranolol EM+CM, Stovner 2014	3.56	-18.93	-39.59 to 1.74	0.07263				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	HALO EM, Dodick 2018 + EPAR Propranolol EM+CM, Stovner 2014	0.26	-1.84	-12.54 to 17.62		0.93	0.51 to 1.69	0.80701	
Monthly days with reduction in number of days with acute headache medication, change from baseline	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Propranolol EM, Diener 2004	3.80	-25.64	-55.42 to 4.14	0.09153				
Proportion of patients who experiences adverse events leading to discontinuation	HALO CM, Silberstein 2017 + EPAR HALO EM, Dodick 2018 + EPAR Propranolol EM, Diener 1996 Propranolol EM, Diener 2004	0.02	-1.24	-1.70 to 0.02		0.37	0.14 to 1.01	0.05206	
Percent reduction of mean monthly headache days	HALO CM, Silberstein 2017 + EPAR Propranolol EM+CM, Stovner 2014	5.75	-27.48	-67.81 to 12.86	0.18180				

5.10 Clinical Question 2

RDs were derived from RR estimates using the ACR approach. Consequently, since the RD results are not independent, but simply a restatement of RR analyses, statements about statistical significance or evaluation of statistical properties on the RD scale would be duplication of information, and potentially give a misleading impression of the strength of evidence. To avoid this risk, we did not produce heterogeneity plots for RD outcomes, and did not produce separate p-values for the RD results.

5.10.1 Heterogeneity plots

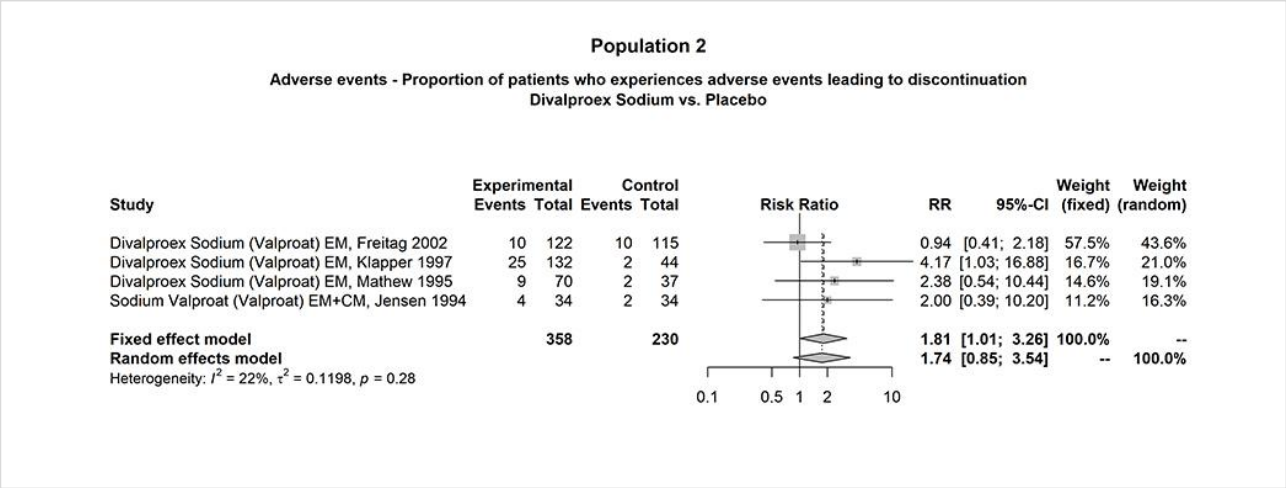

FIGURE 35 HETEROGENEITY PLOT FOR CLINICAL QUESTION 2, RISK RATIO (RR) FOR PROPORTION OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS LEADING TO DISCONTINUATION, DIVALPROEX SODIUM VS. PLACEBO

5.10.2 Results per PICO (Indirect treatment comparison)

TABLE 98 RESULTS PER OUTCOME. FREMANEZUMAB MONTHLY VS. VALPROATE (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Proportion of patients who achieve ≥50% reduction in monthly migraine days	FOCUS Divalproex Sodium (Valproat) EM, Mathew 1995	0.11	1.72	-6.22 to 22.17		1.15	0.45 to 2.97	0.76801	Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who experiences adverse events leading to discontinuation	FOCUS Divalproex Sodium (Valproat) EM, Freitag 2002 Divalproex Sodium (Valproat) EM, Klapper 1997 Divalproex Sodium (Valproat) EM, Mathew 1995 Sodium Valproat (Valproat) EM+CM, Jensen 1994	0.05	-1.37	-4.63 to 15.58		0.75	0.14 to 3.88	0.72758	

TABLE 99 RESULTS PER OUTCOME. FREMANEZUMAB QUARTERLY VS. VALPROATE (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Proportion of patients who achieve ≥50% reduction in monthly migraine days	FOCUS Divalproex Sodium (Valproat) EM, Mathew 1995	0.11	1.78	-6.20 to 22.32		1.16	0.45 to 2.98	0.76141	Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who experiences adverse events leading to discontinuation	FOCUS Divalproex Sodium (Valproat) EM, Freitag 2002 Divalproex Sodium (Valproat) EM, Klapper 1997 Divalproex Sodium (Valproat) EM, Mathew 1995 Sodium Valproat (Valproat) EM+CM, Jensen 1994	0.05	-4.36	-5.31 to 5.69		0.19	0.02 to 2.05	0.17249	

TABLE 100 RESULTS PER OUTCOME. FREMANEZUMAB MONTHLY VS. AMITRIPTYLINE (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	FOCUS Amitriptyline EM, Goncalves 2016	5.00	-48.00	-78.62 to -17.38	0.00212				*Bucher analysis for indirect treatment comparison using random effect*
Proportion of patients who achieve ≥50% reduction in monthly migraine days	FOCUS Amitriptyline EM, Goncalves 2016	0.14	15.52	0.01 to 47.62		2.07	1.00* to 4.29	0.04975	
Proportion of patients who experiences adverse events leading to discontinuation	FOCUS Amitriptyline EM+CM, Couch 2011	0.04	-1.07	-3.29 to 10.21		0.72	0.14 to 3.66	0.69335	

*The CI lower limit is 1.0008.

TABLE 101 RESULTS PER OUTCOME. FREMANEZUMAB QUARTERLY VS. AMITRIPTYLINE (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	FOCUS Amitriptyline EM, Goncalves 2016	5.00	-40.00	-70.62 to -9.38	0.01046				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	FOCUS Amitriptyline EM, Goncalves 2016	0.14	15.65	0.07 to 47.91		2.08	1.00* to 4.31	0.04855	
Proportion of patients who experiences adverse events leading to discontinuation	FOCUS Amitriptyline EM+CM, Couch 2011	0.04	-3.13	-3.77 to 3.65		0.19	0.02 to 1.95	0.16074	

*The CI lower limit is 1.0047.

5.11 Clinical Question 3

5.11.1 Results per PICO (Indirect treatment comparison)

RDs were derived from RR estimates using the ACR approach. Consequently, since the RD results are not independent, but simply a restatement of RR analyses, statements about statistical significance or evaluation of statistical properties on the RD scale would be duplication of information, and potentially give a misleading impression of the strength of evidence. To avoid this risk, we did not produce separate p-values for the RD results.

TABLE 102 RESULTS PER OUTCOME. FREMANEZUMAB MONTHLY VS. BOTOX (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	FOCUS Botox, Aurora 2011	10.90	-13.76	-22.93 to -4.60	0.00325				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	FOCUS Botox, Aurora 2011	0.22	44.78	21.11 to 81.28		2.99	1.94 to 4.61	0.00000	
Point reduction quality of life (HIT-6)	FOCUS Botox, Aurora 2011	60.70	-1.50	-3.15 to 0.15	0.07456				
Monthly days with reduction in number of days with acute headache medication, change from baseline	FOCUS Botox, Aurora 2011	8.50	-30.59	-42.20 to -18.97	0.00000				
Proportion of patients who experiences adverse events leading to discontinuation	FOCUS Botox, Aurora 2011	0.01	-0.68	-1.04 to 1.26		0.40	0.07 to 2.13	0.28030	

TABLE 103 RESULTS PER OUTCOME. FREMANEZUMAB QUARTERLY VS. BOTOX (RANDOM EFFECTS)

Results per outcome			Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	ACR	Difference	CI	*P* value	Risk Ratio	CI	*P* value	
Percent reduction of mean monthly migraine days	FOCUS Botox, Aurora 2011	10.90	-10.09	-19.26 to -0.93	0.03091				Bucher analysis for indirect treatment comparison using random effect
Proportion of patients who achieve ≥50% reduction in monthly migraine days	FOCUS Botox, Aurora 2011	0.22	45.06	21.27 to 81.78		3.00	1.95 to 4.64	0.00000	
Point reduction quality of life (HIT-6)	FOCUS Botox, Aurora 2011	60.70	-0.60	-2.26 to 1.06	0.47905				
Monthly days with reduction in number of days with acute headache medication, change from baseline	FOCUS Botox, Aurora 2011	8.50	-27.06	-38.67 to -15.44	0.00000				
Proportion of patients who experiences adverse events leading to discontinuation	FOCUS Botox, Aurora 2011	0.01	-1.01	-1.11 to 0.13		0.10	0.01 to 1.12	0.06138	

Medicinrådet

Medicinrådets protokol for vurdering af klinisk merværdi for fremanezumab til forebyggende behandling af migræne

Versionsnr.: 1.1

Om Medicinrådet

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

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

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

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

Om protokollen

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

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	28. februar 2019
Ikrafttrædelsesdato	28. februar 2019
Dokumentnummer	44105
Versionsnummer	1.1

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, 28. februar 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Ajovy
Generisk navn	Fremanezumab
Firma	Teva
ATC-kode	N02CX07
Virkningsmekanisme	Humant monoklonalt antistof som selektivt binder til CGRP-peptid, som er en del af patofysiologien for migræne. Fremanezumab binder til både α- og β-isoformerne af CGRP-liganden, men ikke til receptoren.
Administration/dosis	225 mg hver måned (ca. hver 4. uge) 675 mg hvert kvartal (ca. hver 12. uge)
Forventet EMA-indikation	Forebyggende behandling af migræne blandt voksne med mindst fire månedlige migrænedage.

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 fremanezumab som mulig standardbehandling af patienter med migræne. I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende fremanezumab modtaget den 16. januar 2019.

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

4 Baggrund

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 hovedpinetype, f.eks. spændingshovedpine. Dette skal opfattes som et kontinuerligt spektrum, hvor den enkelte patient i perioder kan gå fra episodisk til kronisk migræne og omvendt.

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, men at der ikke findes 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 tilsiger 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.

De lægemidler, der på nuværende tidspunkt tilbydes som forebyggende behandling af migræne, blev oprindeligt udviklet til andre formål, f.eks. antihypertensiva (blodtryksmedicin), antiepileptika (medicin mod epilepsi) og antidepressiva (medicin mod depression). Disse lægemidler viste sig også at have effekt på forebyggelse af migræne, og visse blev godkendt til dette formål. 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). Derudover er Botox 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. den enkelte patients risikoprofil, andre sygdomme og tidligere erfaring.

Kortfattet kan man dog konkludere, at der generelt er 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 Botox – som andetvalgslægemidler. Ved behandlingssvigt/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 Fremanezumab

Fremanezumab 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. Fremanezumab administreres subkutant og indgives månedligt eller kvartalsvis. Den månedlige dosering er 225 mg, mens den kvartalsvise dosering er 675 mg (3 x 225 mg).

5 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

5.1 Klinisk spørgsmål 1

Hvad er den kliniske merværdi af fremanezumab til patienter med migræne, der har mindst fire migrænedage pr. måned sammenlignet med eksisterende standardbehandling?

Population
Patienter, der har mindst fire migrænedage pr. måned.

Intervention
Fremanezumab 225 mg subkutant 1 gang om måneden (månedlig dosering)
Fremanezumab 675 mg subkutant 1 gang hver tredje måned (kvartalsvis dosering)

Komparator
Betablokkere (metoprolol 50-200 mg dagligt/propranolol 40-240 mg dagligt)
Lisinopril 20 mg dagligt
Candesartancilexetil 16-32 mg dagligt
Topiramat 25-200 mg dagligt

Effektmål
Se tabel 1.

5.2 Klinisk spørgsmål 2

Hvad er den kliniske merværdi af fremanezumab til patienter med migræne, der har mindst fire migrænedage pr. måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med eksisterende standardbehandling?

Population
Patienter der har mindst fire migrænedage pr. måned og har oplevet behandlingssvigt på to tidligere forebyggende behandlinger.

Intervention
Fremanezumab 225 mg subkutant 1 gang om måneden (månedlig dosering)
Fremanezumab 675 mg subkutant 1 gang hver tredje måned (kvartalsvis dosering)

Komparator
Tricykliske antidepressiva (amitriptylin 10-100 mg dagligt/nortriptylin 25-100 mg dagligt)
Valproat 500-1800 mg dagligt

Effektmål
Se tabel 1.

5.3 Klinisk spørgsmål 3

*Hvad er den kliniske merværdi af fremanezumab til patienter med **kronisk migræne**, som har oplevet behandlingssvigt på tidligere forebyggende behandlinger indenfor to lægemiddelgrupper (antihypertensiva og antiepileptika) sammenlignet med Botox?*

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
Fremanezumab 225 mg subkutant 1 gang om måneden (månedlig dosering)
Fremanezumab 675 mg subkutant 1 gang hver tredje måned (kvartalsvis dosering)

Komparator
Botulinum type A toxin 155 enheder fordelt på 31-39 injektionssteder.

Effektmål
Se tabel 1.

5.4 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og kategori.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vil den foreløbige kategorisering af effekten for det pågældende effektmål basere sig på den halve værdi af den retningsgivende mindste klinisk relevante forskel. Den halve værdi af den retningsgivende mindste klinisk relevante forskel benævnes den justerede mindste klinisk relevante forskel. Rationalet herfor er, at man ved denne tilgang kan sikre, at mindst halvdelen af konfidensintervallet ligger tættere på den retningsgivende mindske kliniske relevante forskel end på 'ingen forskel' (absolut effektforskel på 0). Den kliniske relevans (værdi) vurderes med udgangspunkt i den justerede mindste klinisk relevante forskel 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 hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre kategorier ("dødelighed" "livskvalitet, alvorlige symptomer og bivirkninger" og "ikkealvorlige symptomer og bivirkninger").

Effektmål*	Vigtighed	Kategori	Måleenhed	Retningsgivende mindste klinisk relevante forskel	Justeret mindste klinisk relevante forskel
For både episodisk og kronisk migræne patienter:					
Frekvens af migrænedage	Kritisk	Alvorlige symptomer og bivirkninger	Reduktion af månedlige migrænedage	10 %-point	5 %-point
	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patientpopulation, som opnår ≥ 50 % reduktion af månedlige migrænedage	5 %-point	2,5 %-point

Livskvalitet	Kritisk	Livskvalitet	Gennemsnitlig ændring fra baseline på HIT-6	-1,5 point for patienter med episodisk migræne -2,3 point for patienter med kronisk migræne	-0,75 point for patienter med episodisk migræne -1,15 point for patienter med kronisk migræne
Anfalds-sværhedsgrad	Vigtig	Alvorlige symptomer og bivirkninger	Reduktion af antal dage med anfaldsbehandling pr. måned	10 %-point	5 %-point
Bivirkninger	Vigtig	Alvorlige symptomer og bivirkninger	Andel patienter som oplever bivirkninger, der medfører behandlingsophør	5 %-point	2,5 %-point
			Kvalitativ gennemgang af bivirkninger	-	-
Kun for patienter med kronisk migræne (NB! Patienter med kronisk migræne indgår i alle kliniske spørgsmål):					
Frekvens af hovedpinedage	Vigtig	Alvorlige symptomer og bivirkninger	Reduktion af månedlige hovedpinedage (non-migræne)	10 %-point	5 %-point

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Den minimale opfølgningstid til vurdering af forebyggende migrænebehandling er 3 måneder, hvilket skyldes, at man i klinisk praksis normalt venter 3 måneder, inden man vurderer behandlingsresponsen hos den enkelte patient. Den samlede kliniske merværdi af fremanezumab baseres på længst mulig opfølgningstid.

Frekvens af migrænedage

Et af de primære behandlingsmål med forebyggende behandling er at reducere frekvensen af migræneanfald. Fagudvalget vil vurdere fremanezumabs effekt på anfaldsfrekvens ved at se på migrænedage pr. måned og ≥ 50 % responderrate. Begge er mål for anfaldsfrekvens, men supplerer hinanden da migrænedage pr. måned vil udtrykke den gennemsnitlige reduktion af migrænedage, mens responderraten vil vise, om en eventuel reduktion i antallet af migrænedage vil gavne en større eller mindre andel af patientpopulationen, samt om der kan opnås en forbedring af migræne uden nødvendigvis symptomfrihed hos den enkelte patient.

Månedlige migrænedage (kritisk)

En "migrænedag" er et effektmål i studier, der undersøger forebyggende migrænebehandling. Definitionen af en migrænedag følger retningslinjerne fra *International Headache Society* [4]. Forebyggende migrænebehandling tilbydes normalt til patienter, der har mindst 2 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 fremanezumab kan reducere antal migrænedage pr. måned. Idet der er stor variation blandt migrænepatienter i antal migrænedage/måned, fastsættes den mindste klinisk relevante forskel i procentuel forskel i stedet for i absolutte tal. Ud fra fagudvalgets kliniske erfaring vurderes den eksisterende standardbehandling at reducere migrænedage pr. måned med ca. 30-40 %. Fagudvalget vurderer migrænedage som et kritisk effektmål og mener, at en yderligere reduktion på 10 %-point i antal migrænedage i forhold til, hvad der kan opnås med eksisterende behandlingsmuligheder, opfattes som klinisk relevant.

Migræneanfald (≥ 50 % responderrate) (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 medicinbivirkninger. Patienterne er i øvrigt ofte i den skole- eller erhvervsaktive alder, hvor migræne kan medføre et betydeligt fravær. Effektmålet er traditionelt blevet brugt til at beskrive andelen af patienter, der opnår forbedring (minimum halvering) af migrænedage uden nødvendigvis at opnå fuldstændig sygdomsfrihed. Det er fagudvalgets erfaring, at ca. 40 % af patienterne opnår mindst en halvering i deres migrænedage med de gængse lægemidler. Det er fagudvalgets vurdering, at en yderligere øgning af andelen af disse patienter med 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 "The Head Impact Test", også kaldet HIT-6. HIT-6 er et valideret spørgeskema [5] og består af 6 spørgsmål. I spørgeskemaet vurderes patientens "arbejdsdygtighed" over de seneste 4 uger. Der indgår 6 spørgsmål, der måler frekvensen af svær hovedpine, hovedpine som begrænser den daglige aktivitet, ønske om at lægge sig ned under hovedpineepisoden, træthed relateret til hovedpine, irritabilitet pga. hovedpine samt koncentrationsbesvær pga. hovedpine. Scoringssystemet er fra 36-78; højere scoring indikerer sværere symptomer. Dette spørgeskema er et af de mest kendte blandt danske patienter og er således fagudvalgets foretrukne spørgeskema i vurderingen af fremanezumab. I litteraturen er der angivet mindste klinisk relevante forskelle på hhv. -2,3 point for patienter med kronisk migræne og -1,5 for patienter med episodisk migræne [6,7].

Ansøger har angivet, at HIT-6 ikke er anvendt i studiet, der undersøger effekten af fremanezumab hos patienter med episodisk migræne. Findes der ikke livskvalitetsdata på HIT-6, kan ansøger alternativt 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 [8]. MSQ måler livskvaliteten indenfor de seneste 4 uger på tværs af tre subskalaer: Restriktiv funktion, forebyggende funktion og emotionel funktion. Scoren spænder fra 0 til 100 i hvert domæne, hvor en højere score angiver forbedring i livskvalitet. Der er 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 restriktiv funktion, forebyggende funktion og emotionel funktion [9].

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. Fagudvalget vurderer, at en 10 %-pointreduktion i forbrug af anfaldsbehandling er klinisk relevant.

Bivirkninger (vigtig)
Det er velkendt, at forebyggende behandling af migræne med de gængse lægemidler må afbrydes mange gange på grund af bivirkninger [4], herunder bivirkninger som i væsentlig grad påvirker patientens

livskvalitet og medfører skift til andet præparat. Fagudvalget vurderer således, at en 5 %-pointreduktion af bivirkninger, der medfører behandlingsophør, er relevant.

Herudover ønsker fagudvalget en kvalitativ beskrivelse af de hyppigst forekommende bivirkninger ved behandling med fremanezumab, herunder sedation, svimmelhed, vægtøgning og affektive symptomer.

Hovedpinedage pr. måned (non-migræne) (kun for patienter med kronisk migræne) (vigtig)
Patienter med kronisk migræne har ≥ 15 hovedpinedage om måneden, heraf mindst 8 dage som migrænehovedpine. Disse patienter har således et betydeligt antal dage med andre non-migrænehovedpineformer, oftest spændingshovedpine. 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 non-migrænehovedpine. Effekten kan for andre lægemidler dog være indirekte, således at 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 yderligere 10 %'s reduktion i antal hovedpinedage i forhold til den gængse behandling hos patienter med kronisk migræne opfattes som klinisk relevant.

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 fremanezumab er sammenlignet direkte med de angivne komparatorer.

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af fremanezumab og de angivne komparatorer.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af fremanezumab og de angivne komparatorer. Det betyder, at der både skal søges efter primærstudier af fremanezumabs effekt og efter primærstudier af effekten af henholdsvis betablokkere (metoprolol/propranolol), topiramat, candesartancilexetil og lisinopril for klinisk spørgsmål 1, amitriptylin/nortriptylin og valproat for klinisk spørgsmål 2 samt botulinum type A toxin for klinisk spørgsmål 3. 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	1 and 2	Samlet søgning for populationen
#4	fremanezumab[nm] OR framanezumab[tiab] OR TEV-48125[tiab] OR Ajovy[tiab]	Søgetermer for interventionen
#5	propranolol[MeSH] OR propranolol[tiab]	Komparatorer til klinisk spørgsmål 1
#6	metoprolol[MeSH] OR metoprolol[tiab] OR metoprololsuccinat*[tiab]	
#7	lisinopril[MeSH] OR lisinopril[tiab]	

#8	Candesartan cilexetil[nm] OR candesartan[nm] OR "candesartan cilexetil"[tiab] OR candesartan*[tiab]	
#9	Topiramate[MeSH] OR topiramat*[tiab]	
#10	amitriptyline[MeSH] OR amitriptylin*[tiab]	Komparatorer til klinisk spørgsmål 2
#11	nortriptyline[MeSH] OR nortriptylin*[tiab]	
#12	Valproic Acid[MeSH] OR valproat*[tiab] valproic*[tiab]	
#13	Botulinum Toxins, Type A[MeSH] OR botulinum*[tiab] OR onabotulinum*[tiab]	Komparator klinisk spørgsmål 3
#14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	Samlet for alle komparatorer
#15	3 and 14	Cochrane RCT filter
#16	randomized controlled trial[pt]	
#17	controlled clinical trial[pt]	
#18	randomized[tiab] OR randomised[tiab]	
#19	placebo[tiab]	
#20	clinical trials as topic[mesh:noexp]	
#21	randomly[tiab]	
#22	trial[ti]	
#23	16 or 17 or 18 or 19 or 20 or 21 or 22	
#24	animals[mh] NOT humans [mh]	
#25	23 not 24	
#26	#15 and #25	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	(#1 or #2) and #3	Samlet søgning for populationen
#5	(fremanezumab or TEV-48125 or Ajovy):ti,ab,kw	Interventionen
#6	[mh Propranolol]	Komparatorer til klinisk spørgsmål 1
#7	propranolol:ti,ab,kw	
#8	[mh Metoprolol]	
#9	metoprolol:ti,ab,kw	
#10	[mh Lisinopril]	
#11	lisinopril:ti,ab,kw	
#12	candesartan*:ti,ab,kw	
#13	topiramat*:ti,ab,kw	
#14	[mh Amitriptyline]	Komparatorer til klinisk spørgsmål 2
#15	amitriptylin*:ti,ab,kw	
#16	[mh Nortriptyline]	
#17	nortriptylin*:ti,ab,kw	
#18	[mh "Valproic Acid"]	
#19	(valproic* or valproat*):ti,ab,kw	
#20	[mh "Botulinum Toxins, Type A"]	Komparator klinisk spørgsmål 3
#21	(botulinum* or onabotulinum*):ti,ab,kw	
#22	{or #5-#21}	Samlet for alle komparatorer
#23	#4 and #22	
#24	("conference abstract" or review):pt OR NCT*:au	
#25	#23 not #24	
#26	"Pubmed":an	
#27	#25 not #26 in Trials	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 fremanezumab og de nævnte komparatorer ved brug af placebo kontrollerede studier. Der ønskes således ikke en indbyrdes sammenligning af komparatorerne. For de komparatorer i klinisk spørgsmål 1 og 2, hvor der findes studier, der muliggør separate analyser for henholdsvis episodisk og kronisk migræne, ønsker fagudvalget effektforskellen opgjort separat for episodisk og kronisk migræne.

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

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9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende migræne

Formand	**Indstillet af**
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Medicinrådets sekretariat

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10 Versionslog

Version	Dato	Ændring
1.0	25.02.2019	Godkendt af Medicinrådet.
1.1	28.02.2019	Rettelse vedrørende populationen i klinisk spørgsmål 2.

11 Bilag 1: Tabel 1

(Markeret med rød = "off-label")

	Dansk Hovedpine Selskab (2010)	Dansk Neurologisk Selskab (2016)	SST (2015)	Pro.medicin.dk
1.Valg	1. Betablokkere (metoprolol 50-200 mg eller propranolol 40-240 mg) - Antiepileptika (topiramat 25-100(200) mg eller valproat 500-1800 mg) - Flunarizin 5-10 mg	- Betablokkere (metoprolol 50-200 mg, propranolol 40-240 mg) - Candesartan 16-32 mg - Antiepileptika (topiramat 25-100(200) mg, valproat 500-1.800 mg) - Flunarizin 5-10 mg	1. Betablokkere (metoprolol 50-200 mg, propranolol 40-240 mg) - Candesartan 16 mg - Antiepileptika (topiramat 25-100(200) mg, valproat 500-1.800 mg) - Flunarazin 5-10 mg	- Betablokkere (metoprolol 50-200 mg, propranolol 40-240 mg)
2.Valg	- Amitriptylin 10-100 mg - Naproxen 500 x2 - Bisoprolol 5-10 mg	* Henvises til Dansk Hovedpine Selskab		- Candesartan 16 (24-32 mg)
3.Valg	- Candesaratn 16 mg - Lisinopril 20 mg - Pizotifen 1,5-3 mg - 6 andre "off-label"	* Henvises til Dansk Hovedpine Selskab		- Antiepileptika (topiramat 25-100(200) mg, valproat 500-1.800 mg) - Flunarizin 5-10 mg
Andre		- Botox (ved kronisk migræne)	- Amitriptylin - Naproxen - Lisinopril - Riboflavin - Coenzym Q10 - Pizotifen	

	IRF (2009)
Rekommanderet	Candesartan 16 mg Lisinopril 20 mg Metoprolol 150 mg Propranolol 160 mg
Rekommanderet med forbehold eller i særlige tilfælde	Flunarizin 10 mg Naproxen 1.000 mg Pizotifen 1,5 mg Topiramat 100 mg Valproat 100 mg
Ikke rekommanderet	Clonidin

SST: "Der er endnu ikke demonstreret en effekt af at kombinere flere former for profylaktiske midler, og der er ikke sikker evidens for, at en type profylaktisk migrænemedicin virker bedre ved en bestemt migræne-subtype. Der er heller ikke sikker evidens for, at et præparat er mere effektivt end andre, så valg må bero på de forskellige stoffers bivirkningsprofil, komorbiditet og kontraindikationer". (7)