Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende fenfluramin til behandling af Dravet syndrom

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Fenfluramin

Dravet syndrom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

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

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

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspris
SUDEP	*Sudden Unexpected Death in Epilepsy*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for fenfluramin i tillæg til standardbehandling, der inkluderer stiripentol ca. [redacted] DKK pr. patient sammenlignet med standardbehandling alene. Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 2,2 mio. DKK pr. patient.

De inkrementelle omkostninger er overvejende drevet af lægemiddelprisen for fenfluramin, der potentielt kan være en livslang behandling.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af fenfluramin som mulig standardbehandling vil være ca. [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 6,8 mio. DKK i det femte år.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af fenfluramin som mulig standardbehandling på danske hospitaler til behandling af Dravet syndrom.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Zogenix. Medicinrådet modtog den endelige ansøgning den 9. december 2021.

3.1 Patientpopulation

Dravet syndrom er en sjælden, alvorlig epilepsiform, der typisk debuterer inden for det første leveår. Dravet syndrom er karakteriseret ved hyppige, ofte daglige anfald. Hyppigheden af anfald er størst hos børn under 5 år og aftager med alderen. Med nuværende behandling ses der hos 0-18-årige typisk 20-50 epileptiske anfald månedligt, mens voksne patienter oftest oplever korte, natlige anfald med et spænd i hyppighed fra flere anfald dagligt til månedlige anfald. For alle aldersgrupper ses der dermed stor individuel variation i anfaldshyppigheden.

Dravet syndrom er forbundet med væsentlig overdødelighed bl.a. grundet risikoen for pludselig uventet død *(Sudden Unexpected Death in Epilepsy* (SUDEP)), ulykker ifm. anfald og status epilepticus (SE), som er en potentielt livstruende tilstand med vedvarende anfald [1–3]. De fleste dødsfald sker før 10 års-alderen. I et kohortestudie af 100 patienter med Dravet syndrom blev der rapporteret en 15 % risiko for død inden for 10 år efter diagnose [4].

Det anslås, at der i Danmark er ca. 45.000-55.000 patienter med epilepsi på tværs af alle epilepsiformer. Patienter med Dravet syndrom udgør en lille del af denne patientpopulation. Fagudvalget vurderer, at der i Danmark er ca. 50 børn og unge samt 30-40 voksne diagnosticeret med Dravet syndrom. Disse patienter behandles overvejende på Epilepsihospitalet Filadelfia. Et dansk epidemiologisk studie fra 2015 estimerede, at den årlige forekomst af Dravet syndrom er 1 ud af 22.000 nyfødte, hvilket svarer til, at der årligt bliver født 2-3 børn med Dravet syndrom i Danmark [5].

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

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

Klinisk spørgsmål 1:

Hvilken værdi har fenfluramin sammenlignet med stiripentol for patienter med Dravet syndrom i alderen 2 år og op, som er i en behandlingskombination, der ikke omfatter stiripentol?

Klinisk spørgsmål 2:

Hvilken værdi har fenfluramin sammenlignet med placebo for patienter med Dravet syndrom i alderen 2 år og op, som er i en behandlingskombination, der omfatter stiripentol?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for fenfluramin som tillæg til en standardbehandling, der indeholder stiripentol sammenlignet med standardbehandling alene, svarende til klinisk spørgsmål 2. Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

Ansøger har valgt ikke at indsende en økonomisk analyse, der kan belyse de inkrementelle omkostninger og budgetkonsekvenserne ved klinisk spørgsmål 1, hvor den ønskede patientpopulation er stiripentol-naive patienter.

[redacted]

[redacted] Ansøger mener yderligere ikke, at de studier, der er tilgængelige, giver mulighed for at lave en sammenligning af fenfluramin og stiripentol til stiripentol-naive patienter. Ansøger har i stedet valgt at lave en analyse, hvor fenfluramin sammenlignes med placebo for patienter, der tidligere har modtaget stiripentol baseret på Study 1.

Medicinrådet bemærker dog, at det kliniske studie, study 1, både indeholder patienter, der er stiripentol-naive og tidligere behandlet med stiripentol.

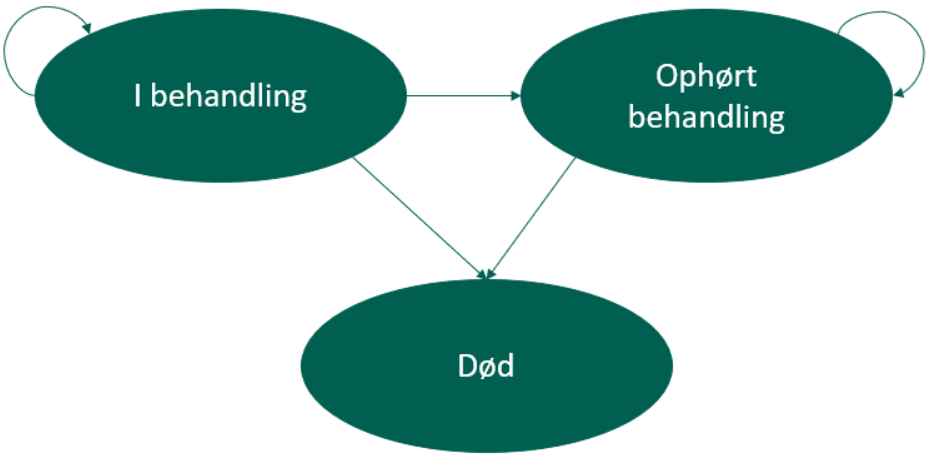
Da analysen ikke belyser de sundhedsøkonomiske aspekter af det kliniske spørgsmål, der efterspørges i Medicinrådets protokol, vil den ikke blive præsenteret yderligere.

Analysen, som belyser de inkrementelle omkostninger ved tillæg af fenfluramin for patienter, der modtager standardbehandling, der inkluderer stiripentol, er lavet på baggrund af data fra studie 1504. Yderligere information om studiet kan findes i vurderingsrapporten for fenfluramin.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en Markov model til at estimere omkostningerne forbundet med behandlingen med fenfluramin.

Den indsendte model har en cykluslængde på 28 dage, og består af tre helbredsstadier: i behandling, ophørt behandling og det absorberende stadie død. Modellens struktur er vist i Figur 1.



Figur 1. Markov modellens struktur

For patienter, der behandles med henholdsvis fenfluramin som tillæg til standardbehandling indeholdende stiripentol og standardbehandling alene, er modellen identisk, kun patienternes bevægelse mellem de forskellige helbredsstadier afviger mellem behandlingsalternativerne.

Til at estimere sandsynligheden for behandlingsophør anvendes studie 1504, mens *open-label extention (OLE)* blev anvendt som input til behandlingsophør efter studietiden. I

Tabel 4-1 er anvendte sandsynligheder for behandlingsophør vist. Patienterne, der ophørte med behandling i studietiden, stoppede hovedsaligt pga. bivirkninger og manglende behandlingseffekt.

Patienter med Dravet syndrom har en øget risiko for død i forbindelse med SUDEP, status epileptikus og ulykker. Data for mortalitet for patienter med Dravet syndrom er begrænset, og der var ikke observeret nogen dødsfald i studie 1504. For at kunne estimere mortaliteten har ansøger anvendt et studie af Cooper et al. fra 2016. Studiet rapporterer en rate for dødsfald uanset årsag hos patienter med Dravet syndrom på 15,84 pr. 1.000 personår. Studiet rapporterer en SUDEP-mortalitetsrate på 9,32 pr. 1.000 personår.

På baggrund af et studie af Cross et. al fra 2021 estimerer ansøger, at SUDEP-mortalitetsraten for patienter i behandling med fenfluramin er 1,7 pr. 1.000 patientår [6]. Grundet begrænset data antager ansøger kun en forskel for mortaliteten i forbindelse med SUDEP og ikke en forskel i dødelighed forbundet med generel sygdom for patienterne i fenfluramin- og placeboarmen. I Tabel 4-1 er mortalitetsrater anvendt i modellen vist.

Udover mortalitet i forbindelse med Dravet syndrom har ansøger også anvendt mortalitetsraten for den generelle danske befolkning til at estimere patienternes overlevelse.

Medicinrådets vurdering af ansøgers model

Medicinrådet finder, at antagelserne vedrørende behandlingsophør og mortalitet er meget usikre, da det er baseret på et begrænset datagrundlag. På baggrund heraf udføres der en række følsomhedsanalyser, for at belyse hvordan disse antagelser påvirker resultaterne. Estimaterne, som indgår i hovedanalysen, er præsenteret i Tabel 4-1. På baggrund af de anvendte estimater bliver den gennemsnitlige behandlingstid med fenfluramin i tillæg til standardbehandling, der indeholder stiripentol 8,6 år.

Tabel 4-1. Behandlingsophør og mortalitetsrate for fenfluramin og placebo anvendt i modellen

	Fenfluramin	Placebo
Andel, der ophører behandling i studiet	16,3 %	6,8 %
Behandlingsophør pr. cyklus, cyklus 1-4	4,3 %	1,8 %
Behandlingsophør pr. cyklus, cyklus > 4	[redacted] %	[redacted] %
Generel mortalitet (dødsfald pr. 1.000 personår)	8,22	15,84
SUDEP-mortalitet (dødsfald pr. 1.000 personår)	1,7	9,32

	Fenfluramin	Placebo
Pr. cyklus mortalitetsrisiko	0,06 %	0,12 %

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men udfører en række følsomhedsanalyser, der undersøger betydningen af antagelserne vedr. behandlingsophør og mortalitet.

4.1.2 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 10 år, men der er mulighed for at vælge en længere tidshorisont, der går op til 91 år, hvilket ansøger argumenterer vil være svarende til livstid, hvis patienterne gennemsnitligt er 9 år, når de påbegynder behandlingen med fenfluramin.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 % pr. år. Omkostninger, der ligger efter år 35, bliver diskonteret med en rate på 2,5 % pr. år, og efter 71 år diskonteres de med 1,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådets fagudvalg forventer, at behandlingen med fenfluramin vil være livslang, såfremt behandlingen er effektiv. På baggrund af dette ændres analysens tidshorisont til 91 år, således at analysen opfanger alle forskelle i omkostninger mellem behandlingen med fenfluramin og placebo. En tidshorisont på 91 år betyder ikke, at alle patienter vil være i behandling så længe, men at alle patienter inden for denne periode vil have ophørt behandlingen.

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv, men ændrer tidshorisonten til at være livslang.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af fenfluramin sammenlignet med placebo. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger. Ansøger argumenterer for, at der vil være et tværsektorielt og kommunalt ressourceforbrug for patienter med Dravet syndrom, men har ikke inkluderet disse omkostninger i den indsendte analyse, da de ikke har fundet data, der kan understøtte, at der skulle være en forskel mellem fenfluramin og placebo.

Omkostningerne er i modellen cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i stadiet.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP).

Ansøger har inkluderet omkostninger til fenfluramin, anfaldsbrydende medicin og stiripentol. Der er ikke inkluderet omkostninger for valproat og clobazam, da det antages, at der ikke vil være forskel i anvendelsen af disse mellem fenfluramin- og placeboarmen.

Patienter, der modtager stiripentol samtidig med fenfluramin, anbefales en opstartsdosis på 0,1 mg/kg to gange dagligt. Efter en uge kan dosis øges til 0,2 mg/kg to gange dagligt, som er den anbefalede vedligeholdelsesdosis. Den maksimale daglige dosis må ikke overstige 17 mg svarende til 4 ml to gange dagligt.

Ansøger antager, at der ikke vil være lægemiddelspild ved behandlingen med fenfluramin, da flasker indeholdende fenfluramin udleveres til patienter eller pårørende, der trækker den mængde, der skal anvendes, op i en sprøjte, i forbindelse med administration af fenfluramin.

På baggrund af input fra en klinisk ekspert, antager ansøger, at der vil blive anvendt rektal diazepam eller bukkal midazolam som anfaldsbrydende medicin. Den anvendte dosis stammer fra pro.medicin.dk, hvor den er angivet som en dosis for børn, der oplever konvulsiv status epilepticus. Den anvendte dosis for midazolam er beregnet som den gennemsnitlige dosis angivet for børn i alderen 2-13 måneder, 1-5 år og 5-10 år på pro.medicin.dk.

Ansøger anvender studiet af Nabbout et al. fra 2020 til at estimere gennemsnitligt antal dage, patienterne modtager anfaldsbrydende medicin. For patienterne i fenfluraminarmen estimeres 1,4 dage at være den gennemsnitlige tid, mens patienterne i placeboarmen estimeres at modtage anfaldsbrydende medicin i gennemsnitligt 1,2 dage.

Patienterne modtog samtidig behandling med stiripentol, og ansøger antager, at der for hver modelcyklus (28 dage) bliver brugt 42.588 mg stiripentol pr. patient.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 4-2.

Tabel 4-2. Anvendte lægemiddelpriser, SAIP (januar 2022)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Fenfluramin	792 mg	1 stk.	[redacted]	Amgros
Stiripentol	250 mg	60 stk.	[redacted]	Amgros
Diazepam	5 mg	5 stk.	[redacted]	Amgros

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Midazolam	5 mg	4 stk.	[redacted]	Amgros

Medicinrådets fagudvalg er enige i, at der ikke forventes at være forskel i anvendelsen af valproat og clobazam mellem patienter, der modtager fenfluramin og stiripentol sammen, og de patienter, der modtager stiripentol alene. Skulle der være en forskel, vurderes det at have minimal betydning for analysens resultat, da valproat og clobazam udgør en meget begrænset omkostning.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Ansøger har inkluderet omkostninger til monitorering, akutte indlæggelser, bivirkninger og til ekkokardiografi.

Administrationsomkostninger

Både fenfluramin og stiripentol er administreret oralt, og behandlingen kan derfor ske uden for hospitalet. Derfor er der ikke inkluderet omkostninger til administration af lægemidler i analysen.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
I forbindelse med opstart af behandlingen forventer fagudvalget, at dette vil ske ambulant hvorved det er forbundet med omkostninger til et enkelt ambulant besøg. Set i forhold til de høje lægemiddelomkostninger og den livslange behandling vurderes det dog at have minimal indflydelse på analysens resultat, og derfor accepteres ansøgers tilgang.

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger.

Monitoreringsomkostning

Ansøger har konsulteret en klinisk ekspert for at kortlægge behandlingen af patienter med Dravet syndrom. På baggrund af udsagn fra den kliniske ekspert antager ansøger, at patienterne, i behandling med fenfluramin i tillæg til standardbehandling og standardbehandling alene, i gennemsnit vil have 2,5 ambulante monitoreringsbesøg om året. Derudover antages patienterne at have 6 telefoniske konsultationer om året.

I forbindelse med behandling med Fenfluramin mod fedme, har der tidligere været observeret en øget risiko for valvulær hjertesygdom, dog ved en højere dosis end indiceret til Dravet syndrom. Derfor angives det i SmPC'et at det er nødvendigt med hjertemonitorering ved hjælp af ekkokardiografi. Baseret på SmPC'et antages det, at ekkokardiografi vil blive foretaget hver 6. måned i de første to behandlingsår og derefter årligt, så længe behandlingen med fenfluramin fortsætter. Til at estimere omkostningen i forbindelse med ekkokardiografi anvendes DRG-taksten 01MA09, Anfaldssygdomme og hovedpine, pat. 1-17. år, på 3.826 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Fagudvalget mener, at antagelserne vedrørende monitorering er realistiske. Medicinrådet mener ikke, at den valgte DRG-takst til prissætning af ekkokardiografi er passende og udskifter denne med taksten 05PR05, Kardiologisk undersøgelse, udvidet på 1.910 DKK.

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men ændrer DRG-taksten for ekkokardiografi.

Omkostninger til anfald

Dravet syndrom er karakteriseret ved hyppige og svære konvulsive anfald, og derfor inkluderer ansøger omkostninger til hospitalsbehandling i forbindelse med disse anfald. Ikke alle anfald medfører hospitalskontakt eller indlæggelse, men nogle af anfaldene vil medføre akut indlæggelse på hospitalet. Ansøger har anvendt ikke-offentliggjort data til at estimere det gennemsnitlige antal indlæggelsesdage pr. cyklus. Ud over gennemsnitligt antal indlæggelsesdage anvender ansøger også et studie af Lagae et al., et studie af Nabbout et al. og data on file fra studie 1504 [7,8] til at estimere andelen af anfald, der fører til hospitalsindlæggelse, og gennemsnitligt antal dage med anfald pr. cyklus.

Til at prissætte en sengedag anvender ansøger en enhedsomkostning på 8.876 DKK fra Rigshospitalets takstkatalog fra 2017.

Medicinrådets vurdering af ansøgers antagelser vedr. omkostninger til anfald
Fagudvalget er blevet adspurgt, om ansøgers antagelser omkring anfald og indlæggelse i forbindelse hermed stemmer overens med deres oplevelse fra klinisk praksis. Fagudvalget vurderer, at det estimerede antal dage med anfald om måneden passer meget godt med deres oplevelse, men at antal indlæggelsesdage er lidt højt sat. De anvendte estimater i modellen er vist i Tabel 4-3. På baggrund heraf vælger Medicinrådet at udføre en følsomhedsanalyse, hvor antal indlæggelsesdage pr. cyklus reduceres med 20 %.

Ansøger anvender en takst fra Rigshospitalets takstkatalog fra 2017 til at estimere prisen for en sengedag. Medicinrådet vælger at skifte denne ud med DRG-2022-taksten 01MA09, Anfaldssygdomme og hovedpine, pat. 1-17 år på 3.826 DKK.

Tabel 4-3. Gennemsnitligt antal anfald og indlæggelsesdage pr. cyklus

	Fenfluramin	Placebo
Gennemsnitligt antal dage med anfald pr. cyklus	6,4	9,0
Andel af dage med anfald, der medfører indlæggelse	19 %	19 %
Indlæggelsesdage pr. cyklus	1,2	1,7

Medicinrådet accepterer ansøgers tilgang til estimering af gennemsnitligt antal anfald og indlæggelsesdage, men udfører en følsomhedsanalyse, der undersøger, hvilken betydning det har for resultatet, hvis det gennemsnitlige antal indlæggelsesdage pr. cyklus reduceres. Derudover ændres den anvendte enhedsomkostning til prissætning af en sengedag til at være baseret på DRG-taksten 01MA09.

Bivirkningsomkostninger

Ansøger beskriver i sin ansøgning, at i studie 1504 oplevede 97,7 % af patienterne i fenfluraminarmen behandlingsrelaterede bivirkninger, til sammenligning var det 95,5 % af patienterne i placeboarmen.

Ansøger argumenterer, at disse bivirkninger, ifølge deres kliniske ekspert, typisk ikke vil medføre en yderligere omkostning, da de håndteres ved de allerede planlagte monitoreringsbesøg og telefonkonsultationer. Derfor har ansøger ikke inkluderet omkostninger til håndtering af behandlingsrelaterede bivirkninger i analysen.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger.

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af hospitalsbesøg og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 3,52 DKK pr. km, jf. Medicinrådets værdisætning af enhedsomkostninger.

Ansøger har antaget, at patienterne i gennemsnit vil have 50 km til hospitalet, hvilket giver en distance på 100 km pr. hospitalsbesøg. Ansøger antager derudover, at køreturen vil tage to timer.

Ansøger estimerer, at patienter i behandling med fenfluramin i gennemsnit vil have 1,4 hospitalsbesøg pr. cyklus. Patienter i placeboarmen estimeres at have 1,9 hospitalsbesøg pr. cyklus. Forskellen i antal hospitalsbesøg skyldes, at patienter i behandling med fenfluramin antages at have færre anfald. Ansøger antager, at et hospitalsbesøg inklusive transporttid vil tage 9 timer i gennemsnit.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger

Da behandlingen af patienter med Dravet Syndrom udelukkende foregår ét sted i Danmark, vurderes det at være rimeligt at antage en gennemsnitlig længde på 50 km til hospitalet i forbindelse med monitoreringsbesøg. Ved anfald vil patienterne blive behandlet på det nærmeste hospital, derfor vurderes det at 50 km til hospitalet vil være en overestimering. Medicinrådet ændrer derfor denne afstand til at være 14 km.

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger, men ændre afstanden til hospitalet, i forbindelse med anfaldsbehandling, til at være 14 km.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

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

Tabel 4-4. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Følsomhedsanalyse 1 – Tidshorisonten	To scenarier, et hvor tidshorisonten ændres til 1 år, og et hvor den ændres til 91 år.
Følsomhedsanalyse 2 – Fenfluramindosis	To scenarier, et hvor fenfluramindosis reduceres med 20 %, og et hvor den øges med 20 %.
Følsomhedsanalyse 3 – Risiko for død	To scenarier, et hvor risiko for død reduceres med 20 %, og et hvor den øges med 20 %, for både intervention og komparator.
Følsomhedsanalyse 4 – Sandsynlighed for behandlingsophør	To scenarier, et hvor risiko for behandlingsophør reduceres med 20 %, og et hvor det øges med 20 %.
Følsomhedsanalyse 5 – Antal hospitalsbesøg	To scenarier, et hvor antal hospitalsbesøg pr. cyklus reduceres med 20 %, og et hvor det øges med 20 %, for både intervention og komparator.
Følsomhedsanalyse 6 – Antal indlæggelsesdage	To scenarier, et hvor antal indlæggelsesdage pr. cyklus reduceres med 20 %, og et hvor det øges med 20 %, for både intervention og komparator.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser

Ansøger har udført en række følsomhedsanalyser, men da alle analyserne er baseret på AIP og andre DRG-takster, end de Medicinrådet mener bør anvendes, vil resultaterne ikke blive præsenteret. Medicinrådet udfører selv en række følsomhedsanalyser, der undersøger betydningen af at ændre på antagelserne omkring behandlingsophør og mortalitet.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser, men vælger selv at udføre en række følsomhedsanalyser.

4.4 Opsummering af basisantagelser

I Tabel 4-5 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 4-5. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	10 år	91 år
Inkluderede omkostninger	Lægemiddelomkostninger Monitoreringsomkostninger Patientomkostninger	Lægemiddelomkostninger Monitoreringsomkostninger Patientomkostninger
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse, med undtagelse af de væsentligste ændringer, der fremgår af Tabel 4-5.

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

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 2,2 mio. DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 5-1.

Tabel 5-1. Resultatet af Medicinrådets hovedanalyse ved sammenligning med stiripentol, DKK, diskonterede tal

	Fenfluramin + Stiripentol	Stiripentol	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	1.975.517	2.020.142	-44.624
Patientomkostninger	904.874	929.029	-24.155
Totale omkostninger	[redacted]	[redacted]	[redacted]

De inkrementelle omkostninger er næsten udelukkende drevet af prisen på fenfluramin.

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser, som i Medicinrådets hovedanalyse for meromkostninger, har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 5-2.

Tabel 5-2. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Reduktion af antal indlæggelsesdage pr. cyklus	[redacted]
Øget behandlingsophør for fenfluramin (+20 %)	[redacted]
Reduceret behandlingsophør for fenfluramin (-20 %)	[redacted]
Ens mortalitet for fenfluramin- og placeboarmen	[redacted]

6. Budgetkonsekvenser

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

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

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

6.1 Estimat af patientantal og markedsandel

Ansøger har antaget, at der vil være ca. 27,5 patienter, der vil være kandidater til at få fenfluramin i tillæg til standardbehandling indeholdende stiripentol. De efterfølgende år antager ansøger, at der vil være en ny patient hvert år.

Ansøger antager, at ved en anbefaling vil alle patienter opstarte behandlingen fra år 1, mens ingen patienter vil blive behandlet, hvis ikke fenfluramin bliver anbefalet.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse

Fagudvalget er blevet konsulteret i forhold til patientantal, hvis fenfluramin anbefales som mulig standardbehandling, og hvis ikke fenfluramin anbefales. Fagudvalget estimerer, at 55 patienter pr. år forventes at være kandidater til behandling med fenfluramin og at mindst halvdelen af patienterne samtidig, vil modtage behandling med stiripentol, se Tabel 6-1.

Tabel 6-1. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Fenfluramin + stiripentol	28	2	2	2	2
Stiripentol	0	0	0	0	0
			Anbefales ikke		
Fenfluramin + stiripentol	0	0	0	0	0
Stiripentol	28	2	2	2	2

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet er ændret til 28 patienter i første år og 2 nye patienter pr. år efterfølgende.

6.2 Medicinrådets budgetkonsekvensanalyse

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

- 28 prævalente patienter
- 2 incidente patienter pr. år

Medicinrådet estimerer, at en anbefaling af fenfluramin vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i Tabel 6-2.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 6,8 mio. DKK i år 5.

Tabel 6-2. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

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

7. Diskussion

Behandling med fenfluramin i tillæg til standardbehandling der inkluderer stiripentol er forbundet med inkrementelle omkostninger på ca. [redacted] DKK sammenlignet med behandling med standardbehandling alene. De inkrementelle omkostninger er næsten udelukkende drevet af prisen for fenfluramin.

Hvis mortaliteten for patienter i behandling med fenfluramin i tillæg til standardbehandling og patienter i standardbehandling alene antages at være ens, [redacted] de inkrementelle omkostninger med ca. [redacted] DKK

Budgetkonsekvenserne ved anvendelse af fenfluramin estimeres til at være ca. [redacted]. DKK i 5. år efter en anbefaling. Budgetkonsekvensernes begrænsede størrelse, i forhold til den gennemsnitlige omkostning per patient, skyldes de relativt få nye patienter, der forventes at komme i behandling årligt. Samtidig dækker den gennemsnitlige omkostning per patient over en livslang tidshorisont, mens budgetkonsekvenserne kun medtager omkostninger for de første 5 år.

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04/03-2022
MGK/CAF/SNI

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.03.2022
Leverandør	Zogenix
Lægemiddel	Fenfluramin (Fintepla)
Ansøgt indikation	Behandling af krampeanfald forbundet med Dravet syndrom som tillægsterapi til andre antiepileptiske lægemidler hos patienter i alderen 2 år og op.

Forhandlingsresultat

Amgros har opnået følgende pris på fenfluramin:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Fenfluramin	132 mg oral opløsning	60 ml	9.125,56	[redacted]	[redacted]
Fenfluramin	264 mg oral opløsning	120 ml	18.251,12	[redacted]	[redacted]
Fenfluramin	792 mg oral opløsning	360 ml	54.753,36	[redacted]	[redacted]

Prisen er **ikke** betinget af Medicinrådets anbefaling.

Amgros har forhandlet en aftale med leverandøren. Leverandøren har mulighed for at sætte prisen yderligere ned i hele aftaleperioden.

[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på området. [redacted]

Tabel 2: Årlige lægemiddelpriser for fenfluramin

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Børn*					
Fenfluramin *(opstartsår)*	Uge 1: 0,1 mg/kg 2 gange dagligt	792 mg/360 ml (2,2 mg/ml)	[redacted]	[redacted]	[redacted]

	Uge 2 - 52: 0,2 mg/kg 2 gange dagligt				
Fenfluramin *(vedligeholdelsesår)*	0,2 mg/kg 2 gange dagligt	792 mg/360 ml (2,2 mg/ml)	[redacted]	[redacted]	[redacted]
Voksne**					
Fenfluramin	17 mg (8,6 mg 2 gange dagligt)	792 mg/360 ml (2,2 mg/ml)	[redacted]	[redacted]	[redacted]

*Børn gennemsnitsvægt: 33,8 kg
**Voksne: maksimum dosis 17 mg/kg

Status fra andre lande

Norge: Under vurdering[1].

[redacted]

England: Under vurdering[2].

Konklusion

Det er Amgros vurdering, at der er opnået den bedst mulige pris på fenfluramin, som det er muligt at opnå på nuværende tidspunkt.

[1] https://nyemetoder.no/metoder/fenfluramin
[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10373

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1st March 2022

Danish medicines council
Dampfærgevej 21-23, 3. sal
2100 København Ø

Dear Mette,

Thank you for sending the draft assessment report for fenfluramine (Fintepla) – an add on treatment for patients with Dravet syndrome. As requested, please see our response below:

Clinical question 1
We are in alignment with the judgement of the expert committee that due to differences in study designs (including study definitions of convulsive seizures), as well as differences in concomitant treatment with anti-seizure medicines between the studies, it is not feasible to determine the comparative value of fenfluramine versus stiripentol (STP) as an add-on therapy in patients with Dravet syndrome treated with valproate and/or clobazam in the first line.

We would also like to emphasize that we do not anticipate that fenfluramine, as a newly licensed add-on therapy to standard of care (SoC) anti-epileptic drugs (AEDs), will routinely be used before STP has been tried in patients for whom STP would be considered to be an eligible treatment option. Therefore, concordant with the clinical expert advice received, Zogenix also considers and proposes that the positioning of fenfluramine in routine clinical practice, is as an add-on to SoC AEDs for use:

I. without concomitant STP in patients for whom **STP is not considered to be an eligible treatment option** (i.e., in a subpopulation of clinical question 1).
   - Please note that in clinical practice, the vast majority of patients will have experienced STP earlier in their treatment pathway and so its use at this positioning in the treatment sequence is anticipated to be negligible.

or

II. Without concomitant STP in patients who have **previously tried STP** (i.e., in a subpopulation of clinical question 1, which we refer to as clinical question 1a),

- Please note that in clinical practice, we anticipate <10% of STP-experienced patients will receive fenfluramine without STP.

or

in addition to STP in patients requiring further seizure control (as in clinical question 2).
-Please note that in clinical practice, we anticipate the majority (~90%) of STP-experienced patients will receive fenfluramine with STP.

Clinical question 2

We agree with the overall assessment of the expert committee, that for patients with Dravet syndrome who receive SoC AEDs which includes stiripentol, the addition of fenfluramine provides 'moderate added' value compared to SoC AEDs that includes STP alone.

We would like to highlight the expert committee's emphasis that fenfluramine when added to SoC which includes STP, has a 'moderate added value' (compared to placebo) for the critical effect target of convulsive seizures, as assessed against two metrics outlined in the Danish Medicines Council protocol. Furthermore, fenfluramine carries 'high added value' in one of the two key metrics (proportion of patients achieving at least a 50% reduction in the number of convulsive seizures). In addition, the point estimates for both metrics are significantly above the minimum clinically relevant difference.

We accept that the data, according to the Danish Medicines Council's methods, does not allow the expert committee to categorize the value of fenfluramine added to SoC, when compared to SoC alone, in the other metrics requested as subpopulation analyses in the assessment protocol, such as reduced rescue medication use and improvement in QoL.

Uncertainty and Quality of evidence

Whilst the overall aims of treatment in Dravet syndrome are ultimately to enable patients to live a life free from seizures (or "seizure freedom"), this is unfortunately rarely achievable for many patients and their families. Most patients experience uncontrolled daily seizures (evident by the patients enrolled in the phase III trials), and have exhausted the limited number of available treatment options (e.g. clinical question 2). It is therefore considered that a critical treatment goal for patients is to achieve a significant reduction in their seizure frequency, that increases seizures-free days, and that in turn provides a meaningful improvement in quality of life for the patients and their caregivers.

It is also recognised that since seizures are spontaneous events, and in actual clinical practice a patient's treatment is individually tailored and based upon the priority needs of the patient and their families at the time; there is inherent variation in the underlying SoC

treatments between patients, alongside a general heterogeneity in a studied cohort over time. Collectively, these clinical characteristics of the studied population create a degree of uncertainty in collected data. Consequently, the assessment has suggested that the quality of evidence has been assessed as very low according to the applied methodology. This should however be pragmatically considered in the context of a rare disease with limited treatment options. The substantive evidence-base for fenfluramine comprising two randomised control trials, open-label extension studies and real-world data, are arguably the largest and most robust that underpin a licensed treatment for patients with Dravet syndrome. In addition, Danish patients have been included in the fenfluramine clinical program and are currently in the open-label extension studies and are continuing to receive treatment with fenfluramine.

Considering the constraints of an orphan disease, we believe that the robust trial designs; significant magnitude of benefits for the protocol-assigned and Regulatory Agency required key metrics; and the long term follow up data make up a robust evidence package and alleviate some of these uncertainties.

Economic analysis

The time horizon in the economic models submitted by Zogenix was set to a default of 10 years. In the review process, assessors proposed to use a time horizon of analyses that extended to 90 years. We would like to emphasize that Fenfluramine is covered by orphan drug designation marketing exclusivity (10 years from granting of the MAA). This expires in 2030 after which the price of fenfluramine may decrease dramatically. Therefore, it is considered that a time horizon of 8 years (2022 to 2030) is the most appropriate timeframe when projecting any life-time cost calculations at the current drug price.

Fenfluramine in Denmark

Since licensing, fenfluramine, has demonstrated a clinically meaningful difference to patients and their families throughout Europe and internationally. In Denmark, due to increasing demand from clinicians and patients alongside delays in the assessment process we have set up a patient access program (ZAP - Zogenix access program). This has allowed some patients with high unmet need an early access to fenfluramine treatment. Currently there are 11 patients receiving fenfluramine on the ZAP. Additionally, there are 8 clinical trial patients currently continuing to receive treatment in an open label extension study.

Finally, we would like to thank the Committee, Assessors, and clinical experts for their time in reviewing fenfluramine as a treatment option for Danish patients with Dravet syndrome -

a much-needed therapy option for a small number of complex and highly impaired patients. We hope the committee may enable the benefits of fenfluramine be added to the routine treatment options available for patients in Denmark, so as to reduce their seizure burden, improve their quality of life, and to reduce the daily burden for their caregivers.

Your sincerely,

Mamuka Teneishvili
Director Market access Europe
Zogenix International ltd.

Medicinrådet

Medicinrådets vurdering vedrørende fenfluramin til behandling af Dravet syndrom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om vurderingsrapporten

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

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

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

Dokumentoplysninger	
Godkendelsesdato	23. februar 2022
Dokumentnummer	135654
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 24. februar 2022

1. Medicinrådets konklusion

Medicinrådet har vurderet fenfluramin som tillægsbehandling til to grupper af patienter med Dravet syndrom, der får standardbehandling med clobazam og/eller valproat:

- Medicinrådet vurderer, at patienter, der får fenfluramin som tillægsbehandling, ikke ser ud til at have dårligere effekt eller sikkerhed end patienter, der får stiripentol som tillægsbehandling. Den samlede værdi af fenfluramin sammenlignet med stiripentol, begge som tillægsbehandlinger, kan dog ikke kategoriseres efter Medicinrådets metoder. Det skyldes, at ansøger har indsendt data for to studier, som er så forskellige, at det ikke er muligt at foretage en sammenlignende analyse af data for lægemidlernes effekt eller sikkerhed.
- Medicinrådet vurderer, at patienter, der bliver behandlet med clobazam og/eller valproat samt stiripentol og derudover får tillægsbehandling med fenfluramin, oplever færre epileptiske anfald og dermed opnår en bedre effekt end patienter, der ikke får tillægsbehandling med fenfluramin. Efter Medicinrådets metoder har behandlingen derfor en moderat merværdi i den undersøgte population.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

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

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

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

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

2. Begreber og forkortelser

ASM:	Antiepileptisk lægemiddel (*anti-seizure medication*)
CI:	Konfidensinterval
CSF:	Anfaldsfrekvens (*convulsive seizure frequency*)
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
Gns:	Gennemsnit
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HR:	*Hazard ratio*
IA:	Ikke angivet
ITT:	*Intention to treat*
mITT:	*Modified intention to treat*
OR:	*Odds ratio*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP:	*Per Protocol*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
SD:	Standardafvigelse
SMD:	*Standardized Mean Difference*
SMEI:	*Severe myoclonic epilepsy in infancy*
SUDEP:	*Sudden unexpected death in epilepsy*

3. Introduktion

Formålet med Medicinrådets vurdering af fenfluramin til Dravet syndrom er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Zogenix. Medicinrådet modtog ansøgningen den 9. december 2021.

De kliniske spørgsmål er:

1. Hvilken værdi har fenfluramin sammenlignet med stiripentol for patienter med Dravet syndrom i alderen 2 år og op, som er i en behandlingskombination, der ikke omfatter stiripentol?
2. Hvilken værdi har fenfluramin sammenlignet med placebo for patienter med Dravet syndrom i alderen 2 år og op, som er i en behandlingskombination, der omfatter stiripentol?

3.1 Dravet syndrom

Dravet syndrom er en sjælden, alvorlig epilepsiform, der typisk debuterer inden for det første leveår. Oftest skyldes tilstanden en genmutation i et natriumkanal-gen (*SCN1A*), men hos omkring 10 % af tilfældene er det ikke muligt at finde frem til en genetisk årsag.

Ved debut er anfaldene ofte fremprovokeret af temperaturstigninger og kan både begynde i en afgrænset del af hjernen (fokale anfald) eller i begge hjernehalvdele (generaliserede anfald) [1–3]. Dravet syndrom er karakteriseret ved hyppige, ofte daglige anfald. Anfaldstyperne kan være meget forskellige, men en stor del af anfaldene vil være konvulsive, som enten viser sig ved: *i)* trækninger og rykninger (kloniske anfald), som enten udspringer fra en afgrænset del af hjernen eller fra begge hjernehalvdele, og dels *ii)* en stivhed i kroppen (toniske anfald) og trækninger og rykninger (klonisk fase), også kaldet tonisk-kloniske anfald. Disse anfaldstyper defineres her samlet som konvulsive anfald og kan opstå i mange kombinationer. Anfaldene kan være langvarige (over fem minutter) med behov for anvendelse af anfaldsbrydende medicin. Hyppigheden af anfald er størst hos børn under 5 år og aftager med alderen. Med nuværende behandling ses der hos 0-18-årige typisk 20-50 epileptiske anfald månedligt, mens voksne patienter oftest oplever korte, natlige anfald med et spænd i hyppighed fra flere anfald dagligt til månedlige anfald. For alle aldersgrupper ses der dermed stor individuel variation i anfaldshyppigheden.

Dravet syndrom er forbundet med væsentlig overdødelighed bl.a. grundet risikoen for pludselig uventet død (*Sudden Unexpected Death in Epilepsy* (SUDEP)), ulykker ifm. anfald og status epilepticus, som er en potentielt livstruende tilstand med vedvarende anfald [1,2,4]. De fleste dødsfald sker før 10 års-alderen. I et kohortestudie af 100 patienter med Dravet syndrom blev der rapporteret en 15 % risiko for død inden for 10 år efter diagnose [5]. Patienter har oftest forskellige ledsagetilstande, bl.a. forringet finmotorik, autismelignende adfærd, indlæringsvanskeligheder, sprogforstyrrelser samt

mental retardering i varierende grad. Barnet og dets familie har et væsentligt støttebehov, og kun et fåtal af voksne patienter kan klare sig uafhængigt af andre [4].

Det anslås, at der i Danmark er ca. 45.000-55.000 patienter med epilepsi på tværs af alle epilepsiformer. Patienter med Dravet syndrom udgør en lille del af denne patientpopulation. Fagudvalget vurderer, at der i Danmark er ca. 50 børn og unge samt 30-40 voksne diagnosticeret med Dravet syndrom. Disse patienter behandles overvejende på Epilepsihospitalet Filadelfia. Et dansk epidemiologisk studie fra 2015 estimerede, at den årlige forekomst af Dravet syndrom er 1 ud af 22.000 nyfødte, hvilket svarer til, at der årligt bliver født 2-3 børn med Dravet syndrom i Danmark [3].

3.2 Fenfluramin

Fenfluramin er indiceret til behandling af krampeanfald forbundet med Dravet syndrom som tillægsterapi til andre antiepileptiske lægemidler hos patienter i alderen 2 år og op.

Lægemidlet administreres peroralt to gange dagligt. Døgndosis er ved opstart af behandling 0,2 mg/kg og kan justeres i ugentlige intervaller.

Fenfluramin er et serotoninfrigivende stof, som virker ved at stimulere serotoninreceptorer i hjernen. Det vurderes, at denne mekanisme bidrager til, at fenfluramin nedsætter hyppigheden af anfald. Den præcise virkningsmekanisme for fenfluramin ved Dravet syndrom kendes dog ikke.

Fenfluramin er substrat for en række CYP450-enzymer, og koncentrationen af fenfluramin kan derfor påvirkes, hvis virkningen af disse enzymer hæmmes (inhiberes) eller øges (induceres). Lægemidlet stiripentol, som også anvendes til behandling af Dravet syndrom, hæmmer CYP450-enzymer, og samtidig behandling med stiripentol hæmmer omsætningen af fenfluramin. Særligt hvis stiripentol gives som kombinationsbehandling med valproat og clobazam, kan det medføre en stigning i koncentrationen af fenfluramin hos patienten. Behandlingen med fenfluramin skal derfor tilpasses, afhængigt af om patienten modtager samtidig behandling med stiripentol. For patienter, som *ikke* er i samtidig behandling med stiripentol, er den maksimale døgndosis 0,7 mg/kg og højeste døgndosis 26 mg (fordelt på to daglige doseringer). For patienter i samtidig behandling med stiripentol er den maximale døgndosis 0,4 mg/kg og højeste døgndosis 17 mg (fordelt på to daglige doseringer).

Fenfluramin fik i januar 2014 *orphan drug designation* status hos EMA, hvilket bl.a. reducerer kravene til antallet af deltagere i de kliniske forsøg. Fenfluramin har tidligere været markedsført som et anoreksikum, men blev i 1997 taget af markedet grundet mistanke om øget risiko for forhøjet blodtryk i lungekredsløbet samt hjerteklapsygdom. De anvendte doser ved overvægt var 60-120 mg/dag. EMA godkendte i december 2020 fenfluramin til behandling af Dravet syndrom. EMAs produktresumé for fenfluramin til behandling af Dravet syndrom angiver aorta- eller mitralklapsygdom samt pulmonal arteriel hypertension (forhøjet blodtryk i lungekredsløbet) som kontraindikationer, og det er påkrævet at overvåge hjertefunktionen ved hjælp af ekkokardiografi før og under behandlingen [6].

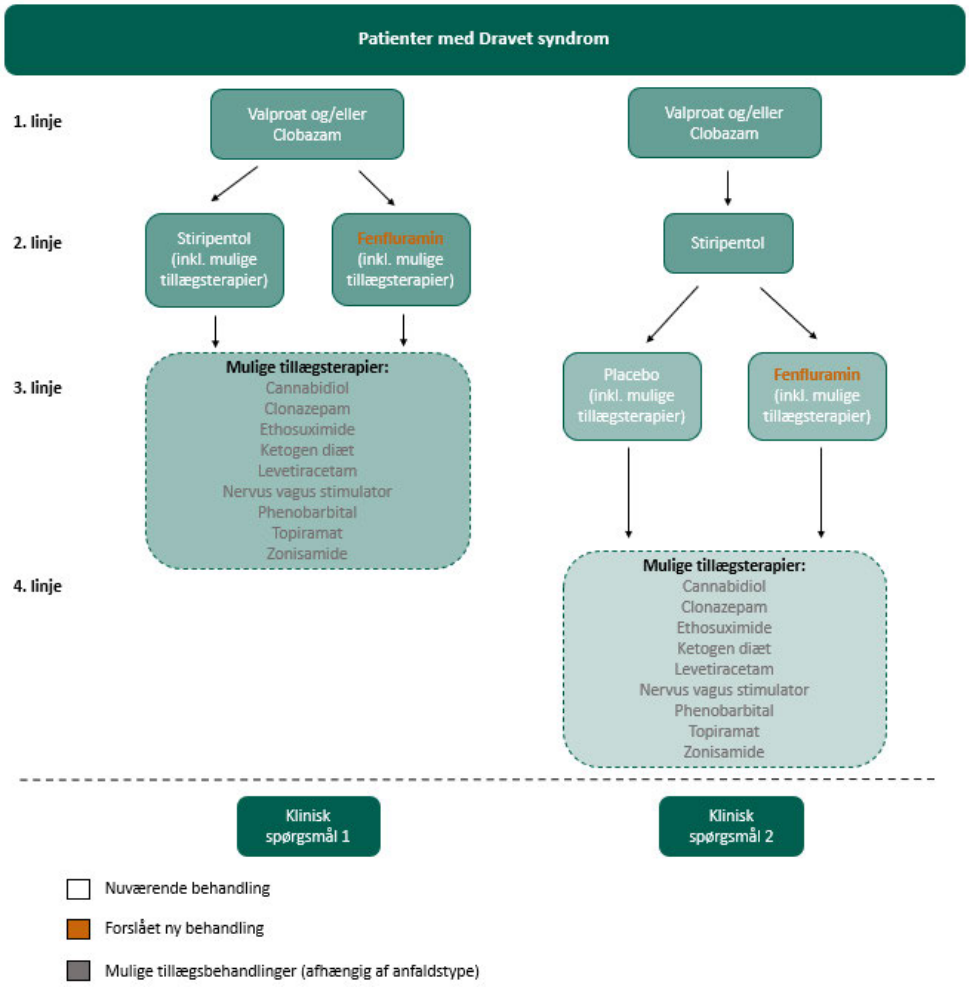
3.3 Nuværende behandling

Behandlingsmålet er at reducere antallet af anfald og ideelt set at opnå anfaldsfrihed. Sidstnævnte er dog stort set aldrig muligt med nuværende behandlingsmuligheder, og tilstanden er med nuværende behandling behandlingsresistent. I tillæg til den farmakologiske antiepileptiske behandling kan ketogen diæt forsøges ved Dravet syndrom. Herudover behandles ledsagetilstande, såsom autismelignende adfærd og forringet fin- og grovmotorik, både med og uden lægemidler.

Den antiepileptiske behandling består oftest af valproat og/eller clobazam evt. med tillæg af stiripentol eller endnu en tillægsterapi såsom cannabidiol eller topiramat. Præparaterne er forbundet med bivirkninger såsom hovedpine, sedation, svimmelhed, gastrointestinale gener m.fl. samt sjældnere bivirkninger såsom alvorlige hudreaktioner og leversvigt. Antiepileptisk behandling af Dravet syndrom er i udgangspunktet livslang, men kan stoppes, hvis der ikke opnås effekt eller efter ønske fra patient og/eller pårørende.

Hvis der opstår længerevarende anfald, som kræver anfaldsbrydende medicin, såkaldt *rescue medication*, kan der behandles med benzodiazepiner.

Figur 3-1 illustrerer fagudvalgets vurdering af fenfluramins mulige indplaceringer i den nuværende behandlingstilgang og skitserer, hvordan de kliniske spørgsmål adresserer hver af de mulige indplaceringer.



Figur 3-1. Mulig indplacering af fenfluramin i behandlingsrækkefølgen for patienter med Dravet syndrom. Valproat og/eller clobazam er 1. linjebehandling. Herefter kan enten stiripentol eller fenfluramin anvendes som tillægsterapi i 2. linje, efterfulgt af en række øvrige mulige tillægsterapier i 3. linje. Hvis stiripentol anvendes som tillægsterapi i 2. linje, kan fenfluramin anvendes som tillægsterapi i 3. linje efterfulgt af en række øvrige mulige tillægsterapier i 4. linje.

Fagudvalget vurderer, at ca. 55 ud af de ca. 85 patienter med Dravet syndrom i Danmark oplever utilstrækkeligt respons eller uacceptable bivirkninger med eksisterende behandling (clobazam, valproat og eventuelt stiripentol). Disse patienter vurderes derfor at have behov for supplerende behandling og vil således være kandidater til behandling med fenfluramin. Fagudvalget vurderer derudover, at op imod 90 % af patienter med Dravet syndrom har afprøvet behandling med stiripentol, og at mindst halvdelen af patienterne samtidig modtager behandling med stiripentol.

4. Metode

Medicinrådets protokol for vurdering vedrørende fenfluramin til behandling af Dravet syndrom beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Det kliniske spørgsmål er:

Hvilken værdi har fenfluramin sammenlignet med stiripentol for patienter med Dravet syndrom i alderen 2 år og op, som er i en behandlingskombination, der ikke omfatter stiripentol?

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt to fuldtekstartikler fra to kliniske studier, der stemmer overens med in- og eksklusionskriterierne fra Medicinrådets protokol. Artiklerne omhandler ét klinisk studie for fenfluramin (Study 1) [7] og ét klinisk studie for stiripentol (STICLO-France) [8]. Ansøger har derudover anvendt *data on file* fra Study 1 til besvarelsen af det kliniske spørgsmål, da data for effektmålene gennemsnitlig procentuel ændring i antallet af konvulsive anfald samt alvorlige uønskede hændelser ikke er rapporteret i den publicerede artikel [7]. Desuden indgår EMAs EPAR og produktresuméer for fenfluramin [6,9] og stiripentol [10,11].

Tabel 5-1. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Lagae L et al. 2019 [7] samt *data on file*	Study 1 (1501 og 1502)	NCT02682927 og NCT02826863	Børn og unge med Dravet syndrom, der ikke modtog samtidig behandling med stiripentol	Fenfluramin 0,7 mg/kg/dag vs. placebo

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Chiron C et al. 2000 [8]	STICLO-France	Studiet er ikke registeret på clincialtrials.gov	Patienter med Dravet syndrom*	Stiripentol 50 - 100 mg/kg/dag vs. placebo

*I studiet af Chiron et al. [8] blev inkluderet patienter med *severe myoclonic epilepsy in infancy* (SMEI), hvilket er en ældre betegnelse for Dravet syndrom.

Study 1

Study 1 omfatter to identiske randomiserede, multinationale, dobbeltblindede placebo-kontrollerede fase 3 studier (studie 1501 og 1502), der havde til formål at undersøge effekt og sikkerhed af to doser af fenfluramin sammenlignet med placebo blandt børn og unge med Dravet syndrom. Grundet ufuldstændig inklusion af patientdeltagere i studie 1501 (NCT02682927) og studie 1502 (NCT02826863) blev datasættene kombineret, før blændingen af resultaterne blev løftet.

Studiet bestod af en 6-ugers baseline periode efterfulgt af en 2-ugers titreringsperiode. Herefter fulgte en 12-ugers vedligeholdelsesperiode, og studiet forløb dermed samlet over 14 uger. Ved screeningsbesøget blev patienter randomiseret 2:2:1:1 til behandling med 0,2 mg/kg fenfluramin; 0,7 mg/kg fenfluramin eller til én af to placeboarme. I løbet af den 6-ugers lange baselineperiode blev den initiale egnethed fra screeningsbesøget fastslået, hvorefter patienternes baseline anfaldsaktivitet blev vurderet i løbet af en observationsperiode. Patientens daglige anfaldsaktivitet blev registreret og skrevet ind i en elektronisk dagbog.

Efter baselineperioden blev patienterne randomiseret 1:1:1 til 0,2 mg/kg fenfluramin; 0,7 mg/kg fenfluramin eller placebo. Herefter blev alle patienter i løbet af en 2-ugers periode optitreret til deres randomiserede dosis (0,2 mg/kg/dag på dag 1-4, 0,4 mg/kg/dag på dag 5-8 og til sidst 0,7 mg/kg/dag). Patienter fortsatte behandling i en 12-ugers vedligeholdelsesbehandling, efterfulgt af enten en 2-ugers nedtrapnings-/overgangsperiode eller overgik til et *open label extension* (OLE) studie (Study 1503). I alt blev 119 patienter inkluderet i studiet, og 110 patienter gennemførte studiet (34 i fenfluramin 0,7 mg/kg-, 39 i fenfluramin 0,2 mg/kg- og 37 i placebo-armen). ITT-populationen bestod af alle patienter, der blev randomiseret til behandling, mens den modificerede ITT-population (mITT) bestod af alle patienter, der modtog mindst en dosis fenfluramin eller placebo og havde mindst en uge rapporteret i den elektroniske dagbog.

Inklusionskriterierne omfattede patienter med Dravet syndrom i alderen 2-18 år, hvor behandling med antiepileptiske lægemidler (*anti-seizure medication*; ASM) ikke havde tilfredsstillende effekt på forekomsten af konvulsive anfald. Patienter skulle bl.a. have mindst 4 konvulsive anfald pr. 4-ugers periode i 12 uger forud for studiestart. Patienter, der modtog samtidig behandling med stiripentol, blev ekskluderet. Derudover blev patienter med bl.a. pulmonal hypertension, kardiovaskulær eller cerebrovaskulær sygdom samt myokardieinfarkt ekskluderet.

Studiets primære endemål var gennemsnitlig ændring i frekvensen af konvulsive anfald (*convulsive seizure frequency*; CSF) pr. 28 dage, og et sekundært endemål var bl.a. andel af patienter, der opnåede mindst 50 % reduktion i antallet af konvulsive anfald. Øvrige endemål inkluderede brug af anfaldsbrydende medicin og livskvalitet. Endemål forbundet med klinisk effekt blev opgjort efter 14 uger, mens sikkerhed blev opgjort efter et opfølgende besøg, som blev afholdt 3-6 måneder efter den sidste modtagne dosis af behandlingen.

Statistiske analyser af det primære endemål samt alle vigtige sekundære endemål blev udført i mITT-populationen, mens sikkerhed blev analyseret blandt alle patienter, der modtog mindst én dosis fenfluramin eller placebo. Manglende data blev ikke imputeret.

STICLO-France
STICLO-France er et randomiseret, placebo-kontrolleret, dobbelt-blindet studie, der undersøgte effekten af stiripentol blandt patienter med SMEI, som er en ældre betegnelse for Dravet syndrom.

Efter en måneds baselineperiode blev patienter randomiseret til enten stiripentol (n = 22) eller placebo (n = 20) som tillægsterapi til clobazam og valproat. Patienterne blev vurderet hver måned i den 2-måneders dobbelt-blindede periode samt i løbet af den efterfølgende ublindede periode på mindst en måneds varighed.

Den maksimale dosis valproat var 30 mg/kg pr. dag og 0,5 mg/kg pr. dag for clobazam. Dosis af stiripentol kunne øges fra 50 til 100 mg/kg pr. dag, og komedicineringen kunne ændres, hvis patienten fortsatte med at opleve anfald. I den dobbeltblindede periode var den daglige gennemsnitlige dosis af stiripentol 49,3 mg/kg pr. dag (95 % CI: 47,4; 51,2).

Én patient i stiripentol-armen overholdt ikke studieprotokollen og blev udelukket fra undersøgelsen. I løbet af den dobbeltblindede periode blev fem patienter seponeret (én i stiripentol-armen og fire i placebo-armen), hvilket resulterede i, at i alt 36 patienter fuldførte forsøget (20 i stiripentol-armen og 16 i placebo-armen).

Inklusionskriterierne var patienter i alderen 3 år og opefter med SMEI, der oplevede mindst 4 kloniske (eller tonisk-kloniske), generaliserede anfald pr. måned. Alle patienter skulle være i samtidig behandling med clobazam og valproat. Patienter, der modtog andre lægemidler, undtagen progabid, blev ekskluderet.

Studiets primære endemål var procentdelen af respondere på stiripentol og på placebo, defineret som patienter, der havde opnået mindst 50 % reduktion i hyppigheden af kloniske (eller tonisk-kloniske) anfald i den anden måned af den dobbeltblindede periode sammenlignet med baseline. Patienter, der fik status epilepticus i den dobbeltblindede periode, blev betragtet som ikke-responderende. Sekundære endemål inkluderede antallet af kloniske (eller tonisk-kloniske) anfald i den anden måned af den dobbeltblindede periode (normaliseret til 30 dage) og den procentuelle ændring fra baseline. Alle endemål blev analyseret i ITT-populationen. I publikationen er det ikke angivet, hvorledes manglende data blev håndteret.

Open-label extension (OLE) studier

For fenfluramin er effekt vurderet i et OLE-studie (Study 1503), der havde til formål at undersøge sikkerheden ved langsigtet behandling med fenfluramin. Der er ikke identificeret peer-reviewede publicerede resultater fra OLE-studiet, men ansøger har indsendt data baseret på interim analyser fra studiet. Data fra OLE-studiet inddrages under afsnittet 'Andre overvejelser' med henblik på at belyse den vedvarende effekt af fenfluramin udover opfølgningstiden i de randomiserede studier.

Baselinekarakteristika for de behandlingsarme, som er relevante i denne vurderingsrapport, er vist i Tabel 5-2.

Tabel 5-2. Baselinekarakteristika for Study 1 og STICLO-France

	Study 1		STICLO-France	
	Fenfluramin 0,7 mg/kg/dag (n = 40)	Placebo (n = 40)	Stiripentol (n = 21)	Placebo (n = 20)
Alder, år				
Gns. (SD)	8,8 (4,4)	9,2 (5,1)	9,4 (3–16,7)¤	9,3 (3,2–20,7)¤
Range	2–18	2–18	IA	IA
Patienter yngre end 6 år	11 (28)	11 (28)	IA	IA
Mænd	21 (52)	21 (52)	6	11
Etnicitet				
Kaukasisk	34 (85)	31 (78)	IA	IA
Asiatisk	1 (3)	4 (10)	IA	IA
Andre eller ikke rapporteret	5 (12)	5 (12)	IA	IA
Kropsvægt (kg), gns. (SD)	31,8 (13,5)	31,7 (16,2)	32 (14–60)¤	31 (15–70)¤
BMI (kg/m^2), gns. (SD)	18,5 (3,5)	18,0 (3,8)	IA	IA
SCN1A-mutationer	33 (82)	31 (78)	IA	IA
Region				
USA og Canada	24 (60)	24 (60)	IA	IA
Resten af verden	16 (40)	16 (40)	IA	IA

	Study 1		STICLO-France	
	Fenfluramin 0,7 mg/kg/dag (n = 40)	Placebo (n = 40)	Stiripentol (n = 21)	Placebo (n = 20)
Samtidig antiepileptisk behandling				
Antal samtidige antiepileptiske lægemidler, gns. (SD)	2,3 (0,9)	2,5 (0,9)	IA	IA
Valproat (alle former)	25 (62)	22 (55)	21 (100)	20 (100)
Clobazam	24 (60)	22 (55)	21 (100)	20 (100)
Topiramat	11 (28)	9 (22)	0 (0)	0 (0)
Levetiracetam	4 (10)	11 (28)	0 (0)	0 (0)
Gns. dosis valproat (mg/kg/dag) (IQR)	IA	IA	23,7 (10–46,4)	24 (13.8–50)
Gns. dosis clobazam (mg/kg/dag), gns. (IQR)	IA	IA	0,53 (0,05–1,04)	0,55 (0,14–1,18)
Patienter i samtidig behandling med progabid*	IA	IA	5	2
Patienter, der modtog maksimal dosis fenfluramin (26 mg/dag)	12 (30)	0	IA	IA
Frekvens af konvulsive anfald (CSF) ved baseline[§]				
Gns. (SD)	31,4 (30,6)	44,2 (40,2)	IA	IA
Median (range)	20,7 (4,8–124)	27,3 (3,3–147,3)	18 (4–73)#	19 (4–76)#

Resultater er opgjort som antal af patienter (%), med mindre andet er angivet. [¤]Gns. (IQR). [§]Frekvensen af konvulsive anfald er opgjort som det gennemsnitlige antal anfald over en periode på 28 dage i studiet af fenfluramin, mens det er opgjort pr. måned i studiet af stiripentol. #Median (IQR). *Progabid er blevet anvendt til behandling af SMEI, men var i studieperioden ved at blive fjernet fra markedet. CSF: Frekvens af konvulsive anfald; Gns.: Gennemsnit; IA: Ikke angivet.

Studiepopulationernes sammenlignelighed

Fagudvalget bemærker, at baselinekarakteristikken af STICLO-France er sparsom, hvilket gør det vanskeligt at sammenligne populationerne. Dog vurderer fagudvalget, at patientpopulationerne i Study 1 og STICLO-France er sammenlignelige ift. alder og anfaldsfrekvens. I Study 1 bemærker fagudvalget, at patientpopulationen er heterogen,

hvad angår anfaldsfrekvens (CSF) pr. 28 dage, idet anfaldsfrekvensen spænder fra 4,8 til 124 og fra 3,3 til 147,3 blandt patienter i hhv. fenfluramin- og placebo-armen, mens den gennemsnitlige anfaldsfrekvens pr. 28 dage mellem de to studiearme er 31,4 og 44,2 for hhv. fenfluramin- og placeboarmen. Fagudvalget vurderer dog, at denne forskel ikke er betydende for vurderingen af fenfluramin.

I begge studier modtog størstedelen af patienterne behandling med clobazam og/eller valproat. I Study 1 modtog en del patienter derudover andre ASMs såsom topiramat og levetiracetam, mens få patienter i STICLO-France modtog anden ASM-behandling i form af progabid. Da behandling med andre ASMs kan have betydning for forekomsten af bivirkninger samt den kliniske effekt, vil fagudvalget medtage forskellene i den samtidige behandling i vurderingen af effektmålene.

Fagudvalget vurderer, at patienterne i de kliniske studier har en højere sygdomsbyrde i form af flere anfald sammenlignet med den danske patientpopulation. Dette skyldes hovedsageligt, at studiepopulationerne udelukkende inkluderer børn og unge, mens den danske patientpopulation også indeholder en betydelig andel af voksne patienter, som forventes at have lavere anfaldsfrekvens end børn. Da studierne udelukkende inkluderer unge patienter, forventes studiepopulationerne også at have en lavere forekomst af komorbiditeter sammenlignet med den danske patientpopulation.

På trods af disse forskelle vurderer fagudvalget dog, at den relative effekt af lægemidlerne vil være sammenlignelig med den forventede effekt i en dansk patientpopulation.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål ved klinisk spørgsmål 1 beskrevet.

Der findes ikke en direkte sammenligning af fenfluramin og stiripentol til patienter med Dravet syndrom. Ansøger har ikke udført formelle sammenlignende statistiske analyser mellem fenfluramin og stiripentol, da de ikke har fundet grundlag for det.

Ansøger fremhæver bl.a., at STICLO-France er et ældre studie, mens Study 1 er et nyere studie, der mere præcist kan afspejle den aktuelle kliniske behandling af patienter med Dravet syndrom. I begge studier er anfald vurderet og registreret af pårørende til patienter med Dravet syndrom, og registreringen af konvulsive anfald vurderes derfor at være sammenlignelig på tværs af de to studier. Der er dog vigtige forskelle i vurderingen af endepunkter for konvulsive anfald, idet Study 1 udover tonisk-kloniske og kloniske anfald, som er inkluderet i STICLO-France, også inkluderede fokale anfald med en signifikant motorisk komponent blandt de inkluderede typer krampeanfald.

I Study 1 blev reduktion i konvulsive anfald målt som den procentvise ændring i frekvensen af konvulsive anfald (*convulsive seizure frequency*; CSF) mellem baseline- og T+M-perioder (pr. 28 dage), og der blev bl.a. udført en parametrisk vurdering af procentvis reduktion fra baseline i frekvensen af konvulsive anfald pr. 28 dage sammenlignet med placebo (dvs. den yderligere reduktion i forhold til placebo). I STICLO-France blev reduktionen i krampeanfald målt som den procentvise ændring fra baseline i

CSF efter 1. måned og efter 2. måneds behandlingsperiode sammenlignet med baseline. I STICLO-France blev der desuden ikke foretaget en vurdering gennem hele behandlingsperioden eller en parametrisk vurdering af procentvis reduktion fra baseline i frekvensen af konvulsive anfald pr. 28 dage sammenlignet med placebo (dvs. den yderligere reduktion i forhold til placebo). I henhold til protokollen har ansøger dog suppleret med en beregning af den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald (baseret på data on file). Fagudvalget vurderer, at resultatet af denne analyse i større grad vil være sammenligneligt med det rapporterede resultat fra STICLO-France.

Mht. andelen af patienter, der opnåede mindst 50 % reduktion i frekvensen af konvulsive anfald, rapporterede Study 1 på CSF over en kombineret T+M-periode (pr. 28 dage) som et sekundært endepunkt, mens STICLO-France rapporterede på CSF for 2. måneds behandlingsperiode sammenlignet med baseline (pr. 30 dage) som et primært endepunkt, og der blev ikke foretaget nogen vurdering gennem hele behandlingsperioden.

Mens Study 1 vurderede endepunkter for konvulsive anfald over hele behandlingsperioden på 14-15 uger, vurderede STICLO-France endepunkter for konvulsive anfald i de sidste fire uger af en otte ugers behandlingsperiode. Derudover blev effektmålet procentuel ændring i konvulsive anfald i STICLO-France ikke justeret for placebo.

Medicinrådet accepterer ansøgers tilgang. Fagudvalget vurderer, at forskellene i studiedesigns og analysemetode kan have betydning for den observerede effekt af lægemidlerne, og at studierne derfor ikke kan sammenlignes direkte. Fagudvalget bemærker derudover, at manglende data ikke er blevet imputeret i hverken Study 1 eller STICLO-France. Det er uklart, hvorledes manglende data i studierne kan påvirke resultaterne for de udvalgte effektmål. Fagudvalget har med disse forbehold valgt at basere deres vurdering af fenfluramin på en narrativ gennemgang af data for henholdsvis fenfluramin og stiripentol overfor placebo.

5.1.3 Evidensens kvalitet

Da vurderingen af fenfluramin er baseret på en narrativ sammenligning med stiripentol, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen. Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at der er forbehold ift. risikoen for bias ved begge de underliggende kliniske studier.

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

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle fra Study 1 og STICLO-France, som fagudvalget anvender i vurderingen af klinisk spørgsmål 1. For fenfluramin er anvendt data fra behandlingsarmen med en dosis på 0,7 mg/kg fra Study 1.

Tabel 5-3. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Studiearm	Fenfluramin vs. placebo Study 1			Stiripentol vs. placebo STICLO-France		
				Gns. (95 % CI) eller % (n/N)	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)	Gns. (95 % CI) eller % (n/N)	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)
Konvulsive anfald	Gns. procentuel ændring i antallet af konvulsive anfald pr. 28 dage (MKRF: 20 %)	Kritisk	Intervention	[redacted]	[redacted]	*Kan ikke estimeres	-69 % (-88 %; -50 %)	-76 %-point (IA)	*Kan ikke estimeres
			Placebo	[redacted]			7 % (-11 %; 25 %)		
	Andel patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald (MKRF: 20 %-point)	Kritisk	Intervention	67,5 % (27/40)	55,6 %-point (16,69; 146,51)	RR: 5,45 (2,34; 12,72)	71 % (15/21)	66 %-point (IA)	Ikke beregnet
			Placebo	12,5 % (5/40)			5 % (1/20)		
Behov for anfalds-brydende medicin (*rescue medica-tion*)	Gns. antal dage/28 dage, hvor anfaldsbrydende medicin anvendes (MKRF: 1 dag)	Vigtig	Intervention	0,9 dage (0,32; 1,48)	-2,2 dage (-3,8; -0,65)	*Kan ikke estimeres	Ingen data	-	-
			Placebo	3,1 dage (1,66; 4,54)					
	Andel patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes (MKRF: 20 %-point)	Vigtig	Intervention	[redacted]	[redacted]	Ikke beregnet	Ingen data	-	-
			Placebo	[redacted]					
Livskvalitet		Kritisk	Intervention	5,9 (1,22; 10,58)	7,5 (1,81; 13,19)		Ingen data	-	-

Effektmål	Målenhed (MKRF)	Vigtig-hed	Studiearm	Fenfluramin vs. placebo Study 1			Stiripentol vs. placebo STICLO-France		
				Gns. (95 % CI) eller % (n/N)	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)	Gns. (95 % CI) eller % (n/N)	Absolut forskel (95 % CI)	Relativ forskel (95 % CI)
	Gennemsnitlig ændring i PedsQL (MKRF: 4,5 point)		Placebo	-1,6 (-4,83; 1,63)		*Kan ikke estimeres			
	Andel patienter, som scorer 1 eller 2 i CGI-I (MKRF: 5 %-point) *(vurdering foretaget af patient eller omsorgsperson)*	Kritisk	Intervention	55,0 % (22/40)	47,1 %-point (11,64; 140,90)	RR: 5,71 (2,16; 15,09)	Ingen data	-	-
			Placebo	10,0 % (4/40)					
	Andel patienter, som scorer 1 eller 2 i CGI-I (MKRF: 5 %-point) *(vurdering foretaget af behandler (investigator))*	Kritisk	Intervention	62,5 % (25/40)	58,5 %-point (16,23; 169,02)	RR: 6,85 (2,62; 17,90.	Ingen data	-	-
			Placebo	10,0 % (4/40)					
Uønskede hændelser	Andel patienter med mindst én alvorlig uønsket hændelse (SAE) (MKRF: 5 %-point)	Vigtig	Intervention	[redacted]	[redacted]	[redacted]	23,8 % (5/21)	18,8 %-point	Ikke beregnet
			Placebo				5 % (1/20)		
	Kvalitativ gennemgang af bivirkningsdata	Vigtig	Se afsnit 5.1.4 Gennemgang af bivirknings-profil						
Konklusion									
Samlet kategori for lægemidlets værdi	**Kan ikke kategoriseres.** Fagudvalget vurderer, at der ikke er noget i de tilgængelige data, der indikerer, at fenfluramin har en dårligere effekt eller sikkerhedsprofil end stiripentol.								

CI = konfidensinterval, RR = relativ risiko. *Det er ikke muligt at beregne en relativ risiko for effektmålet, da det er opgjort på en kontinuerlig skala

Konvulsive anfald

Som beskrevet i protokollen er effektmålet konvulsive anfald kritisk for vurderingen af lægemidlets værdi for patienterne, da en høj forekomst af konvulsive anfald er forbundet med en høj risiko for udvikling af sygelighed og dødelighed samt forringet livskvalitet.

Medicinrådet har ønsket konvulsive anfald belyst ved den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage samt ved andelen af patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald.

Den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage

I publikationen af Lagae et al. [7] er ændring i anfaldsfrekvens pr. 28 dage baseret på Study 1 analyseret vha. en ANCOVA model med behandlingsarm, aldersgruppe og baseline anfaldsfrekvens som forklarende variable. Baseret på denne analyse viste fenfluramin en ændring i anfaldsfrekvens på -62,3 % (95 % CI: -72,8 %; -47,7 %) sammenlignet med placebo. Lagae et al. rapporterer derudover den mediane procentuelle ændring i anfaldsfrekvens pr. 28 dage til at være -74,9 % (range: –100; 196,4) og -19,2 % (range: –76,1; 51,8] for hhv. fenfluramin og placebo.

I protokollen har fagudvalget dog efterspurgt den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage, og ansøger har beregnet dette vha. *data on file* fra Study 1. Blandt patienter (n = 40) behandlet med fenfluramin var den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage [redacted], mens ændringen var [redacted] blandt patienter (n = 40) behandlet med placebo. Dette svarer til, at patienter i behandling med fenfluramin oplevede en gennemsnitlig ændring i antallet af konvulsive anfald pr. 28 dage på [redacted] sammenlignet med placebo.

I STICLO-France-studiet var den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 30 dage -69 % (95 % CI: -88 %; -50 %) blandt patienter (n = 21) behandlet med stiripentol, mens ændringen var 7 % (95 % CI: -11 %; 25 %) blandt patienter (n = 20) behandlet med placebo. Dette svarer til, at patienter i behandling med stiripentol oplevede en gennemsnitlig reduktion i antallet af konvulsive anfald pr. 28 dage på 76 %-point sammenlignet med placebo.

Fagudvalget vurderer, at de kliniske studier viser god effekt af både fenfluramin og stiripentol ift. at reducere frekvensen af konvulsive anfald. Grundet forskelle i studiedesigns, herunder studiernes definitioner af konvulsive anfald, samt forskelle i samtidig behandling med ASMs mellem studierne, er det ikke muligt for fagudvalget at vurdere, hvorvidt der er en betydende forskel mellem fenfluramin og stiripentol målt på den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald.

Andel patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald

I Study 1 opnåede 27 ud af 40 (67,5 %, 95 % CI: 53 %; 82 %) patienter i behandling med fenfluramin en 50 % reduktion i antallet af konvulsive anfald, mens det samme var tilfældet for 5 ud af 40 (12,5 %, 95 % CI: 2,3 %; 22,7 %) af patienterne i behandling med placebo. Den absolutte forskel mellem fenfluramin og placebo var dermed 55,6 %-point (95 % CI: 16,69; 146,51), mens den relative forskel var 5,45 (95 % CI: 2,34; 12,72).

I STICLO-France-studiet opnåede 71 % (95 % CI: 52,1 %; 90,7 %) af patienter (n = 21) i behandling med stiripentol en 50 % reduktion i antallet af konvulsive anfald, mens det samme var tilfældet for 5 % (95 % CI: 0 %; 14,6 %) af patienterne (n = 20) i behandling med placebo. Dermed opnåede 66-%-point flere patienter i behandling med stiripentol en 50 % reduktion, sammenlignet med patienter i behandling med placebo.

Fagudvalget vurderer, at data umiddelbart tyder på, at fenfluramin og stiripentol har en sammenlignelig effekt målt på andelen af patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald. Som tidligere fremhævet er der dog forskelle i studiernes designs, som kan have betydning for den observerede kliniske effekt i studierne, og som bevirker, at det ikke er muligt at se en betydende forskel. På den baggrund er det ikke muligt for fagudvalget at vurdere effekten af fenfluramin sammenlignet med stiripentol målt på dette delmål.

Samlet konklusion vedr. effektmålet konvulsive anfald
Baseret på ovenstående gennemgang af effektmålets to delmål finder fagudvalget, at effektmålet ikke kan kategoriseres efter Medicinrådets metoder. Fagudvalget vurderer, at forskelle i studiedesigns kan have betydning for den observerede kliniske effekt i studierne. På den baggrund er det ikke muligt for fagudvalget at vurdere, om de relativt begrænsede forskelle mellem studieestimaterne udgør en betydende forskel i den kliniske effekt mellem fenfluramin og stiripentol målt på konvulsive anfald.

Behov for anfaldsbrydende medicin (rescue medication)
Effektmålet behov for anfaldsbrydende medicin (rescue medication) er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi behov for anfaldsbrydende medicin er et indirekte mål for sværhedsgraden/varigheden af de mest alvorlige anfald.

Medicinrådet har ønsket behovet for anfaldsbrydende medicin belyst ved andelen af patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes samt det gennemsnitlige antal dage/28 dage, hvor anfaldsbrydende medicin anvendes.

Andel patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes
Data for andelen af patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes er ikke angivet i publikationen af Lagae et al. Ansøger har derfor undersøgt effektmålet baseret på *data on file* fra Study 1. I ansøgers analyse er patienter, der ikke modtager anfaldsbrydende medicin i baselineperioden, ekskluderet.

[redacted]

Da patienternes behov for anfaldsbrydende medicin ikke er undersøgt i STICLO-France, er det ikke muligt at foretage en komparativ analyse ift. behov for anfaldsbrydende medicin.

Baseret på data fra Study 1 vurderer fagudvalget dog, at fenfluramin sammenlignet med placebo viser god effekt ift. andelen af patienter, der opnår en 50 % reduktion i antallet af dage, hvor anfaldsbrydende medicin anvendes.

Gennemsnitligt antal dage/28 dage, hvor anfaldsbrydende medicin anvendes
I Study 1 var det gennemsnitlige antal dage/28 dage, hvor anfaldsbrydende medicin blev anvendt, 0,9 dage (95 % CI: 0,32; 1,48) og 3,1 dage (95 % CI: 1,66; 4,54) for patienter i behandling med hhv. fenfluramin og placebo. Forskellen i antallet af dage med behov for anfaldsbrydende medicin var dermed -2,2 dage (95 % CI: -3,8; -0,65) til fordel for fenfluramin.

Da patienternes behov for anfaldsbrydende medicin ikke er undersøgt i STICLO-France, er det ikke muligt at foretage en komparativ analyse ift. behov for anfaldsbrydende medicin.

Baseret på data fra Study 1 vurderer fagudvalget dog, at fenfluramin sammenlignet med placebo viser god effekt ift. at reducere det gennemsnitlige antal af dage, hvor anfaldsbrydende medicin anvendes.

Samlet konklusion vedr. behov for anfaldsbrydende medicin
Da der ikke foreligger data, der muliggør en sammenligning af fenfluramin og stiripentol ift. behov for anfaldsbrydende medicin, kan værdien af fenfluramin ikke kategoriseres for dette effektmål.

Livskvalitet
Effektmålet livskvalitet er kritisk for vurderingen af lægemidlets værdi for patienterne, fordi livskvalitet er et afgørende helbredsrelateret mål for den enkelte patient.

Medicinrådet har ønsket livskvalitet belyst ved den gennemsnitlige ændring i PedsQL samt ved andelen af patienter, der scorer 1 eller 2 i CGI-I.

Gennemsnitlig ændring i PedsQL
PedsQL består af 4 funktionsskalaer, der måler fysisk, følelsesmæssig, social og skolemæssig funktion. Den samlede score er baseret på registreringerne indenfor alle 4 funktionsskalaer. En høj værdi indikerer forbedring i livskvalitet. Registrering af PedsQL blev foretaget af en forælder eller anden omsorgsperson på vegne af patienten.

I Study 1 var den gennemsnitlige ændring i total PedsQL score fra baseline 5,9 (95 % CI: 1,22; 10,58) og -1,6 (95 % CI: -4,83; 1,63) for patienter i behandling med hhv. fenfluramin og placebo. Den gennemsnitlige forskel i total PedsQL score mellem fenfluramin og placebo var dermed 7,5 (95 % CI: 1,81; 13,19).

Da patienternes livskvalitet ikke er undersøgt i STICLO-France, er det ikke muligt at foretage en komparativ analyse med livskvalitetsdata. Fagudvalget vurderer dog samlet

set, at data fra Study 1 tyder på, at patienternes livskvalitet ser ud til at udvikle sig positivt ved behandling med fenfluramin sammenlignet med placebo.

Andel patienter, der scorer 1 eller 2 i CGI-I
CGI-I skalaen udgør en vurdering af patientens generelle helbredstilstand efter en given intervention relativt til før denne intervention. CGI-I spænder fra 1: *'very much improved',* til 7: *'very much worse'*, mens 4 svarer til ingen ændring. Fagudvalget har ønsket at vurdere resultater for andelen af patienter, som scorer 1 eller 2 på skalaen (dvs. *very much improved* eller *much improved*).

I Study 1 blev CGI-I vurderet både af en forælder eller anden omsorgsperson samt af behandler (*investigator*). Fagudvalget finder, at vurderingen foretaget af patient eller omsorgsperson forventeligt vil være mere patientnær, idet omsorgspersonen som udgangspunkt bedst vil kunne vurdere ændringer i patientens livskvalitet. Dog kan opståede bivirkninger som f.eks. insomnolens medføre, at en omsorgsperson vil have større tilbøjelighed til at antage, at patienten modtager aktiv behandling. Dette vil i så fald kunne påvirke vurderingen af livskvaliteten. Derudover forventer fagudvalget, at en omsorgsperson, som typisk vil være en forælder, vil være lettere påvirkelig ift. evt. ændringer i livskvalitet end en behandler. Omvendt kan en behandler have tendens til at tillægge en evt. reduktion i anfaldshyppighed betydende vægt i vurderingen af patientens livskvalitet. Typer af bivirkninger, f.eks. kvalme, kan af en omsorgsperson tillægges betydende vægt ift. patientens livskvalitet, mens dette ikke nødvendigvis vil være tilfældet for behandleren, så længe patienten ikke taber sig. Der kan således ligge forskellige opfattelser af vigtighed til grund for de to vurderinger af livskvaliteten. Fagudvalget vurderer, at de to typer af registreringer reflekterer forskellige aspekter og vælger på denne baggrund at medtage begge registreringstyper i vurderingen.

<u>CGI-I foretaget af patient eller omsorgsperson:</u>
Blandt patienter behandlet med fenfluramin opnåede 22 ud af 40 patienter (55,0 %; 95 % CI: 39,6 %; 70,4 %) en score på 1 eller 2, mens det samme var tilfældet for 4 ud af 40 patienter (10,0 %; 95 % CI: 0,7 %; 19,3 %) i behandling med placebo. Den absolutte forskel i andelen af patienter, der opnåede en score på 1 eller 2 var dermed 47,1 %-point (95 % CI: 11,64; 140,90), mens den relative forskel var 5,71 (95 % CI: 2,16; 15,09).

<u>CGI-I foretaget af behandler (investigator):</u>
Blandt patienter behandlet med fenfluramin opnåede 25 ud af 40 patienter (62,5 %, 95 % CI: 47,5%; 77,5 %) en score på 1 eller 2, mens det samme var tilfældet for 4 ud af 40 patienter (10,0 %; 95 % CI: 0,7 %; 19.3 %) i behandling med placebo. Den absolutte forskel i andelen af patienter, der opnåede en score på 1 eller 2 var dermed 58,5 %-point (95 % CI: 16,23; 169,02), mens den relative forskel var 6,85 (95 % CI: 2,62; 17,90).

Da patienternes livskvalitet ikke er undersøgt i STICLO-France, er det ikke muligt at foretage en komparativ analyse med livskvalitetsdata. Fagudvalget vurderer dog samlet set, at data fra Study 1 tyder på, at patienternes livskvalitet ser ud til at udvikle sig positivt ved behandling med fenfluramin sammenlignet med placebo.

Samlet konklusion vedr. effektmålet livskvalitet
Da der ikke foreligger data, der muliggør en sammenligning af fenfluramin og stiripentol ift. livskvalitet, kan værdien af fenfluramin ikke kategoriseres for dette effektmål.

Uønskede hændelser
Effektmålet uønskede hændelser er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi uønskede hændelser kan være til stor gene for patienten, og belastningen fra uønskede hændelser/bivirkninger skal stå i rimeligt forhold til den terapeutiske effekt. Særligt for livslang behandling kan væsentlige bivirkninger resultere i behandlingsophør eller ringe adhærens.

Andel patienter med mindst én alvorlig uønsket hændelse (SAE)
I Study 1 blev der rapporteret mindst én alvorlig uønsket hændelse (*serious adverse events*; SAEs) [redacted] ud [redacted] af patienterne i behandling med fenfluramin 0,7 mg/kg, mens det var tilfældet for [redacted] ud af [redacted] af patienterne i behandling med placebo (*data on file*). Dermed oplevede [redacted] patienter i behandling med fenfluramin mindst én alvorlig uønsket hændelse, sammenlignet med placebo.

I STICLO-France oplevede i alt 5 ud af 21 (23,8 %; 95 % CI: 5,6 %; 42,0 %) patienter i behandling med stiripentol uønskede hændelser, som blev vurderet til at være alvorlige (*severe*). Tilsvarende var dette tilfældet for 1 ud af 21 (5 %; 95 % CI: 0 %; 14,6 %) af patienterne i behandling med placebo. Dermed opnåede 18,8 %-point flere patienter i behandling med stiripentol mindst én alvorlig uønsket hændelse, sammenlignet med placebo.

Fagudvalget bemærker, at der muligvis er forskel i de rapporterede hændelser for de to kliniske studier, idet det publicerede studie af Lagae rapporterer serious AEs, men studiet af Chiron et al. rapporterer *severe* uønskede hændelser. Fagudvalget har derfor orienteret sig i EPAR'en for stiripentol, hvor det fremgår, at der var 9 tilfælde af SAEs i STICLO-France (n = 6 i stiripentol-armen og n = 3 i placebo-armen). Ud af de 6 hændelser i stiripentol-armen blev 4 vurderet at være *severe* men ikke *serious* [11]. Fagudvalget vurderer derfor, at det er usikkert, om forekomsten af alvorlige uønskede hændelser kan sammenlignes på tværs af de to kliniske studier. Derudover er der i de kliniske studier forskel i andelen af patienter, der modtager anden antiepileptisk behandling. Da behandling med flere ASMs kan medføre en øget forekomst af bivirkninger, kan forskellen mellem studierne dermed bidrage til yderligere usikkerhed i vurderingen. Overordnet set vurderer fagudvalget dog, at data ikke tyder på en øget forekomst af alvorlige uønskede hændelser ved behandling med fenfluramin sammenlignet med stiripentol.

Kvalitativ gennemgang af bivirkningsdata
I produktresuméet for fenfluramin fremgår det, at de hyppigst indberettede bivirkninger er nedsat appetit (44,2 %), diarré (30,8 %), feber (25,6 %), træthed (25,6 %), øvre luftvejsinfektion (20,5 %), letargi (sløvhed) (17,5 %), somnolens (sygelig søvnighed) (15,4 %) og bronkitis (11,6 %). I kliniske studier er rapporteret forekomst af status epilepticus blandt 6,6 % og 2,4 % af patienter, der modtog hhv. fenfluramin og placebo.

Sikkerheden ved længerevarende brug af fenfluramin er blevet vurderet ud fra 330 patienter i op til 3 år, og de hyppigste bivirkninger var nedsat appetit (18,8 %), unormalt ekkokardiogram (meget let klapinsufficiens) (8,2 %), vægttab (6,1 %) og unormal adfærd (5,2 %) [6].

I Study 1 var de hyppigste non-cardiovaskulære uønskede hændelser ligeledes nedsat appetit, diarré, forkølelse (nasopharyngitis), letargi, somnolens og feber. Alvorlige uønskede hændelser blev rapporteret hos 5, 4 og 4 patienter i behandling med hhv. fenfluramin 0,7 mg/kg, fenfluramin 0,2 mg/kg og placebo. De hyppigste alvorlige uønskede hændelser inkluderede hospitalsindlæggelse for status epilepticus. Én patient i behandling med fenfluramin 0,7 mg/kg ophørte behandling grundet uønskede hændelser (nedsat appetit og vægttab) [7].

I produktresuméet for stiripentol fremgår det, at de hyppigst rapporterede bivirkninger er anoreksi, vægttab, søvnbesvær, døsighed, ataksi (koordinationsbesvær), hypotoni (nedsat muskeltonus) og dystoni (ufrivillig muskelspænding) [10].

I studiet af Chiron et al. var de hyppigste uønskede hændelser ligeledes træthed og nedsat appetit. Hos 5 og 1 patienter i behandling med hhv. stiripentol og placebo blev de uønskede hændelser (træthed og vægttab) vurderet som værende alvorlige (*severe*). Én patient i behandling med placebo ophørte behandling grundet uønskede hændelser [8].

Samlet vurdering af bivirkningsprofiler
Fagudvalget bemærker på baggrund af ovenstående gennemgang af bivirkningsprofilerne for hhv. fenfluramin og stiripentol, at bivirkningsprofilerne er forskellige, hvor begge lægemidler kan medføre en række uønskede hændelser. For begge lægemidler ses der en betydelig risiko for påvirkning af patientens vægt og appetit samt øget forekomst af forskellige grader af træthed og sløvhed. Fagudvalget vurderer dog, at behandling med ASM generelt medfører sløvhed, særligt ved opstart af behandling.

For fenfluramin ses derudover en høj forekomst af luftvejsinfektioner, men fagudvalget finder det usikkert, hvorvidt disse infektioner er medicininducerede eller til en vis grad kan skyldes, at luftvejsinfektioner er hyppige blandt børn. Derudover er der rapporteret tilfælde af tilbageløb fra mavesækken til spiserør (sure opstød, også kaldet regurgitation) ved behandling med fenfluramin, men fagudvalget vurderer, at dette forventeligt vil forekomme i alle patientpopulationer med Dravet syndrom.

Fagudvalget fremhæver, at behandling med fenfluramin forventes at være livslang, såfremt behandlingen er effektiv, og at der derfor vil være risiko for kroniske bivirkninger, blandt andet hjerteklapanomalier. De kliniske studier har for kort opfølgningstid til, at det er muligt for fagudvalget at vurdere risikoen for kroniske bivirkninger på lang sigt. Derudover inkluderer de kliniske studier meget få voksne patienter, og bivirkningsprofilen for fenfluramin er dermed primært baseret på observationer blandt børn. Dog vurderer fagudvalget, at risikoen for bivirkninger vil være anderledes blandt voksne patienter, som forventelig har flere komorbiditeter og risikofaktorer end børn. Voksne patienter kan dermed reagere anderledes på behandling med fenfluramin og opleve andre bivirkninger end børn.

Fagudvalget vurderer, at de tilgængelige data ikke tyder på en betydelig øget forekomst af hjerteklapinsufficiens ved behandling med fenfluramin. Hjerteklapinsufficiens er dog kun undersøgt for fenfluramin, og fagudvalget kan derfor ikke afgøre, hvorvidt der også kan være en øget risiko for hjerteklapinsufficiens forbundet med behandling med stiripentol.

Fagudvalget vurderer, at forskelle i opgørelsesformerne for fenfluramin og stiripentol gør det vanskeligt at vurdere, hvorvidt der er betydende forskelle i forekomsterne af bivirkninger mellem lægemidlerne. Dog vurderer fagudvalget samlet set, at bivirkningsbyrden for fenfluramin og stiripentol er sammenlignelig.

Fagudvalget anbefaler, at risikoen for vægttab og hjerteklapanomalier skal overvejes forud for opstart af behandling med fenfluramin, særligt ved samtidig behandling med andre appetitregulerende lægemidler. Derudover skal patienter i behandling med fenfluramin monitoreres tæt og løbende få foretaget ekkokardiogram som angivet i produktresuméet for fenfluramin [6].

Samlet konklusion vedr. effektmålet uønskede hændelser
Baseret på ovenstående gennemgang af effektmålets to delmål finder fagudvalget, at det ikke er muligt at vurdere, hvorvidt der er en betydende forskel i sikkerheden mellem fenfluramin og stiripentol, målt på andelen af patienter, der oplever alvorlige uønskede hændelser. Ud fra den kvalitative gennemgang af bivirkningsprofiler finder fagudvalget, at bivirkningsprofilerne for lægemidlerne er forskellige, men at de overordnet set er sammenlignelige, hvad angår bivirkningernes type og sværhedsgrad. Fagudvalget bemærker dog, at samtidig behandling med andre ASMs skal forsøges reduceret, idet behandling med flere lægemidler generelt medvirker til øget risiko for bivirkninger og interaktioner. Fagudvalget vurderer desuden, at kvaliteten af data er meget begrænset, og at vurderingen derfor er behæftet med stor usikkerhed.

5.1.5 Fagudvalgets konklusion

For patienter med Dravet syndrom, der i 1. linje behandles med valproat og/eller clobazam, kan fagudvalget ikke afgøre, om der er forskel i værdien af at tillægge fenfluramin eller stiripentol til denne behandling. Datagrundlaget tillader ikke, at sammenligningen mellem fenfluramin og stiripentol kan kategoriseres efter Medicinrådets metoder.

I den samlede vurdering lægger fagudvalget vægt på, at der er forskelle i de tilgængelige kliniske studier, som betyder, at den kliniske effekt mellem fenfluramin og stiripentol ikke kan sammenlignes direkte. Forskellene mellem studierne kan have betydning for den observerede forskel i effekt på konvulsive anfald mellem lægemidlerne og bevirker, at det ikke er muligt for fagudvalget at konkludere, at der reelt er en betydende forskel mellem lægemidlerne.

Dog vurderer fagudvalget, at tillæg af fenfluramin og stiripentol er effektivt sammenlignet med at behandle med valproat og/eller clobazam alene, vurderet ud fra den opnåede reduktion i konvulsive anfald. Baseret på den kvalitative gennemgang af bivirkningsprofilerne for lægemidlerne vurderer fagudvalget, at bivirkningsbyrden for

fenfluramin og stiripentol er sammenlignelig, og at bivirkningsprofilerne for de to lægemidler i en vis udstrækning er ens.

Overordnet vurderer fagudvalget, at der ikke er noget i de tilgængelige data, der indikerer, at fenfluramin har en dårligere effekt eller sikkerhedsprofil end stiripentol. Fagudvalget fremhæver dog, at der er usikkerhed forbundet med vurderingen pga. forskelle i de underliggende studier. Dette betyder, at nye studier med en direkte sammenligning af fenfluramin og stiripentol med høj sandsynlighed kan ændre konklusionen.

5.2 Klinisk spørgsmål 2

Det kliniske spørgsmål er:

Hvilken værdi har fenfluramin sammenlignet med placebo for patienter med Dravet syndrom i alderen 2 år og op, som er i en behandlingskombination, der omfatter stiripentol?

5.2.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen, se afsnit 5.1.1 for yderligere information. Ansøger udvalgte én fuldtekstartikel (Nabbout et al., 2020 [12]), der stemmer overens med in- og eksklusionskriterierne fra Medicinrådets protokol. Artiklen omhandler et klinisk studie for fenfluramin (Study 1504) (se Tabel 5-4). Desuden indgår EMAs EPAR og produktresuméet for fenfluramin [6,9].

Tabel 5-4. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Population	Intervention vs. komparator
Nabbout R et al, 2020 [12]	Study 1504	NCT02926898	Børn og unge med Dravet syndrom, der modtog samtidig behandling med stiripentol.	Fenfluramin 0,4 mg/kg/dag vs. placebo

Study 1504

Study 1504 bestod af 2 dele: Kohorte 1 og 2.

Den første del (Kohorte 1) var et open-label-studie med 18 patienter med Dravet syndrom. Formålet med den første del var at vurdere fenfluramins farmakokinetik og sikkerhed og at definere den terapeutiske dosis af fenfluramin, der skulle bruges i Kohorte 2. Anden del af studiet (Kohorte 2) var dobbeltblindet, randomiseret, to-armet,

fase 3 og placebo-kontrolleret og havde til formål at undersøge den kliniske effekt af fenfluramin i kombination med stiripentol, valproat og/eller clobazam.

Egnetheden til Kohorte 2 blev fastslået under et screeningsbesøg efterfulgt af en 6-ugers baseline observationsperiode. I observationsperioden blev patienternes baseline anfaldsaktivitet vurderet ud fra registrering af den daglige anfaldsaktivitet i en elektronisk dagbog. Efter den seks uger lange baseline observationsperiode blev patienterne randomiseret 1:1 til fenfluramin 0,4 mg/kg/dag eller placebo. Randomiseringen blev stratificeret efter alder (< 6 år, ≥ 6 år). Undersøgelsen bestod af en titrering, vedligeholdelse og nedtrapning/overgangsperiode, som alle var dobbeltblindede. Patienterne blev titreret til deres randomiserede dosis over en tre-ugers titreringsperiode (0,2 mg/kg/dag i syv dage titreret til 0,4 mg/kg/dag). Efter titreringsperioden fortsatte patienterne behandlingen med deres randomiserede dosis i en 12-ugers vedligeholdelsesperiode. Ved slutningen af vedligeholdelsesperioden (eller ved tidlig seponering) gennemgik patienterne en 2-ugers blindet nedtrapnings- eller overgangsperiode, afhængigt af om de forlod undersøgelsen eller overgik til det efterfølgende langsigtede OLE-studie. For patienter, der fuldførte den fulde titrerings- og vedligeholdelsesperiode (T+M), var den samlede behandlingsvarighed 15 uger.

I alt blev 115 patienter initielt screenet, og 87 patienter blev inkluderet i studiet og randomiseret til behandling med fenfluramin 0,4 mg/kg/dag (n = 43) eller placebo (n = 44). I alt gennemførte 77 patienter studiet (36 i fenfluramin-armen og 41 i placebo-armen). Alle randomiserede patienter modtog mindst én dosis fenfluramin eller placebo og havde mindst én uges dagbogsdata, og ITT-, sikkerheds- og mITT-populationerne var derfor identiske.

Inklusionskriterierne var patienter i alderen 2 til 18 år med Dravet syndrom, hvor anden epileptisk behandling ikke havde tilfredsstillende effekt på forekomsten af konvulsive anfald. Ved inklusion i studiet var der ikke krav om et minimum antal anfald. Patienter skulle være i behandling med clobazam og/eller valproat samt stiripentol. Primære eksklusionskriterier var pulmonal arteriel hypertension samt kardiovaskulær eller cerebrovaskulær sygdom.

Studiets primære endemål var gennemsnitlig ændring i CSF, og et vigtigt sekundært endemål var andel af patienter, der opnåede mindst 50 % reduktion i antallet af konvulsive anfald. Øvrige sekundære endemål var bl.a. livskvalitet og sikkerhed. Endemål forbundet med klinisk effekt blev opgjort efter 15 uger, mens sikkerhed blev opgjort efter et opfølgende besøg, som blev afholdt 3-6 måneder efter den sidste modtagne dosis af behandlingen.

Patienter fra både Study 1504 og Study 1 havde efterfølgende mulighed for at overgå til OLE-studiet (Study 1503).

Tabel 5-5. Baselinekarakteristika for Study 1504

	Fenfluramin 0,4 mg/kg/dag (n = 43)	Placebo (n = 44)
Alder (år), gns. (SD) [range]	8,8 (4,6) [2-18]	9,4 (5,1) [2-19]
Patienter yngre end 6 år	12 (28)	12 (27)
Mænd	23 (53)	27 (61)
Etnicitet		
Kaukasisk	23 (53)	29 (66)
Afroamerikansk	1 (2)	2 (5)
Asiatisk	2 (5)	1 (2)
Andre	3 (7)	1 (2)
Ikke rapporteret eller manglende[1]	13 (30)	11 (25)
Ukendt	1 (2)	0 (0)
BMI, gns. (SD)	17,3 (2,7)	19,1 (4,9)
Frekvens af konvulsive anfald (CSF) per 28 dage ved baseline		
Median (range)	14,0 (3-213)	10,7 (3-163)
Gns. (SD)	27,9 (36,9)	21,6 (27,6)
Antal samtidige antiepileptiske lægemidler ved baseline		
2	1 (2)	1 (2)
3	19 (44)	26 (59)
4	16 (37)	16 (36)
5	7 (16)	1 (2)
Anden antiepileptisk behandling i ≥10 % af subgruppe[2,3]		
Stiripentol	43 (100)	44 (100)
Clobazam	40 (93)	42 (96)
Valproat	38 (88)	39 (89)

	Fenfluramin 0,4 mg/kg/dag (n = 43)	Placebo (n = 44)
Topiramat	14 (33)	7 (16)
Levetiracetam	6 (14)	5 (11)
Kropsvægt (kg)		
Gns. (SD)	31,3 (14,85)	36,2 (21,08)
Median	27,9	30,5
BMI (kg/m^2)		
Gns. (SD)	17,32 (2,72)	19,14 (4,89)
Median	16,58	17,51

Resultater er opgjort som antal af patienter (%), med mindre andet er angivet. [1] Privatlivslovgivning i nogle regioner og lande udelukker videregivelse af visse personlige oplysninger. [2] Samtidig behandling i mindre end 10 % af patienterne inkluderede acetazolamid, clonazepam, diazepam, ethosuximid, felbamat, gamma-aminobutyric syre, lorazepam, phenobarbital, pregabalin og zonisamid. [3] Antallet af patienter på en ketogen diæt var 4 (5 %) i den samlede population, mens antallet af patienter med en vagusnervestimulatorimplantation var 5 (6 %). Gns.: Gennemsnitlig; SD: standardafvigelse.

Baseret på studiepopulationernes baselinekarakteristika kan fagudvalget ikke påpege forskelle, der er af væsentlig betydning i sammenligningen af studiearmene. Fagudvalget bemærker dog, at patientpopulation er heterogen hvad angår anfaldsfrekvens (CSF). Således spænder anfaldsfrekvensen fra 3 til 213 og fra 3 til 163 blandt patienter i hhv. fenfluramin- og placebo-armen, mens den gennemsnitlige anfaldsfrekvens mellem de to studiearme er 27,9 og 21,6 for hhv. fenfluramin- og placeboarmen. Fagudvalget vurderer, at denne forskel ikke er betydende. Fagudvalget bemærker, at der er flere patienter i fenfluramin-armen, der modtager samtidig behandling med topiramat. Dette kan have en betydning ift. vurderingen af uønskede hændelser, idet samtidig behandling med topiramat kan forøge risikoen for vægttab. Ligeledes kan forskellen i andelen af patienter, der modtager samtidig behandling med topiramat have betydning for vurderingen af den kliniske effekt. Dog vurderer fagudvalget, at størrelsen på denne forskel ikke er bekymrende og ikke vil have betydning for vurderingen. Fagudvalget vurderer derudover, at der ikke er betydende forskel i patienternes baselinekarakteristika ift. alder, vægt eller etnicitet eller samtidig behandling.

Fagudvalget vurderer, at patienterne i det kliniske studie har en højere sygdomsbyrde i form af flere anfald sammenlignet med den danske patientpopulation. Dette skyldes hovedsageligt, at studiepopulationen udelukkende inkluderer børn og unge, mens den danske patientpopulation også indeholder en betydelig andel af voksne patienter, som forventes at have lavere anfaldsfrekvens end børn. Ligeledes forventes studiepopulationen også at have en lavere forekomst af komorbiditeter sammenlignet med den danske patientpopulation.

På trods af disse forskelle vurderer fagudvalget dog, at den relative effekt af lægemidlet vil være sammenlignelig med den forventede effekt i en dansk patientpopulation.

5.2.2 Databehandling og analyse

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

Ansøgningen indeholder data for alle effektmål, som er defineret i Medicinrådets protokol, og for samtlige effektmål har ansøger foretaget en direkte sammenligning af fenfluramin og placebo med data fra Study 1504. Ansøger har indsendt data for klinisk effekt efter 15 ugers opfølgningstid, mens data for sikkerhed er opgjort 3-6 mdr. efter modtagelse af sidste dosis af behandlingen.

I det kliniske studie [12] blev effektmålet procentuel ændring i antallet af konvulsive anfald pr. 28 dage beregnet vha. en ANCOVA model med behandlingsarm, aldersgrupper (< 6 år og ≥ 6 år) og baseline anfaldsfrekvens som forklarende variable. I henhold til protokollen har ansøger dog suppleret med en beregning af den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald fra baseline, hvilket er baseret på en ujusteret analyse af *data on file*.

For effektmålet livskvalitet har ansøger indsendt data for deleffektmålet CGI-I, som er baseret på en vurdering af hhv. patient/omsorgsperson eller behandler (investigator). Fagudvalget vurderer, at de to typer af registreringer reflekterer forskellige aspekter og vælger på denne baggrund at medtage begge registreringstyper i vurderingen (se afsnit 5.1.4 for fagudvalgets vurdering af registreringstyperne).

Den direkte sammenligning af fenfluramin og placebo er i henhold til Medicinrådets metoder. Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

5.2.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Overordnet er evidensens kvalitet meget lav for sammenligningen mellem fenfluramin og placebo på baggrund af 1504-studiet. Evidensen er nedgraderet på baggrund af inkonsistens (kun ét studie), indirekthed (studiepopulationen er forskellig for den danske patientpopulation) samt unøjagtighed (konfidensintervallerne for to ud af tre deleffektmål for livskvalitet er meget brede og indeholder flere mulige konklusioner).

Den samlede evidenskvalitet er fastlagt ud fra det lavest vurderede kritiske effektmål (livskvalitet) og ender dermed med at være meget lav. En meget lav evidenskvalitet betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

Medicinrådet har vurderet risikoen for bias ved studiet ved Cochrane risk of bias tool 2.0, og den samlede vurdering fremgår af bilag 1.

5.2.4 Effektestimater og kategorier

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

Tabel 5-6. Resultater for klinisk spørgsmål 2

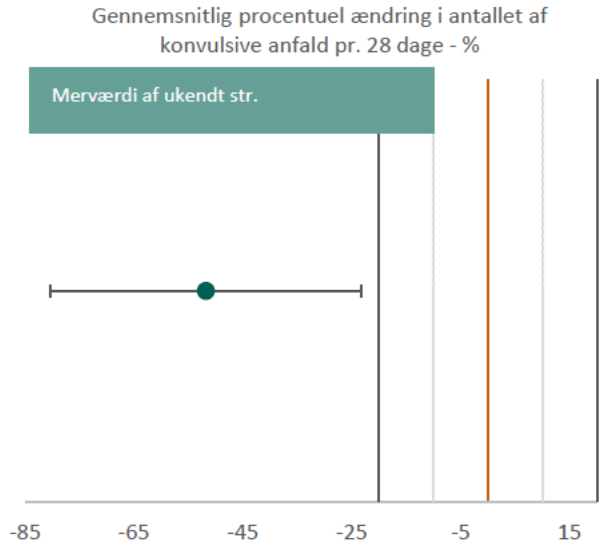
Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Konvulsive anfald	Gns. procentuel ændring i antallet af konvulsive anfald pr. 28 dage (MKRF: 20 %)	Kritisk	[redacted]	Merværdi af ukendt størrelse	*Kan ikke estimeres	Kan ikke kategoriseres	Moderat merværdi
	Andel patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald (MKRF: 20 %-point)	Kritisk	50,8 %-point (9,35; 216,02)	Ingen dokumenteret merværdi	RR: 12,18 (3,06; 48,53)	Stor merværdi	
Behov for anfaldsbrydende medicin (*rescue medication*)	Gns. antal dage/28 dage, hvor anfaldsbrydende medicin anvendes (MKRF: 1 dag)	Vigtig	0,2 dage (-0,81; 1,21)	Kan ikke kategoriseres	*Kan ikke estimeres	Kan ikke kategoriseres	Kan ikke kategoriseres
	Andel patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes (MKRF: 20 %-point)	Vigtig	[redacted]	Kan ikke kategoriseres	[redacted]	Kan ikke kategoriseres	
Livskvalitet	Gennemsnitlig ændring i PedsQL (MKRF: 4,5 point)	Kritisk	-0,6 point (-5,706; 4,496)	Kan ikke kategoriseres	*Kan ikke estimeres	Kan ikke kategoriseres	Kan ikke kategoriseres

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
	Andel patienter, som scorer 1 eller 2 i CGI-I (MKRF: 5 %-point) *(vurdering foretaget af patient eller omsorgsperson)*	Kritisk	14,7 %-point (-3,44; 51,98)	Kan ikke kategoriseres	RR: 1,72 (0,83; 3,54)	Kan ikke kategoriseres	
	Andel patienter, som scorer 1 eller 2 i CGI-I (MKRF: 5 %-point) *(vurdering foretaget af behandler (investigator))*	Kritisk	26,3 %-point (3,87; 74,12)	Merværdi af ukendt størrelse	RR: 2,65 (1,24; 5,66)	Moderat merværdi	
Uønskede hændelser	Andel patienter med mindst én alvorlig uønsket hændelse (SAE) (MKRF: 5 %-point)	Vigtig	-1,96 %-point (-16,9; 13,0)	Kan ikke kategoriseres	RR: 0,88 (0,32; 2,40)	Kan ikke kategoriseres	Kan ikke kategoriseres
	Kvalitativ gennemgang af bivirkningsdata	Vigtig	Se afsnit 5.1.4 for gennemgang af bivirkningsprofil				
Konklusion							
Samlet kategori for lægemidlets værdi	Moderat merværdi.						
Kvalitet af den samlede evidens	Meget lav.						

CI = konfidensinterval, RR = relativ risiko. *Det er ikke muligt at beregne en relativ risiko for effektmålet, da det er opgjort på en kontinuerlig skala.

Konvulsive anfald
Se afsnit 5.1.4 for definition af effektmålet konvulsive anfald.

Den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage
Det kliniske studie rapporterer den mediane procentuelle ændring i anfaldsfrekvens pr. 28 dage til at være -63,1 (range -100; 115) og -1,1 (range -82,8; 435,1) for hhv. fenfluramin og placebo. I protokollen har fagudvalget dog efterspurgt den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage, og ansøger har beregnet dette vha. *data on file* fra Study 1504. Den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage var [redacted] blandt patienter i behandling med fenfluramin, mens ændringen var [redacted] blandt patienter, der modtog placebo. Den absolutte forskel mellem interventionerne var dermed [redacted]



Figur 5-1. Punktestimat og 95 % konfidensinterval for den absolutte forskel for gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

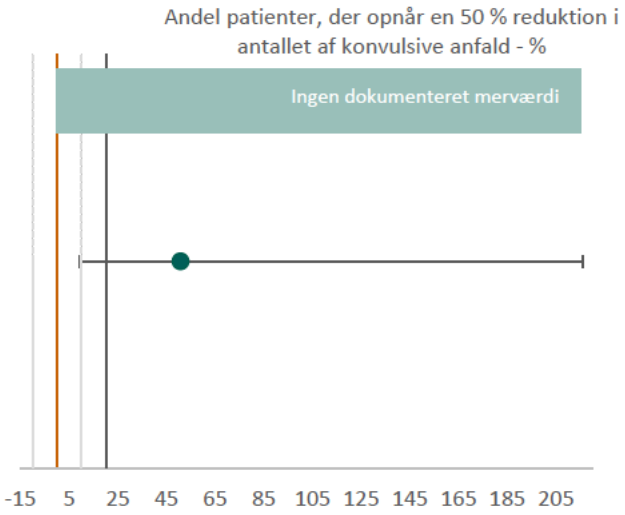
Den absolutte forskel er vist i figur 1 ovenfor.

Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel. Den øvre grænse for konfidensintervallet er tættere på den klinisk relevante forskel end på 0 (ingen effekt). Derfor er den foreløbige værdi af fenfluramin merværdi af ukendt størrelse vedr. den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage.

Den relative effektforskel kan ikke opgøres for deleffektmålet, da det er et kontinuert deleffektmål.

Andel patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald
Blandt patienter i behandling med fenfluramin opnåede 23 ud af 43 (53,5 %) mindst 50 % reduktion i antallet af konvulsive anfald, hvilket var tilfældet for 2 ud af 44 patienter (4,5 %) i behandling med placebo.

Den absolutte forskel er vist i Figur 5-2 nedenfor.



Figur 5-2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andelen af patienter, der opnår en 50 % reduktion i antallet af konvulsive anfald. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel 50,8 %-point afspejler en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effektforskel) end på den mindste klinisk relevante forskel. Omvendt inkluderer konfidensintervallet ikke effektstørrelser med en negativ værdi. Derfor er den foreløbige værdi af fenfluramin ingen dokumenteret merværdi vedr. andelen af patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald.

Baseret på den relative effektforskel, opgjort som en relativ risiko på 12,18 (95 % CI: 3,06; 48,53), har fenfluramin foreløbigt en stor merværdi vedr. andelen af patienter, der opnår en 50 % reduktion i antallet af konvulsive anfald.

Samlet konklusion vedr. konvulsive anfald
Fagudvalget vurderer, at fenfluramin aggregeret har en moderat merværdi vedr. konvulsive anfald sammenlignet med placebo.

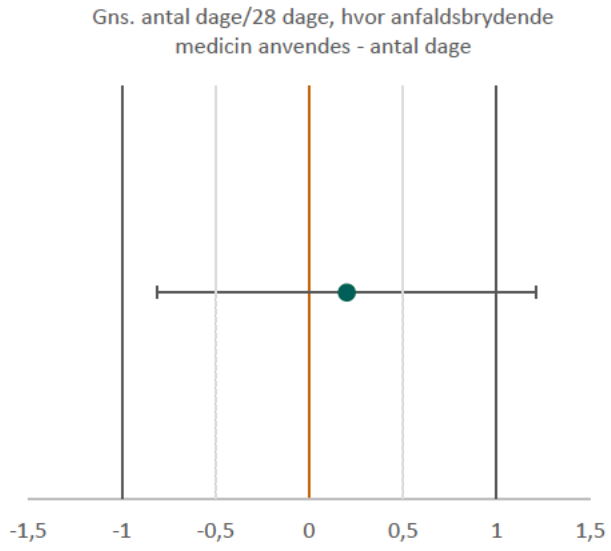
Fagudvalget har lagt vægt på, at den relative forskel for det ene deleffektmål (andel patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald) medfører en stor merværdi for fenfluramin sammenlignet med placebo. Derudover ligger punktestimaterne for begge delmål betydeligt over den mindste klinisk relevante forskel.

Data for effektmålet er baseret på et relativt lille studie, hvor der er stor spredning i effektmålet. De brede konfidensintervaller gør det vanskeligt at fastsætte effekten af fenfluramin, men fagudvalget finder det overvejende sandsynligt, at fenfluramin har en betydende merværdi sammenlignet med placebo. På den baggrund vurderer fagudvalget, at fenfluramin aggregeret har en moderat merværdi sammenlignet med placebo vedr. effektmålet konvulsive anfald.

Behov for anfaldsbrydende medicin
Se afsnit 5.1.4 for definition af effektmålet behov for anfaldsbrydende medicin.

Gns. antal dage/28 dage, hvor anfaldsbrydende medicin anvendes
Blandt patienter i behandling med fenfluramin var det gennemsnitlige antal dage/28 dage, hvor der blev anvendt anfaldsbrydende medicin 1,4 dage (95 % CI: 0,78; 2,04), mens det gennemsnitlige antal dage var 1,2 dage (95 % CI: 0,42; 1,98) blandt patienter, der modtog placebo.

Den absolutte forskel er vist i Figur 5-3 nedenfor.



Figur 5-3. Punktestimat og 95 % konfidensinterval for den absolutte forskel for gennemsnitligt antal dage/28 dage, hvor anfaldsbrydende medicin anvendes. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

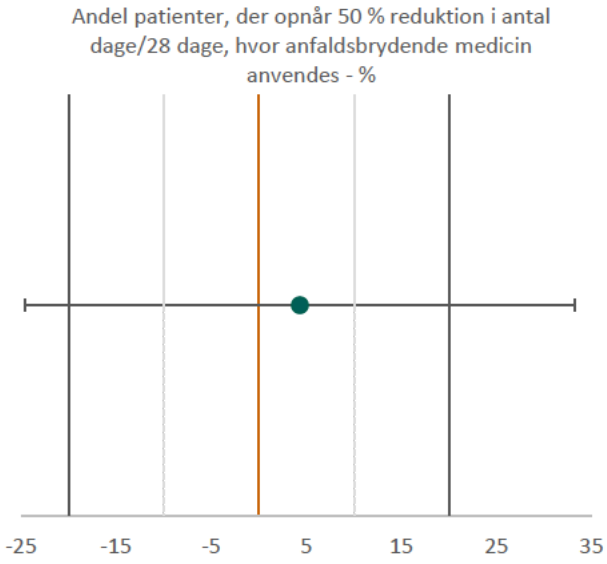
Punktestimatet for den absolutte effektforskel på 0,2 dage afspejler ikke en klinisk relevant effektforskel. Da dette er et negativt effektmål, hvor reduktion betyder en forbedring, ligger den nedre grænse for konfidensintervallet (1,21) tættere på en positiv klinisk relevant forskel end på 0 (ingen effektforskel). Konfidensintervallet er bredt og rummer muligheden for, at fenfluramin har både en negativ, positiv eller ingen værdi sammenlignet med placebo. Derfor kan den foreløbige værdi af fenfluramin vedr. det gennemsnitlige antal dage/28 dage, hvor anfaldsbrydende medicin anvendes, ikke kategoriseres efter Medicinrådets metoder.

Den relative effektforskel kan ikke opgøres for deleffektmålet, da det er et kontinuert deleffektmål.

Andel patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes

Blandt patienter i behandling med fenfluramin opnåede [redacted] en 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes. Blandt patienter i behandling med placebo var dette tilfældet for [redacted] I beregningen er ekskluderet de patienter, der i baselineperioden ikke havde behov for anfaldsbrydende medicin.

Den absolutte forskel er vist i Figur 5-4 nedenfor.



Figur 5-4. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andelen af patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Konfidensintervallet er bredt og rummer muligheden for, at fenfluramin har både en negativ, positiv eller ingen værdi sammenlignet med placebo. Derfor kan den foreløbige værdi af fenfluramin vedr. andelen af patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes, ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, opgjort som en relativ risiko på [redacted] kan værdien af fenfluramin vedr. andelen af patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes, ikke kategoriseres efter Medicinrådets metoder.

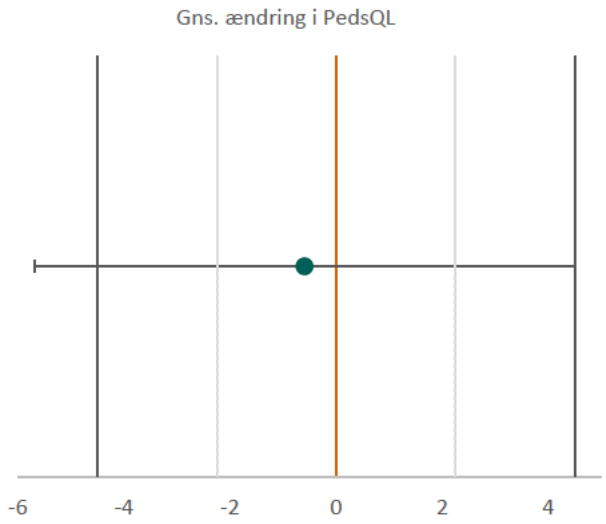
Samlet konklusion vedr. behov for anfaldsbrydende medicin
Fagudvalget vurderer, at den aggregerede værdi af fenfluramin vedr. behov for anfaldsbrydende medicin ikke kan kategoriseres efter Medicinrådets metoder. For begge delmål (det gennemsnitlige antal dage/28 dage, hvor anfaldsbrydende medicin anvendes samt andelen af patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes) er konfidensintervallet for bredt til at vurdere effekten af fenfluramin sammenlignet med placebo. Fagudvalget bemærker, at anfaldsbrydende medicin sjældent er blevet anvendt i det kliniske studie. Dette kan skyldes, at patientpopulationen består af en betydelig del af ældre børn og unge, hvor forekomsten af feberanfald forventes at være lavere end hos helt små børn. Det generelt lave behov for anfaldsbrydende medicin i studiet gør det ikke muligt for fagudvalget at vurdere, hvorvidt der er en forskel mellem fenfluramin og placebo, målt på behov for anfaldsbrydende medicin.

Livskvalitet
Se afsnit 5.1.4 for definition af effektmålet livskvalitet.

Gennemsnitlig ændring i PedsQL
PedsQL består af 4 funktionsskalaer, der måler fysisk, følelsesmæssig, social og skolemæssig funktion. Den samlede score er baseret på registreringerne indenfor alle 4 funktionsskalaer. En høj værdi indikerer forbedring i livskvalitet. I Study 1504 blev registrering af PedsQL foretaget af en forælder eller anden omsorgsperson på vegne af patienten.

Den gennemsnitlige ændring i total PedsQL score fra baseline var -0,9 (95 % CI: -4,43; 2,63) og -0,3 (95 % CI: -3,98; 3,38) blandt patienter i behandling med hhv. fenfluramin og placebo.

Den absolutte forskel er vist i Figur 5-5 nedenfor.



Figur 5-5. Punktestimat og 95 % konfidensinterval for den absolutte forskel for den gennemsnitlige ændring i PedsQL. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af fenfluramin vedr. den gennemsnitlige ændring i PedsQL ikke kategoriseres efter Medicinrådets metoder.

Den relative effektforskel kan ikke opgøres for deleffektmålet, da det er et kontinuert deleffektmål.

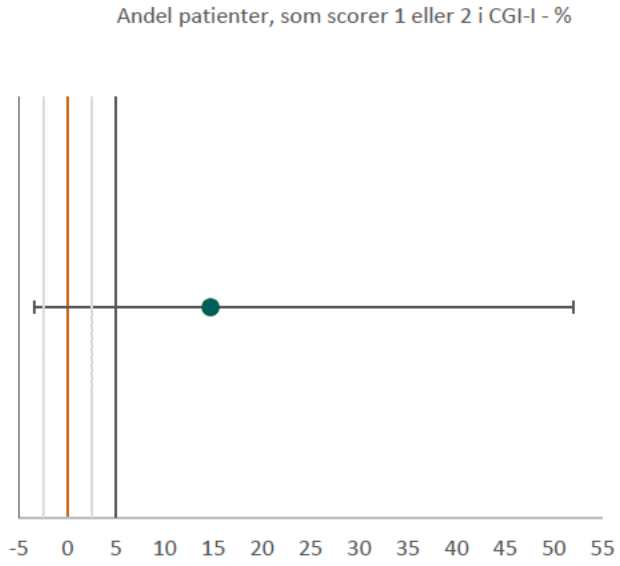
Andel patienter, som scorer 1 eller 2 i CGI-I

I Study 1504 blev CGI-I vurderet både af en forælder eller anden omsorgsperson samt af behandler (*investigator*). Fagudvalget har valgt at inddrage data for begge typer af registreringer i vurderingen af effektmålet (se afsnit 5.1.4 for fagudvalgets vurdering af registreringstyperne).

<u>Vurdering af CGI-I foretaget af patient eller omsorgsperson:</u>

Blandt patienter behandlet med fenfluramin opnåede 14 ud af 43 patienter (32,6 %, 95 % CI: 18,6 %; 46,6 %) en score på 1 eller 2, mens det samme var tilfældet for 9 ud af 44 patienter (20,5 %, 95 % CI: 8,5 %; 32,4 %) i behandling med placebo.

Den absolutte forskel er vist i Figur 5-6 nedenfor.



Figur 5-6. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andelen af patienter, som scorer 1 eller 2 i CGI-I. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til

halvdelen af MKRF. Resultatet er baseret på en vurdering foretaget af patient eller omsorgsperson.

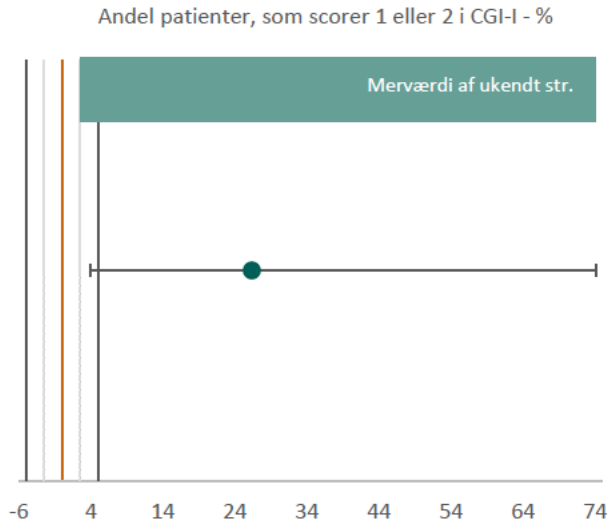
Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor kan den foreløbige værdi af fenfluramin vedr. andelen af patienter, som scorer 1 eller 2 i CGI-I ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, opgjort som en relativ risiko på RR: 1,72 (95 % CI: 0,83; 3,54), kan værdien af fenfluramin vedr. andelen af patienter, som scorer 1 eller 2 i CGI-I baseret på en vurdering af patient eller omsorgsperson ikke kategoriseres efter Medicinrådets metoder.

Vurdering af CGI-I foretaget af behandler (investigator):

Blandt patienter behandlet med fenfluramin opnåede 19 ud af 43 patienter (44,2 %, 95 % CI: 29,3 %; 59,0 %) en score på 1 eller 2, mens det samme var tilfældet for 7 ud af 44 patienter (15,9 %, 95 % CI: 5,1 %; 26,7 %) i behandling med placebo.

Den absolutte forskel er vist i Figur 5-7 nedenfor.



Figur 5-7. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andelen af patienter, som scorer 1 eller 2 i CGI-I. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF. Resultatet er baseret på en vurdering foretaget af behandler (investigator).

Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på den klinisk relevante forskel end på 0 (ingen effekt). Derfor er den foreløbige værdi af fenfluramin merværdi af ukendt størrelse vedr. andelen af patienter, som scorer 1 eller 2 i CGI-I.

Baseret på den relative effektforskel, opgjort som en relativ risiko på RR: 2,65 (95 % CI: 1,24; 5,66), har fenfluramin foreløbigt en moderat merværdi vedr. andelen af patienter, som scorer 1 eller 2 i CGI-I baseret på investigators vurdering.

Samlet konklusion vedr. livskvalitet
Baseret på ovenstående gennemgang af de to deleffektmål for livskvalitet, vurderer fagudvalget, at fenfluramin aggregeret har en værdi, som ikke kan kategoriseres efter Medicinrådets metoder.

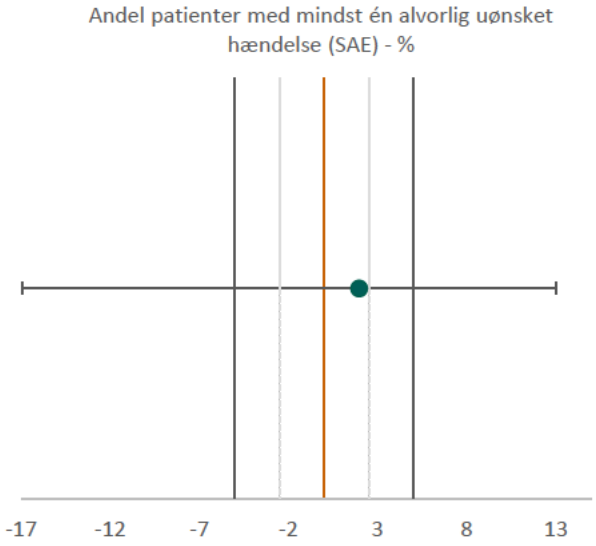
Dette skyldes, at værdien af fenfluramin ikke kan kategoriseres på baggrund af data for PedsQl. Derudover vurderer fagudvalget, at data for deleffektmålet CGI-I afhænger meget af, om vurderingen er foretaget af patient/omsorgsperson eller af investigator. Fagudvalget vurderer, at de to forskellige registreringer reflekterer forskellige aspekter, og at det ikke er muligt direkte at sammenholde de to typer af målinger. Fagudvalget bemærker, at det trods en væsentlig anfaldsreduktion ved behandling med fenfluramin ikke er muligt at påvise en betydende effekt på livskvalitet på tværs af de to deleffektmål. Fagudvalget vurderer, at dette muligvis kan skyldes, at patienterne trods anfaldsreduktion stadig kan have en række komorbiditeter, som kan påvirke livskvaliteten. Ligeledes kan studiernes begrænsede opfølgningstid og størrelser gøre det vanskeligt at påvise en betydende forbedring i livskvaliteten.

Overordnet vurderer fagudvalget, at fenfluramin muligvis kan medføre, at nogle patienter oplever en forbedring i livskvalitet. Dog indikerer data ikke, at populationens samlede livskvalitet forbedres ved behandlingen.

Uønskede hændelser
Se afsnit 5.1.4 for definition af effektmålet uønskede hændelser.

Andel patienter med mindst én alvorlig uønsket hændelse (SAE)
Blandt patienter i behandling med fenfluramin oplevede 6 ud af 43 (14,0 %) mindst én alvorlig uønsket hændelse, mens det var tilfældet for 7 ud af 44 patienter (15,9 %) i behandling med placebo.

Den absolutte forskel er vist i Figur 5-8 nedenfor.



Figur 5-8. Punktestimat og 95 % konfidensinterval for den absolutte forskel for andelen af patienter med mindst én alvorlig uønsket hændelse (SAE). De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Punktestimatet for den absolutte effektforskel afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet ligger tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Konfidensintervallet er bredt og rummer muligheden for, at fenfluramin har både en negativ, positiv og ingen værdi sammenlignet med placebo. Derfor kan den foreløbige værdi af fenfluramin vedr. andelen af patienter med mindst én alvorlig SAE ikke kategoriseres efter Medicinrådets metoder.

Baseret på den relative effektforskel, opgjort som en relativ risiko på RR: 0,88 (95 % CI: 0,32; 2,40), kan værdien af fenfluramin vedr. andelen af patienter med mindst én alvorlig SAE ikke kategoriseres efter Medicinrådets metoder.

Kvalitativ gennemgang af bivirkningsdata
Se afsnit 5.1.4 for en kvalitativ gennemgang af bivirkningsprofilen for fenfluramin.

Samlet konklusion vedr. effektmålet uønskede hændelser
Baseret på ovenstående gennemgang af effektmålets to delmål vurderer fagudvalget, at det ikke er muligt at vurdere, hvorvidt der er en betydende forskel i sikkerheden mellem fenfluramin og placebo, målt på andelen af patienter, der oplever alvorlige uønskede hændelser. Ud fra den kvalitative gennemgang af bivirkningsprofiler finder fagudvalget, at fenfluramin er forbundet med en række generende bivirkninger, men at størstedelen af disse forventes at være milde eller moderate.

Som beskrevet i afsnit 5.1.4 forventer fagudvalget, at behandling med fenfluramin vil være livslang, og at der derfor vil være risiko for kroniske bivirkninger, som ikke observeres i de kliniske studier. Derudover kan der være forskelle i bivirkningsprofilen for

børn og voksne. Dog er Dravet syndrom en alvorlig epilepsiform forbundet med væsentlig overdødelighed, og fagudvalget vurderer på den baggrund, at bivirkningsprofilen for fenfluramin samlet set er acceptabel. Fagudvalget vurderer dog, at kvaliteten af data er meget begrænset, og at vurderingen derfor er behæftet med stor usikkerhed.

Før opstart af behandling med fenfluramin skal risikoen for vægttab og hjerteklapanomalier overvejes, særligt ved samtidig behandling med andre appetitregulerende lægemidler. Ved behandling med fenfluramin skal patienter monitoreres tæt og løbende få foretaget ekkokardiogram, som angivet i produktresuméet for fenfluramin [6]. Derudover skal samtidig behandling med andre ASMs forsøges reduceret, idet behandling med flere lægemidler generelt medvirker til øget risiko for bivirkninger.

5.2.5 Fagudvalgets konklusion

Fagudvalget vurderer, at for patienter med Dravet syndrom, der modtager standardbehandling, der inkluderer stiripentol, giver tillæg af fenfluramin en moderat merværdi sammenlignet med standardbehandling alene.

I den samlede vurdering lægger fagudvalget vægt på, at fenfluramin har en moderat merværdi for det kritiske effektmål konvulsive anfald sammenlignet med placebo, og at den absolutte forskel for effektmålet markant oversteg den mindste klinisk relevante forskel defineret i protokollen. For de øvrige effektmål kan værdien af fenfluramin tillagt standardbehandling sammenlignet med standardbehandling alene ikke kategoriseres efter Medicinrådets metoder.

Intet i de tilgængelige data for disse effektmål indikerer dog, at tillæg af fenfluramin til standardbehandling, der inkluderer stiripentol, kan have en negativ værdi overfor standardbehandling alene, heller ikke når det kommer til andelen af patienter, der oplever alvorlige bivirkninger. Fagudvalget bemærker dog, at de tilgængelige kliniske data er baseret på et forholdsvist lille studie, og vurderingen er derfor behæftet med usikkerhed.

6. Andre overvejelser

6.1 Data for voksne patienter

Fagudvalget har i protokollen efterspurgt en præsentation af kliniske data for voksne patientpopulationer samt ansøgers vurdering af, hvorvidt den kliniske effekt af fenfluramin kan ekstrapoleres til voksne.

Ansøger har foretaget en subanalyse af anfaldsfrekvensen (CSF) blandt patienter ≥ 12 år fra Study 1 og 1504, svarende til [redacted] af den samlede studiepopulation. Ansøger angiver, at patienter, der modtog fenfluramin (blandt de mulige doser på tværs af

studierne, dvs. 0,2; 0,4 eller 0,7 mg/kg/dag) opnåede en gennemsnitlig reduktion i anfaldsfrekvens på [redacted] sammenlignet med placebo.

Fagudvalget finder, at ansøger ikke har besvaret spørgsmålet, idet der er indsendt data for patienter ≥ 12 og ikke ≥ 18 år. Fagudvalget fremhæver, at typen og hyppigheden af anfald typisk ændrer sig fra hyppige feberanfald ved 0-1 årsalderen til færre og andre typer af anfald hos børn på 5-10 år. Fagudvalget vurderer derfor, at der ikke kan forventes en stor forskel i anfaldsfrekvensen hos patienter, som er hhv. ≥ 12 og ≥ 18 år.

Baseret på de indsendte data for reduktion i anfaldsfrekvens vurderer fagudvalget dog, at den relative kliniske effekt af fenfluramin blandt patienter ≥ 12 ikke ser ud til at være væsentlig lavere end for patientpopulationerne i de kliniske studier. Fagudvalget vurderer derudover, at farmakokinetikken for fenfluramin er sammenlignelig blandt patienter ≥ 12 og ≥ 18 år. På den baggrund finder fagudvalget det samlet set er sandsynligt, at den relative kliniske effekt af fenfluramin vil være sammenlignelig for patienter hhv. ≥ 12 og ≥ 18 år. Dog er der en usikkerhed forbundet med vurderingen, idet der kun foreligger data for CSF. Fagudvalget fremhæver, at sikkerheden kan være anderledes hos ældre patienter, som kan have en anden risikoprofil end yngre patienter, bl.a. grundet komedicinering.

6.2 Data for stiripentol-naive patienter

Fagudvalget er bekendt med, at den kliniske effekt af fenfluramin er undersøgt i patienter, der ved studieinklusion enten 1) modtog samtidig behandling med stiripentol (Study 1504) eller 2) ikke havde modtaget stiripentol inden for 21 dage (Study 1). Fagudvalget finder det dog også relevant at se data for stiripentol-naive patienter og har derfor efterspurgt en præsentation af kliniske data for stiripentol-naive patientpopulationer samt ansøgers vurdering af den kliniske effekt af fenfluramin i denne population.

Studiepopulationen i Study 1 bestod af både stiripentol-naive og -erfarne patienter, der i studieperioden ikke modtog samtidig behandling med stiripentol. Ansøger har tilkendegivet, at det ikke er muligt at præsentere data for en subanalyse af stiripentol-naive patienter. Dog viser en post hoc analyse af patienter fra Study 1, som tidligere havde fejlet på stiripentol-behandling (svarende til 48,7 % af den fulde studiepopulation), at behandling med fenfluramin 0,7 mg/kg/dag medførte en reduktion i anfaldsfrekvens (CSF) på 60,8 % fra baseline sammenlignet med placebo. Ansøgers post hoc analyse er baseret på en ANCOVA model med behandlingsarm, aldersgrupper (<6 år og ≥ 6 år) og baseline anfaldsfrekvens som forklarende variable [13]. Ansøger angiver, at reduktionen i CSF blandt stiripentol-erfarne patienter er sammenlignelig med reduktionen i CSF observeret i den fulde studiepopulation (62,3 % reduktion i CSF fra baseline sammenlignet med placebo baseret på en tilsvarende ANCOVA model [7]). Ansøger angiver, at dette indikerer, at fenfluramin har sammenlignelig effekt på CSF hos både stiripentol-naive og -erfarne patienter.

Fagudvalget finder, at ansøger ikke har præsenteret data for stiripentol-naive patienter. På den baggrund finder fagudvalget, at det ikke er muligt at vurdere den kliniske effekt af fenfluramin blandt stiripentol-naive patienter.

Ansøger har derudover fremsendt data for de efterspurgte effektmål for en subpopulation bestående af stiripentol-erfarne patienter fra Study 1 (n = 38). Fagudvalget har vurderet det indsendte materiale og finder, at data overordnet set indikerer, at den kliniske effekt og sikkerhed af fenfluramin for stiripentol-erfarne er sammenlignelig med effekten og sikkerheden set i den fulde studiepopulation. Dermed kan fenfluramin være en behandlingsmulighed for stiripentol-erfarne patienter. Dog bemærker fagudvalget, at data er baseret på en meget lille patientpopulation, og at vurderingen dermed er behæftet med stor usikkerhed.

6.3 Data for patienter, som er i samtidig behandling med både clobazam og valproat

I Danmark gives stiripentol som tillægsterapi til patienter, hvor behandling med clobazam og valproat er utilstrækkelig. Fagudvalget ønsker at vurdere, hvorvidt fenfluramin ligeledes kan gives som tillægsterapi til clobazam og valproat. Fagudvalget har derfor efterspurgt kliniske data for patienter, som er i samtidig behandling med både clobazam og valproat, samt ansøgers vurdering af den kliniske effekt af fenfluramin i denne population.

Ansøger angiver, at 62 % og 60 % af patienterne i Study 1, der modtog fenfluramin 0,7 mg/kg/dag var i samtidig behandling med hhv. valproat og clobazam. Baseret på den samlede studiepopulation modtog patienterne i gennemsnit 2,4 ASMs (SD: 1) ved baseline. Ansøger anfører, at den kliniske effekt af fenfluramin derved forventes at være repræsenteret i form af resultaterne baseret på Study 1. Derudover henviser ansøger til post hoc analyser dels rapporteret af Knupp et al. [14], dels baseret på *data on file* fra de kliniske studier. Iflg. ansøger viser post hoc analyserne, at den kliniske effekt af fenfluramin er uafhængig af, om patienterne modtager samtidig behandling med clobazam og valproat.

Post hoc analysen af Knupp et al. [14] er baseret på poolet data fra Study 1 og 1504 (n = 206) og har undersøgt effekten af fenfluramin på anfaldsfrekvens (CSF) med og uden samtidig behandling med clobazam og/eller valproat.

Patienter, der modtog samtidig behandling med clobazam og valproat opnåede en ændring i CSF på -68,7 % sammenlignet med placebo. Dette var baseret på 36 patienter, der modtog fenfluramin 0,7 mg/kg og 78 patienter, der modtog placebo. Til sammenligning opnåede patienter, der ikke modtog samtidig behandling med både clobazam og valproat en ændring i CSF på -51,6 % sammenlignet med placebo. Dette var dog alene baseret på 4 patienter, der modtog fenfluramin og 6 patienter, der modtog placebo [14].

Fagudvalget vurderer, at data indikerer, at fenfluramin hos patienter, der modtager samtidig behandling med både clobazam og valproat har en effekt på CSF, der er

sammenlignelig med effekten observeret i den fulde patientpopulation fra både Study 1 og Study 1504.

6.4 Risikoen for hypertension i lungekredsløbet samt hjerteklapsygdom

Produktresuméet for fenfluramin til behandling af Dravet syndrom angiver, at det grundet risiko for hypertension i lungekredsløbet samt hjerteklapsygdom er påkrævet at overvåge hjertefunktionen ved hjælp af ekkokardiografi før og under behandlingen. Fagudvalget har derfor efterspurgt ansøgers vurdering af risikoen for ovenstående bivirkninger, særligt hos voksne patienter.

Ansøger angiver, at der skal udføres ekkokardiografi hver 6. måned de første 2 år af behandlingen og derefter 1 gang årligt. Ansøger angiver, at der i de randomiserede kliniske studier ikke var tilfælde af mitralklapinsufficiens, hjerteklapsygdom eller pulmonal arteriel hypertension. Der var ligeledes ikke set tilfælde af disse bivirkninger i OLE-studiet, hvor op til 330 patienter blev behandlet i op til 3 år, eller i det prospektive observationelle studie, der er baseret på op til 5 års behandling med fenfluramin. Derudover er fenfluramin blevet tolereret godt i European Expanded access program (EAP). [redacted] Der blev ikke set tilfælde af hjerteklapsygdom eller pulmonal arteriel hypertension blandt patienter i EAP.

I det prospektive, observationelle real-world studie [15] var der ligeledes ingen tegn på ændring i hjerteklappens struktur eller funktion, og der var heller ingen ekkokardiogramfund, der tydede på pulmonal arteriel hypertension hos nogen patient ved op til 5 års behandling.

I US Expanded access program [16] var der ligeledes ingen patienter, der udviklede hjertesygdom eller pulmonal arteriel hypertension ved op til 180 dages behandling.

Ansøger mener, at disse data samlet understøtter den generelle og kardiovaskulære sikkerhed ved langtidsbehandling med fenfluramin.

Fagudvalget noterer, at forekomsten af hypertension i lungekredsløbet og hjerteklapsygdom ser ud til at være lav ud fra de tilgængelige data. Dog vurderer fagudvalget, at disse alvorlige bivirkninger med stor sandsynlighed ikke vil fremgå i opgørelser med begrænset opfølgningstid. Da fenfluramin som udgangspunkt skal gives som livslang behandling, finder fagudvalget det bekymrende, at der ikke foreligger data med længere opfølgningstid. Derudover forventes risikoen for disse bivirkninger at være anderledes blandt voksne patienter, hvor der foreligger meget begrænset erfaring.

6.5 Påvirkning af patientens vægt ved samtidig behandling med ketogen diæt og/eller topiramat eller zonisamid og fenfluramin

Fagudvalget er bekendt med, at behandling med ketogen diæt og/eller topiramat eller zonisamid kan resultere i vægttab. Fagudvalget har derfor efterspurgt ansøgers vurdering af, hvorledes samtidig behandling med disse lægemidler og fenfluramin kan påvirke patientens vægt.

Ansøger angiver, at 25 % og 24 % af patienterne i Study 1 og Study 1504 modtog samtidig behandling med topiramat. I disse kliniske studier var de hyppigste uønskede hændelser nedsat appetit, diarré og vægttab (7 %). Vægttab blev dog ofte genvundet ved fortsat behandling. [redacted] Ansøger angiver, at det er vanskeligt at konkludere på disse data, idet behandling med andre ASMs, herunder stiripentol, også er forbundet med vægttab. Derudover er Dravet syndrom muligvis også forbundet med vægttab, uafhængigt af ASM behandling [17]. [redacted]

Fagudvalget finder, at ansøger ikke har bidraget med data, som kan belyse den mulige påvirkning af patientens vægt ved samtidig behandling med ketogen diæt og/eller topiramat eller zonisamid. Fagudvalget vurderer derfor, at der er betydelig usikkerhed forbundet med risikoen for vægttab ved samtidig behandling med disse lægemidler. Et vægttab på 7 % kan være et stort vægttab og kan være betydende for den enkelte patient. Om end kropsvægt muligvis kan genvindes, bør der for børn være særlig opmærksomhed forbundet med patientens tilsvarende højdeudvikling. På denne baggrund anbefaler fagudvalget, at kropsvægten for alle patienter monitoreres løbende ved behandling med fenfluramin.

6.6 Overlevelsesdata ved behandling med fenfluramin

Dravet syndrom er forbundet med potentielt livstruende anfald og en væsentlig overdødelighed, og fagudvalget har derfor efterspurgt overlevelsesdata ved behandling med fenfluramin.

Ansøger angiver, at der i et review af Cooper et al., 2016 [5] blev undersøgt dødsfald blandt 100 patienter med Dravet syndrom. Den mediane opfølgningstid var 10 år, og reviewet estimerede den Dravet-specifikke dødsrate til at være 15,84 pr. 1000 patientår, svarende til ca. 15-16 % af studiepopulationen pr. 10 år. Den Dravet-specifikke rate for *Sudden Unexpected Death in Epilepsy* (SUDEP) blev estimeret til 9,32 pr. 1000 patientår (svarende til 9-10 % af studiepopulationen pr. 10 år). Dette tyder på, at de resterende dødsfald, som primært skyldes status epilepticus, sker med en rate på 5-6 % pr. 10 år.

Ansøger angiver derudover, at en artikel af Cross et al., 2021 [18] vurderede betydningen af fenfluramin på den forventede mortalitetsincidens, herunder SUDEP i patienter med Dravet syndrom. I alt blev 732 patienter behandlet med fenfluramin, svarende til eksponering på 1185,3 patientår. Der indtraf 3 dødsfald, alle i fase 3 programmet: Ét dødsfald indtraf i placebo-armen (sandsynligvis SUDEP), og 2 dødsfald indtraf i fenfluramin-armen (et sandsynligvis SUDEP og et sikkert SUDEP). Den overordnede mortalitetsrate og SUDEP-rate ved behandling med fenfluramin var 1,7 pr. 1000 patientår (95 % CI: 0,4, 6,7), hvilket er lavere end det overordnede estimat på 15,8 pr. 1000 patientår (95 % CI: 9,9, 25,4) og SUDEP-estimatet på 9,3 (95 % CI: 5,0; 17,3), som blev rapporteret i Cooper et al. 2016 blandt patienter, der modtog standardbehandling.

Fagudvalget vurderer, at patienter i kliniske studier vil have en lavere forekomst af komorbiditeter og vil være monitoreret tættere end den generelle patientpopulation, og data for disse studier er dermed ikke direkte overførbare til den danske patientpopulation. På denne baggrund finder fagudvalget, at det ud fra de tilgængelige kliniske data ikke er muligt at vurdere, hvorvidt behandling med fenfluramin påvirker mortaliteten forbundet med Dravet syndrom.

6.7 Overvejelser vedr. behandlingsvarighed og eventuel dosisjustering før potentiel seponering af lægemidlet.

Fagudvalget er bekendt med, at nogle patienter først oplever klinisk effekt efter længere tids behandling med fenfluramin, dvs. udover de 12 uger, som anvendes i registreringsstudier. Fagudvalget har derfor efterspurgt ansøgers overvejelser vedr. behandlingsvarighed og eventuel dosisjustering før potentiel seponering af lægemidlet.

Ansøger angiver, at i OLE-studiet (Study 1503), hvor 330 patienter blev behandlet med fenfluramin i op til 3 år, var den mediane eksponeringsvarighed ved Dag 120 Safety data cut-off 631 dage (fra 7 til 1086 dage) (*data on file*). I observationelle real-world settings varierede eksponeringen for daglig behandling med fenfluramin fra 1 til 27 år, og i studiepopulationen med den længste opfølgning var den gennemsnitlige behandlingsvarighed 16,1 år (fra 6 til 27 år) [20]. Denne lange opfølgningstid er tilgængelig fra et belgisk observationelt studie, hvori fenfluramin blev tilladt til behandling af Dravet syndrom, selv efter at lægemidlet var trukket tilbage fra markedet [20].

Ansøger angiver, at data fra OLE-studiet samt real-world data [15,20] samstemmende viser, at den kliniske effekt af fenfluramin er vedvarende, og at der ikke ses tegn på aftagende effekt over tid.

Ift. seponering af lægemidlet angiver ansøger, at dosis skal nedjusteres gradvist, før patienten ophører med behandling. Iflg. produktresuméet for fenfluramin skal nedjusteringen i dosis følge det samme titreringsskema som ved opstart af behandling. Pludselig seponering bør undgås for at mindske risikoen for forhøjet anfaldsfrekvens og status epilepticus [6].

Fagudvalget finder, at ansøger ikke har præsenteret data for patienter, der først opnår klinisk effekt efter 12 ugers behandling. Ansøger har derimod præsenteret studier, der rapporterer langtidsopfølgning af den kliniske effekt af fenfluramin. Fagudvalget bemærker, at langtidsopfølgningen er baseret på OLE-studiet samt real world studier, der inkluderer patienter, der oplever effekt af behandlingen. Derudover er real world data baseret på meget små patientpopulationer (n = 9 i studiet af Schoonjans et al. og n = 10 i studiet af Ceulemans et al.). Ud fra det tilgængelige data finder fagudvalget det derfor ikke muligt at foretage konklusioner vedr. behandlingsvarighed og evt. dosisjustering.

Fagudvalget vurderer, at i klinisk praksis skal der foretages en konsekvent registrering af anfaldshyppighed, før behandling med fenfluramin kan påbegyndes. Denne registrering skal danne grundlag for den efterfølgende vurdering af behandlingens effekt. Registreringsperioden skal være af mindst én måneds varighed, men vil afhænge af anfaldshyppigheden, hvor patienter med lav anfaldsfrekvens skal følges over længere tid for at vurdere den kliniske effekt.

7. Relation til behandlingsvejledning

Medicinrådet har ikke udarbejdet en behandlingsvejledning vedrørende Dravet syndrom.

8. Referencer

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende epilepsi

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jakob Christensen *Overlæge*	Lægevidenskabelige Selskaber og Dansk Neurologisk Selskab
Medlemmer	**Udpeget af**
Hans Christian Laugaard-Jacobsen *Overlæge*	Region Nordjylland
Mette Møller Handrup *Overlæge*	Region Midtjylland
Mette Rokkjær *Overlæge*	Region Syddanmark
Janne Friedrich *Overlæge*	Region Sjælland
Ioannis Tsiropoulos *Overlæge*	Region Hovedstaden
Gesche Jürgens *Overlæge, forskningslektor*	Dansk Selskab for Klinisk Farmakologi
Rikke Kudahl Jensen *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Kern Olofsson *Ledende overlæge*	Inviteret af formanden (fra Epilepsihospitalet Filadelfia)
Deltager ikke	Dansk Sygepleje Selskab
Berit Andersen *Patient/patientrepræsentant*	Danske Patienter
Lotte Hillebrandt *Patient/patientrepræsentant*	Danske Patienter

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10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. februar 2022	Godkendt af Medicinrådet

11. Bilag

Bilag 1: Cochrane – risiko for bias

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

Tabel 11-1. Vurdering af risiko for bias Lagae et al. [7], 2019, Study 1, NCT02682927 og NCT02826863

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Allokering af behandling blev foretaget ved brug af et interaktivt web-responssystem. Randomiseringplanen blev udarbejdet af en uafhængig statistiker, og randomiseringen var stratificeret ift. alder (<6 år, ≥ 6 år). Efter baselineperioden blev patienterne randomiseret 1:1:1 til 0,2 mg/kg fenfluramin; 0,7 mg/kg fenfluramin eller placebo.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor både investigator, patienter, omsorgspersoner og øvrige deltagere var blindede til den allokerede behandling. Opløsningen af fenfluramin og placebo var identiske af udseende og smag. Studiet forløb over 14 uger, hvorefter patienter havde mulighed for at overgå til et open label extension studie.
Manglende data for effektmål	**Forbehold**	Alle primære, vigtige sekundære og andre sekundære effektmål var præspecificeret, med undtagelse af effektmål markeret med "post hoc". Data er opgjort for mITT-populationen, defineret som alle patienter, der modtog mindst en dosis fenfluramin eller placebo og havde mindst en uge rapporteret i den elektroniske dagbog. I alt gennemførte 110 ud af 119 randomiserede patienter studiet. Manglende data blev ikke imputeret.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Forbehold**	Der foreligger data på størstedelen de effektmål, der er beskrevet i studieprotokollen, men data for ikke-konvulsiv anfaldsfrekvens samt antal anfaldsfri dage er ikke rapporteret. Derudover er der rapporteret data for en post hoc analyse af patienter med 0 eller 1 anfald i løbet af studieperioden samt tidsforløb over anfaldsfrekvensen.

Bias	Risiko for bias	Uddybning
Overordnet risiko for bias	**Forbehold**	Manglende data blev ikke tildelt en værdi i de statistiske analyser, og det kan ikke siges, hvorvidt manglende data kan have en indflydelse på de rapporterede resultater. Derudover er data for ikke-konvulsiv anfaldsfrekvens samt antal anfaldsfri dage er ikke rapporteret.

Tabel 11-2. Vurdering af risiko for bias Chiron et al. [8], 2000, STICLO-France

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Efter baselineperioden blev patienter randomiseret til behandling med enten stiripentol eller placebo. Randomiseret allokering af behandling blev foretaget ved brug af en computergenereret liste.
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor stiripentol og placebo blev administreret som tabletter.
Manglende data for effektmål	**Forbehold**	Alle statistiske analyser blev udført i ITT-populationen. I alt gennemførte 36 ud af 42 randomiserede patienter studiet. Det er ikke beskrevet, hvordan manglende data blev håndteret.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Forbehold**	Det er ikke angivet, hvorvidt de rapporterede endemål var præspecificeret i studieprotokollen. Studiet er ikke registreret hos ClinicalTrials.
Overordnet risiko for bias	**Forbehold**	Det er ikke beskrevet, hvordan manglende data blev håndteret. Det er derudover uklart, hvorvidt der er rapporteret data for alle effektmål specificeret i studieprotokollen.

Tabel 11-3. Vurdering af risiko for bias Nabbout et al. [12], 2020, Study 1504, NCT02926898

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Efter baselineperioden blev patienter randomiseret 1:1 til behandling med enten fenfluramin eller placebo. Den randomiserede allokering af behandling blev foretaget ved brug af et interaktivt web-responssystem og var stratificeret ift. alder (<6 år, ≥ 6 år).
Effekt af tildeling til intervention	**Lav**	Dobbeltblindet studie, hvor stiripentol og placebo blev administreret vha. sekventielt nummererede flasker.
Manglende data for effektmål	**Forbehold**	I alt blev 87 patienter randomiseret til behandling med fenfluramin (n = 43) eller placebo (n = 44), hvoraf 77 patienter gennemførte studiet (36 i fenfluramin-armen og 41 i placebo-armen). Statistiske analyser af klinisk effekt blev analyseret i mITT-populationen, defineret som alle randomiserede patienter modtog mindst én dosis fenfluramin eller placebo og havde mindst én uges dagbogsdata. Sikkerhed blev vurderet blandt alle randomiserede patienter, der modtog mindst en dosis af behandling. Da alle randomiserede patienter modtog mindst én dosis fenfluramin eller placebo og havde mindst én uges dagbogsdata, var ITT-, sikkerheds- og mITT-populationerne identiske. Manglende data blev ikke imputeret.
Risiko for bias ved indsamlingen af data	**Lav**	Dobbeltblindet, placebo-kontrolleret studie.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Forbehold**	Alle statistiske analyser blev foretaget iht. en præspecificeret analyseplan. Dog er ikke alle effektmål defineret i analyseplanen rapporteret i studiet. Dette gælder f.eks. data for livskvalitet målt ved QOLCE og EG-5D-5L)
Overordnet risiko for bias	**Forbehold**	Manglende data blev ikke imputeret i de statistiske analyser af endemål vedr. klinisk effekt, og det kan ikke siges, hvorvidt manglende data kan have en indflydelse på de rapporterede resultater. Derudover er der ikke rapporteret data for alle effektmål defineret i analyseplanen.

Bilag 2: GRADE

Klinisk spørgsmål 2 – fenfluramin sammenlignet med placebo til behandling af patienter med Dravet syndrom

Tabel 11-4. GRADE evidensprofil for klinisk spørgsmål 2

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Fenfluramin 0,4 mg/kg/dag	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Gns. procentuel ændring i antallet af konvulsive anfald pr. 28 dage (MKRF: 20 %)												
1	RCT	Forbehold[a]	Alvorlig[b]	Alvorlig[c]	Ingen	Ingen	43	44	*Kan ikke estimeres	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
Andel patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald (MKRF: 20 %-point)												
1	RCT	Forbehold[a]	Alvorlig[b]	Alvorlig[c]	Ingen	Ingen	43	44	RR: 12.178 (3.056, 48.525)	50,8 %-point (9,35; 216,02)	⨁◯◯◯ MEGET LAV	KRITISK
Gns. antal dage/28 dage, hvor anfaldsbrydende medicin anvendes (MKRF: 1 dag)												
1	RCT	Forbehold[a]	Alvorlig[b]	Alvorlig[c]	Meget alvorlig[d]	Ingen	43	44	*Kan ikke estimeres	0,2 dage (-0,81; 1,21)	⨁◯◯◯ MEGET LAV	Vigtig
Andel patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes (MKRF: 20 %-point)												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Fenfluramin 0,4 mg/kg/dag	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Forbehold[a]	Alvorlig[b]	Alvorlig[c]	Meget alvorlig[d]	Ingen	28	19	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIG
Gennemsnitlig ændring i PedsQL (MKRF: 4,5 point)												
1	RCT	Forbehold[a]	Alvorlig[b]	Alvorlig[c]	Meget alvorlig[d]	Ingen	43	44	*Kan ikke estimeres	-0,6 point (-5,696; 4,496)	⨁◯◯◯ MEGET LAV	KRITISK
Andel patienter, som scorer 1 eller 2 i CGI-I (MKRF: 5 %-point) (caregiver assessment)												
1	RCT	Forbehold[a]	Alvorlig[b]	Alvorlig[c]	Alvorlig[e]	Ingen	43	44	RR: 1,72 (0,83; 3,54)	14,7 %-point (-3,44; 51,98)	⨁◯◯◯ MEGET LAV	KRITISK
Andel patienter, som scorer 1 eller 2 i CGI-I (MKRF: 5 %-point) (investigator assessment)												
1	RCT	Forbehold[a]	Alvorlig[b]	Alvorlig[c]	Ingen	Ingen	43	44	RR: 2.65 (1,24; 5,66)	26,3 %-point (3,87; 74,12)	⨁◯◯◯ MEGET LAV	KRITISK
Andel patienter med mindst én alvorlig uønsket hændelse (SAE) (MKRF: 5 %-point)												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	Fenfluramin 0,4 mg/kg/dag	Placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Lav/for-behold[a]	Alvorlig[b]	Alvorlig[c]	Meget alvorlig[d]	Ingen	43	44	RR: 0,88 (0,32; 2,40)	-1,96 %-point (-16,9; 13,0)	⨁◯◯◯ MEGET LAV	VIGTIG
Kvalitet af den samlede evidens	MEGET LAV[f]											

[a] Der er nedgraderet ét niveau, da der var nogle forbehold i vurderingen af risiko for bias.

[b] Der er nedgraderet ét niveau, da der kun var ét studie.

[c] Der er nedgraderet ét niveau, da studiepopulationen kun indeholder børn og unge mens den danske patientpopulation også indeholder en betydelig andel af voksne patienter. Patienter i studiepopulationen vurderes desuden at have en større sygdomsbyrde.

[d] Der er nedgraderet to niveauer, da konfidensintervallet er meget bredt og indeholder både positive og negative konklusioner.

[e] Der er nedgraderet ét niveau, da konfidensintervallet indeholder én beslutningsgrænse.

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

*Det er ikke muligt at beregne en relativ risiko for effektmålet, da det er opgjort på en kontinuerlig skala.

ZOGENIX

Application for the assessment of fenfluramine (Fintepla®) for the treatment of Dravet syndrome

Application to the Danish Medicines Council

Text marked with yellow is strictly confidential and should be deleted before publication.

ZOGENIX

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Contact information	
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Overview of the pharmaceutical	
Proprietary name	Fintepla®
Generic name	Fenfluramine
Marketing authorization holder in Denmark	Zogenix ROI Limited, Trinity House, Charleston Road, Ranelagh, Dublin 6, D06 C8X4, Ireland
ATC code	N03AX26
Pharmacotherapeutic group	Other antiepileptics
Active substance(s)	Fenfluramine hydrochloride
Pharmaceutical form(s)	Oral solution
Mechanism of action	Fenfluramine is a serotonin-releasing agent that stimulates multiple 5-HT receptor subtypes through the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HTiD, 5-HT2A and 5-HT2C receptors and the sigma-1 receptor. The precise mechanism of action of fenfluramine in Dravet syndrome is not known (1).

Overview of the pharmaceutical	
Dosage regimen	Fenfluramine is administered as an oral solution twice daily. The dose depends on patients' weight and if they receive concomitant treatment with stiripentol or not. Patients who are **not** taking stiripentol The starting dose is 0.1 mg/kg per administration (0.2 mg/kg per day). After seven days, if patients tolerate fenfluramine and require a further reduction of seizures, the dose can be increased to 0.2 mg/kg per administration (0.4 mg/kg per day). After an additional seven days, for patients who are tolerating fenfluramine and require further seizure reductions, the dose can be increased to 0.35 mg/kg twice daily (0.7 mg/kg per day). The 0.7 mg/kg per day dose is the recommended maintenance dose for patients who are not taking stiripentol. For patients requiring more rapid titration, the dose may be increased every four days. The maximum dose of 26 mg (13 mg twice daily, i.e. 6.0 mL twice daily) should not be exceeded (1). Patients who are taking stiripentol The starting dose is 0.1 mg/kg per administration (0.2 mg/kg per day). After 7 days, if patients tolerate fenfluramine and requires a further reduction of seizures, the dose can be increased to 0.2 mg/kg per administration (0.4 mg/kg per day). The 0.4 mg/kg per day dose is the recommended maintenance dose for patients who are taking stiripentol. For patients requiring more rapid titration, the dose may be increased every four days. A maximum dose of 17 mg (8.6 mg twice daily, i.e. 4.0 mL twice daily) should not be exceeded (1).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Fenfluramine is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic drugs, in children aged 2 years to 17 years and adults (1).
Other approved therapeutic indications	None.
Will dispensing be restricted to hospitals?	Yes.
Combination therapy and/or co-medication	None required.
Packaging – types, sizes/number of units, and concentrations	Bottle containing 60 mL oral solution, a bottle adaptor and four 3 mL oral syringes with 0.1 mL graduations. Bottle containing 120 mL oral solution, a bottle adaptor and four 3 mL oral syringes with 0.1 mL graduations. Bottle containing 360 mL oral solution, a bottle adaptor and four 6 mL oral syringes with 0.5 mL graduations (1).
Orphan drug designation	Yes (EU/3/13/1219) (1).

2. Abbreviations

AE	Adverse events
AED	Anti-Epileptic Drug
ANCOVA	Analysis of covariance
CGI-I	Clinical Global Impression – Improvement
CLB	Clobazam
CSF	Convulsive seizure frequency
CSR	Clinical study report
DMC	Danish Medicines Council
EOS	End of study
EPAR	European Public Assessment Reports
ITT	Intent-to-treat
mITT	Modified intent-to-treat
OR	Odds ratio
PedsQL	Pediatric Quality of Life Inventory
PK	Pharmacokinetics
SAE	Serious adverse event
SD	Standard deviation
SE	Status epilepticus
SMEI	Severe myoclonic epilepsy of infancy
SoC	Standard of care
STP	Stiripentol
SUDEP	Sudden Unexpected Death in Epilepsy
TEAE	Treatment-emergent adverse event
VPA	Valproate
T+M	Titration + Maintenance
QoL	Quality of life

3. General guidance to readers

During the fenfluramine development programme and the regulatory procedure(s) to gain marketing authorisation for fenfluramine in Europe and the US; several decisions were adopted to provide a common and consistent convention to characterising some features of the clinical development program and analysis methods used. Consequently, some earlier clinical trial reports, regulatory documents and publications may present apparently inconsistent data or descriptions to those currently used and agreed to with the regulators. To assist reviewers of this document, some of these inconsistencies have been highlighted below, to avoid any misunderstanding:

- Pharmacokinetic/dynamic studies with concomitant stiripentol (STP) determined that a dose of 0.5 mg/kg of fenfluramine was therapeutically equivalent to 0.7 mg/kg of fenfluramine without stiripentol
- Following discussions with the Food and Drug Administration (FDA) and during day 120 questions with the European Medicines Agency (EMA); the agencies have requested that fenfluramine dosing be stated based on its molecular weight rather than its weight as a hydrochloride.

This has no impact on the results of the study or study outcomes, only its reporting. This document reflects the most updated dose naming, as summarised in Table 1 and Table 2.

Table 1: Dose terminology

Previous dose	Updated dose	Twice daily dose
0.8 mg/kg/day	0.7 mg/kg/day	0.35 mg/kg/day
0.5 mg/kg/day	0.4 mg/kg/day	0.2 mg/kg/day
0.2 mg/kg/day	0.2 mg/kg/day	0.1 mg/kg/day

Table 2: Maximum capped daily doses for a >30kg patient, not concomitantly receiving STP and patients who are receiving concomitantly STP

Previous maximum dose	Updated dose	Twice daily dose
Maximum capped daily doses for a >30kg patient, not concomitantly receiving STP		
30 mg/day	26 mg/day	13 mg/day
Maximum capped daily doses for a >30kg patient, concomitantly receiving STP		
20 mg/day	17 mg/day	8.5 mg/day

The naming of arms in the fenfluramine trials refers to the maintenance doses received, however, depending on a patient's weight, doses may have been capped on an individual patient basis if a daily maximum dose was reached (e.g., 26 mg without STP, or 17 mg with STP).

It should be noted that the summaries of efficacy results have been adjusted during the EMA assessment with the reanalysed data. Therefore, there may be some deviations comparing to the raw data within the clinical study reports (CSR) compared to that initially submitted to EMA (see

European Public Assessment Report (EPAR) on fenfluramine page 62 (2)). Moreover, changes on the study naming convention have been driven by the FDA:

- Study 1 is unchanged (i.e., 1st cohort from study 1501 and 1502, pooled)
- Study 1504 has become Study 2
- A study previously referred to as Study 2 (i.e., 2nd cohort from study 1501 and 1502, pooled) + Japanese patients, has become Study 3
- Study 1503, an open-label extension (OLE) study is unchanged.

The current SPC mentions "Study 2 ("previously known as 1504)" within. There is currently no reference to Study 3 in the SPC as the data did not underpin the European regulatory filing and is currently under internal review and analyses. The CSR on Study 3 is currently not available. For consistency and in line with the CSRs, regulatory filing, and EMA assessment reports this document refers to "Study 1504" and not Study 2.

As part of the Risk Management Plan agreed with the EMA, the following additional risk minimisation measures will be implemented:

- Healthcare professional educational materials
- Patient educational materials
- Controlled access programme (CAP) to 1) prevent off-label use in the weight management of obese patients and 2) confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring using echocardiography in patients: prior to; periodically throughout; and at the end of treatment with Fintepla
    - Prior to starting treatment, patients must undergo an ECHO to establish a baseline prior to initiating treatment and exclude any pre-existing valvular heart disease or pulmonary hypertension
    - ECHO monitoring should be conducted every 6 months for the first 2 years and annually thereafter
    - If an ECHO indicates pathological valvular changes, a follow-up ECHO should be considered at an earlier timeframe to evaluate whether the abnormality is persistent. If pathological abnormalities on the ECHO are observed, it is recommended to evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver, and cardiologist
    - If treatment is stopped because of aortic or mitral valvular heart disease, appropriate monitoring and follow-up should be provided in accordance with local guidelines for the treatment of aortic or mitral valvular heart disease.

4. Summary

Background

Zogenix has requested for the Danish Medicines Council (DMC) to evaluate fenfluramine (Fintepla) as a treatment of seizures associated with Dravet syndrome as an add-on therapy to standard of care (SoC) anti-epileptic drugs (AEDs) in children aged two years or older. Fenfluramine is a serotonin-releasing agent that is administered as an oral solution twice daily. The dose depends on the patients' weight and if they receive concomitant treatment with stiripentol (STP) as part of their existing SoC, or not.

Methods

The DMC protocol for fenfluramine outlined two clinical questions: clinical question 1, which focuses on fenfluramine as an add-on therapy to a patient's existing combination of SoC AED therapies that do not include stiripentol, with stiripentol as a potential comparator; and clinical question 2, which focuses on fenfluramine as an add-on therapy to a patient's existing combination of SoC AED therapies that do include stiripentol, with SoC AEDs including stiripentol as a comparator.

Based on Danish expert opinion from Filadelfia, other expert opinion in the UK NICE appraisal of fenfluramine (3), and a published literature review that indicates STP is the most frequently recommended Dravet syndrome therapy in international guidelines(4), STP is firmly established as a SoC AED in Dravet syndrome. Further recent discussions with clinicians at Filadelfia indicates that, when considering the use of fenfluramine in current clinical practice 87% of patients are currently receiving STP and the remaining 13% have had prior experience of using STP. This is consistent with other markets. Given this firmly established use of STP as a SoC AED in Danish practice, we do not anticipate that fenfluramine, as a newly licensed add-on to SoC AEDs, will routinely be used before STP has been tried in patients for whom STP is considered to be a treatment option. Zogenix therefore proposes the positioning of fenfluramine in clinical practice, as an add-on to SoC AEDs, is for use:

- without concomitant STP in patients for whom **STP is not considered to be a treatment option** (i.e., in a subpopulation of clinical question 1) – this is anticipated to be negligible use on the grounds that STP is anticipated to be an earlier used SoC treatment option in the vast majority of patients, or
- without concomitant STP in patients who have **previously tried STP** (i.e., in a subpopulation of clinical question 1, which we refer to as clinical question 1a), or
- **in addition to STP** in patients requiring further seizure control (as in clinical question 2).

Based on this anticipated clinical positioning, STP is therefore not a relevant comparator.

We conducted a systematic literature search, using the search terms and criteria defined in the DMC protocol. For the whole of clinical question 1 as defined in the DMC protocol, we identified Study 1 (fenfluramine) and STICLO-France (STP). However, in addition to STP not being a relevant comparator based on the proposed positioning of fenfluramine, there are differences between Study 1 and STICLO-France that mean we are technically unable to present a robust comparative analysis of fenfluramine and STP in clinical question 1.

To answer clinical question 1a, the head-to-head comparison of fenfluramine versus placebo in the subgroup of patients who were STP-experienced in Study 1 was applied. To answer clinical question 2, we applied the head-to-head comparison of fenfluramine versus placebo in patients receiving SoC AED that included STP, as conducted in Study 1504.

Results

Clinical question 1: What is the value of fenfluramine compared to stiripentol for patients with Dravet syndrome (≥2 years of age) who receive combination therapy that does not include stiripentol?

No comparative analysis of fenfluramine and STP was conducted in clinical question 1, as this comparison is not relevant to the proposed positioning of fenfluramine and due to differences between Study 1 and STICLO-France which made it technically unfeasible to conduct a comparison.

In the subpopulation of patients who are STP naïve and for whom STP is not considered to be a treatment option, continued SoC AED without STP (as in the placebo arm of Study 1) would be the relevant comparator. It is not feasible to conduct a subgroup analysis specifically in this subpopulation. We therefore refer the DMC to the results of the whole of Study 1 (presented in the Appendix) as an indication of the results that may be anticipated in this subpopulation.

Clinical question 1a: What is the value of fenfluramine compared to placebo for patients with Dravet syndrome (≥2 years of age) who receive combination therapy that does not include stiripentol and who are stiripentol-experienced?

[redacted] Based on an ANCOVA model, which adjusts for age and baseline convulsive seizure frequency (CSF), the additional reduction in CSF from baseline with fenfluramine was 60.8% (P=0.002). [redacted] These results show that a substantially higher proportion of patients in the fenfluramine arm achieved a 50% reduction in the number of convulsive seizures compared to placebo. [redacted] The absolute difference in the proportion of patients with a clinically meaningful score on CGI-I in the parent/caregiver rating was 34.66 percentage points (95% CI: 10.9, 58.4). The relative difference (RR) was 6.545 (95% CI: 0.919, 46.612). In the investigator rating, the absolute difference was 57.39 percentage points (95% CI: 34.0, 80.7) and the relative difference (RR) was 10.182 (95% CI: 1.487, 69.719) (5). For all efficacy outcomes, fenfluramine met and exceeded the minimal clinically relevant differences defined in the DMC protocol. In terms of serious adverse events (AEs), the absolute difference in the proportion of patients who experienced at least one serious treatment-emergent AE (TEAE) was 18.2 percentage points (95% CI: 2.1, 34.3). The relative risk was 6.652 (95% CI: 0.0383, 115.433).

Clinical question 2: What is the value of fenfluramine compared to placebo for patients with Dravet syndrome (≥2 years of age) who receive combination therapy that includes stiripentol?

The difference in means between fenfluramine and placebo in the outcome: mean percentage change in the number of convulsive seizures per 28 days was -51.82 percentage points (95% CI: -80.2522, -23.3878) in an unadjusted analysis. Based on the primary analysis using a pre-specified ANCOVA model, which adjusts for age and baseline CSF, the additional reduction in CSF from baseline with fenfluramine was 54.04% (95% CI: 35.55, 67.23; P<0.001). In the outcome:

proportion of patients who achieved a 50% reduction in the number of convulsive seizures, the risk ratio was 12.178 (95% CI: 3.056, 48.525), and the absolute difference was 50.8 percentage points (95% CI: 9.35, 216.02). These results show a substantially higher proportion of patients in the fenfluramine arm who achieved a 50% reduction in the number of convulsive seizures compared to placebo. For these seizure-related efficacy outcomes, for which the trial was adequately powered, fenfluramine met and exceeded the minimal clinically relevant differences defined in the DMC protocol. The difference in means in the outcome: mean number of days per 28 days where rescue medication was used was 0.2 days (95% CI: -0.8107, 1.2107). [redacted] In terms of the proportion of patients with a score of 1 or 2 on CGI-I (based on parent/caregiver ratings), the absolute difference between fenfluramine and placebo was 14.7 percentage points (95% CI: -3.44, 51.98). The risk ratio was 1.716 (95% CI: 0.832, 3.541). The proportion of patients with a score of 1 or 2 on CGI-I (based on investigator ratings) was an absolute difference of 26.3 percentage points (95% CI: 3.87, 74.12) and a risk ratio of 2.652 (95% CI: 1.243, 5.659). The absolute difference in the proportion of patients who experienced at least one serious TEAE was -1.96 percentage points (95% CI: -16.9, 13.0) in the fenfluramine arm compared to placebo. The risk ratio was 0.877 (95% CI: 0.321, 2.399), showing a lower risk of serious TEAEs associated with fenfluramine compared to placebo.

5. Literature search

We conducted a systematic literature search, applying the search string defined in the protocol provided by the DMC for fenfluramine. We searched for relevant literature in PubMed and CENTRAL (via Cochrane Library) on 29 July 2021, and the search terms and number of hits in PubMed and CENTRAL can be found in Table 24 and Table 25 in Appendix 10.1, respectively.

The inclusion and exclusion criteria are listed in Table 26 in Appendix 10.1. In general, we excluded references with other patient populations than patients with Dravet syndrome (or severe myoclonic epilepsy of infancy (SMEI)) and references not reporting results on at least one of the defined critical or important outcome measures in the protocol. In addition, we excluded case reports and case studies and references assessing unlicensed doses of fenfluramine or stiripentol.

Figure 1 provides a PRISMA flow diagram showing the number of records identified and the number of included and excluded records.

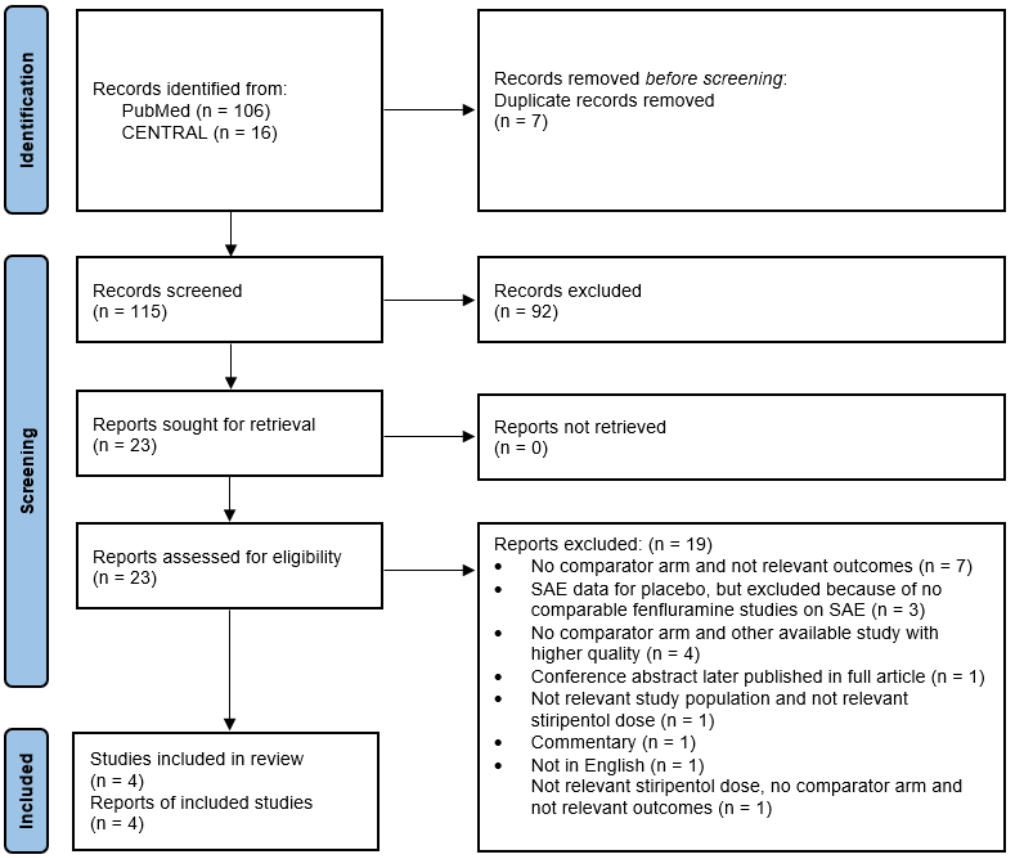

Figure 1: PRISMA flow diagram

We identified 106 records using PubMed and an additional 16 records in CENTRAL. A total of 115 records were identified after duplicates were removed. All references were screened, and 92 records were excluded based on title/abstract. Subsequently, 23 full-text papers were assessed for eligibility. Of these, 19 were excluded. The reason for excluding each reference is provided in Table 27 in Appendix 10.1. In total, four references reporting results from four different studies were included for the purpose of answering the clinical questions outlined in the DMC protocol.

5.1 Relevant studies

In the literature search, we identified four relevant references for the assessment of fenfluramine. These references are presented in Table 3.

Table 3: Relevant studies identified in the literature review

Reference (author, year, title, journal)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Lagae L et al. (2019): Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 394(10216): 2243-54. (6)	Study 1 (1501 and 1502)	NCT02682927 and NCT02826863	Start date: January 2016 (NCT02682927) and July 2016 (NCT02826863) Completion date: July 2020	1
Nabbout R et al. (2020): Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA neurology. 77(3): 300-8. (7)	Study 1504	NCT02926898	Start date: September 2016 Completion date: June 2018	2
Chiron C et al. (2000): Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet. 356(9242): 1638-42. (8)	STICLO-France	Not registered at clincialtrials.gov	Not reported	1
Guerrini R et al. (2002): Stiripentol in SMEI: a placebo-controlled Italian trial. Epilepsia. 43(Suppl 8): Abstract 155, P496. (9)	STICLO-Italy	Not registered at clincialtrials.gov	Not reported	1

We identified three studies relevant for the patient population with Dravet syndrome who are two years or older with unsatisfactory response to treatment with clobazam and/or valproate and who do not receive treatment with stiripentol (clinical question 1) (6,8,9). Study 1, published in Lagae et al. 2019 (6), assessed fenfluramine 0.7 mg/kg per day as add-on therapy compared to placebo as add-on therapy. Two studies (STICLO-France and STICLO-Italy) assessed stiripentol 50 mg/kg per day as add-on therapy compared to placebo as add-on therapy (8,9). The STICLO-Italy trial was not published in a full-text article and only available as an abstract presented at the fifth European congress on Epileptology in October 2002 (9). Moreover, the purpose of STICLO-Italy was to confirm the results of STICLO-France; therefore, we will not apply STICLO-Italy in the assessment of stiripentol in clinical question 1.

In addition, Study 1 included a subpopulation consisting of patients who were stiripentol-experienced and who received fenfluramine 0.7 mg/kg per day. To demonstrate the value of fenfluramine in patients where stiripentol is undesirable due to contraindications, intolerance or lack of effect, we present results from the stiripentol-experienced subpopulation and a comparative analysis with placebo as well, referred to as clinical question 1a.

We identified one study (Study 1504) relevant for the patient population with Dravet syndrome who are two years or older with unsatisfactory response to treatment with clobazam and/or valproate and stiripentol (clinical question 2) (7). Study 1504, published in Nabbout et al. 2020 (7), assessed fenfluramine 0.4 mg/kg per day as add-on therapy that included stiripentol compared to placebo as add-on therapy that included stiripentol.

5.2 Main characteristics of included studies

In this section, we present the main characteristics of the included studies.

Information in the trials described in the following was obtained from the EPAR related to the respective drugs and the publications by Lagae et al. 2019 and Nabbout et al. 2020 for fenfluramine and the publication by Chiron et al. 2000 for stiripentol (6–8). If we were not able to find the desired information on fenfluramine in the EPAR, the CSRs on the fenfluramine studies were applied instead. For information on inclusion and exclusion criteria, baseline characteristics, primary and secondary outcomes, and methods of analysis, please see Appendix 10.2.

Table 4 gives an overview of the study designs, populations, treatments and primary and key secondary endpoints in the included studies.

Table 4: Overview of included studies

Trial	Study design	Population	Treatment	Primary endpoints	Key secondary endpoints
Study 1	Prospective, merged analysis of two identical phase III, randomised, multinational, double-blinded, placebo-controlled trials (trial 1501 and 1502)	Children and young adults with Dravet syndrome	• Fenfluramine 0.2 mg/kg/day divided into two daily doses • Fenfluramine 0.7 mg/kg/day divided into two daily doses • Placebo to match intervention	Change in CSF (mean number of convulsive seizures per 28 days) from baseline to the treatment + maintenance (T+M) period	• Proportion of subjects (n (%)) who achieved a ≥ 50% reduction in CSF from baseline to the T+M period • Duration of the longest convulsive seizure-free interval during the T+M period (days)
Study 1504	Phase III, multicenter, randomised, double-blinded, placebo-controlled parallel-group trial	Children and young adults with Dravet syndrome	• Fenfluramine 0.5 mg/kg/day divided into two daily doses • Placebo to match intervention	Change from Baseline during T+M in the mean convulsive seizure frequency (CSF) per 28 days for the fenfluramine 0.5 mg/kg/day arm compared with the placebo arm	• Proportion of subjects who achieved a ≥50% reduction from Baseline in CSF • Longest interval between convulsive seizures
STICLO-France	**Randomised, placebo-controlled double-blinded add-on trial**	Children (3 years or older) with SMEI	• Stiripentol 50 mg/kg/day twice or three times daily • Placebo to match intervention	Percentage of responders, defined as having experienced at least a 50% reduction of clonic (or tonic-clonic) seizure frequency during the second month of the double-blind period compared with baseline	Absolute count of clonic (or tonic-clonic) seizures during the second month of the double-blind period (normalised to 30 days, by dividing the raw count by the exact number of days of observation and

multiplying by 30) and the percentage of change from baseline

5.2.1 Study 1

Study 1 comprises two identical phase III, randomised, multinational, double-blinded, placebo-controlled trials (trial 1501 and 1502). The purpose of the two trials was to assess the efficacy and safety of two doses of fenfluramine compared to placebo, when used as adjunctive therapy in children and young adults with Dravet syndrome. One trial was done in the USA and Canada (NCT02682927), the other in western Europe and Australia (NCT02826863). Due to incomplete enrolment of patients in both trials, it was decided to merge the datasets before unblinding the results and analysis.

Study 1 consisted of three arms:

- fenfluramine 0.7 mg/kg (N=40);
- fenfluramine 0.2 mg/kg per day (N=39); and
- placebo (N=40).

The study duration comprised of a six-week baseline period followed by a two-week titration period and a 12-week maintenance period, resulting in a total treatment period of 14 weeks. Patients could continue into an open-label extension study. The design of Study 1 is presented in Figure 2.

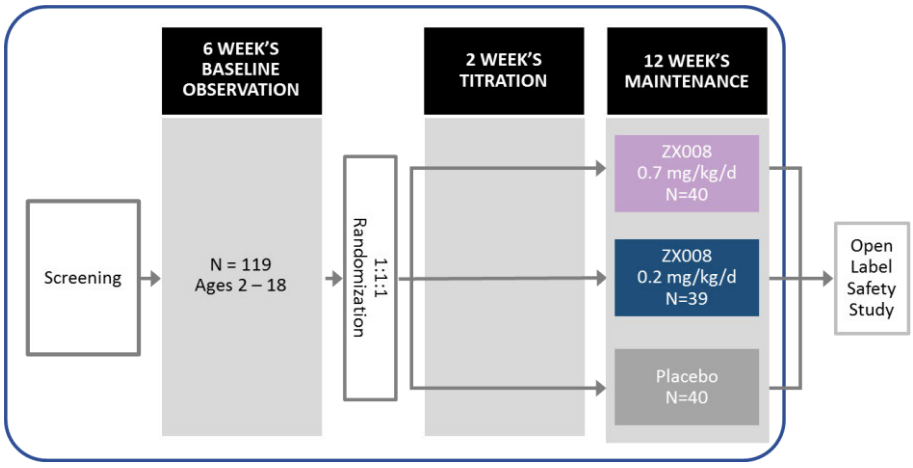

Figure 2: The trial design of Study 1. The figure shows the baseline observation period, the titration period and the maintenance period where patients were randomised 1:1:1 into three arms

At the initial screening visit, patients were randomised to dose group and dose concentrations (two randomisation schemes) to account for dose and dose concentration. This randomisation was conducted using a 2:2:1:1 scheme (0.2 mg/kg/day: 0.7 mg/kg/day: 0.2 placebo: 0.7 placebo) (2). The six-week baseline period consisted of establishing the initial eligibility during the screening visit, followed by an observation period where patients were assessed for baseline seizure activity. Recordings of patient's daily seizure activity were entered into an electronic diary. The usage of STP among patients was an exclusion criterion in Study 1.

Upon completing the six-week baseline period, patients were randomised 1:1:1 to either fenfluramine 0.2 mg/kg per day or 0.7 mg/kg per day (divided into two daily doses) or placebo to match the intervention. Randomisation was stratified by age (<6 years and ≥6 years) (2).

All patients were titrated in a blinded manner to their randomised dose over a two-week titration period (0.2 mg/kg/day in day 1-4 titrated to 0.4 mg/kg/day in day 5-8 and finally titrated to 0.7

mg/kg/day). After titration, patients continued treatment with their assigned dose during a 12-week maintenance period. At the end of the maintenance period (or early discontinuation), patients either underwent a two-week blinded taper or transition period. Patients who were enrolled in the open-label extension study completed transition into this study, while patients who were not enrolled into the open-label extension study underwent a taper off study medication (doses were administrated blinded similar to the titration period, i.e., decreased in four-day increments). Parents or caregivers used an electronic diary every day during the study to record the number and type of seizure, dosing and use of rescue medication.

A total of 173 patients were screened and a total of 119 patients were randomised to the study treatments. The intent-to-treat (ITT) population included all patients randomised to a study treatment: 40 patients in the placebo arm, 39 patients in the fenfluramine 0.2 mg/kg/day arm, and 40 patients in the fenfluramine 0.7 mg/kg/day arm. A modified ITT population was defined (mITT) to comprise patients who received at least one dose of fenfluramine or placebo and had at least one week of diary data available. Overall, there was an equal distribution of male and female patients (64 males, 55 females) with a mean (SD) age of nine years (4.65). A total of 110 patients (92.4%) completed the study with highest completion rate in the fenfluramine 0.2 mg/kg/day arm (100%). 34 patients (85.0%) and 37 patients (92.5%) completed the fenfluramine 0.7 mg/kg/day and placebo arm, respectively (2). An overview of the patient disposition is presented in Figure 3.

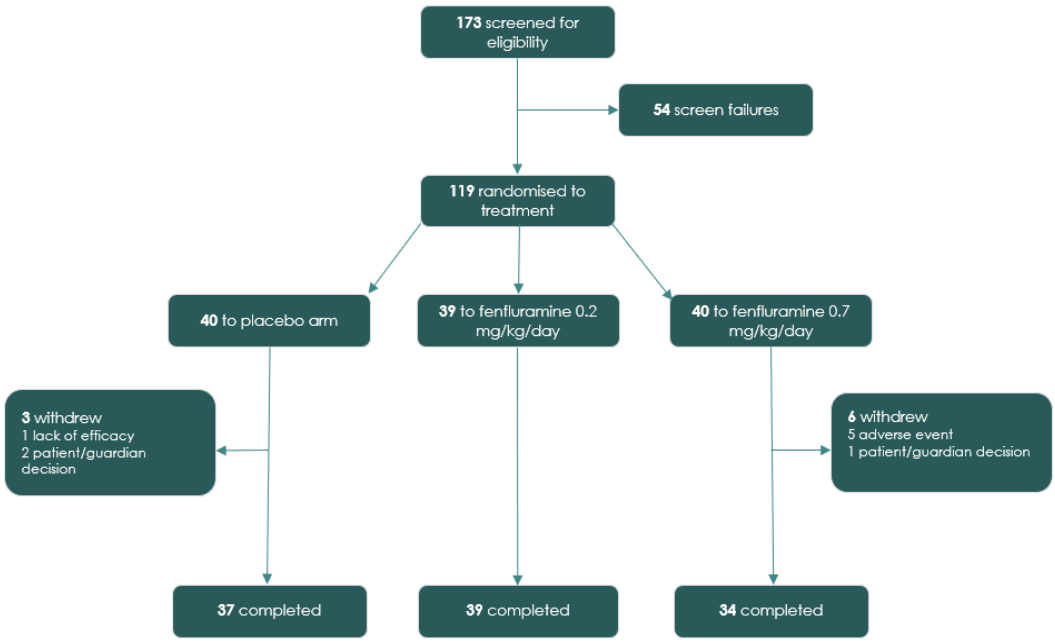

Figure 3: The patient disposition in Study 1 (Lagae et al. 2019)

5.2.2 Study 1504

Study 1504 consisted of two parts: Cohort 1 and Cohort 2.

The first part (Cohort 1) was an open-label study with 18 patients with Dravet syndrome. The purpose of the first part was to assess the pharmacokinetics (PK) and safety of fenfluramine and to define the therapeutic dose of fenfluramine to be used in Cohort 2. Cohort 2 was the second part of the trial and was double-blinded, randomised, two-armed, phase III and placebo-controlled, with the purpose of evaluating fenfluramine in combination with STP, valproate (VPA) and/or clobazam (CLB) (2). The following is a description of the second part of the trial (Cohort 2).

The two arms in Study 1504 were:

- fenfluramine 0.4 mg/kg/day with a maximum of 20 mg/day (N=43); and
- placebo (N=44).

The trial design is shown in Figure 4.

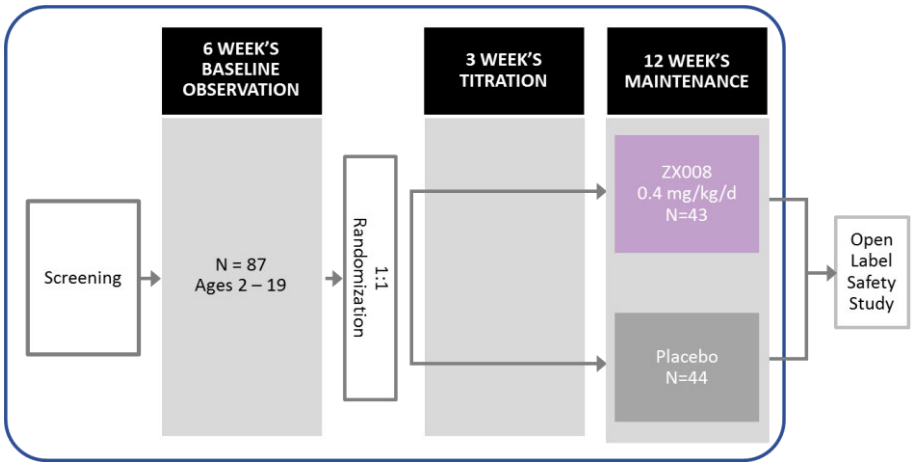

Figure 4: The trial design of Study 1504. The figure shows the baseline observation period, the titration period, and the maintenance period where patients were randomised 1:1:1 into three arms

Initial eligibility for Cohort 2 was established during a screening visit followed by a six-week baseline observation period. During the observation period, patients' baseline seizure activity was assessed based on recording the daily seizure activity in an electronic diary. After the six-week baseline period, patients were randomised 1:1 in a double-blinded manner to receive fenfluramine 0.4 mg/kg/day or placebo. The randomisation was stratified by age (<6 years, ≥6 years) to ensure balance across treatment arms. The study consisted of a titration, maintenance, and taper/transition period, which were all double-blinded. Patients were titrated in a blinded manner to their randomised dose over a three-week titration period (0.2 mg/kg/day for seven days titrated to 0.4 mg/kg/day). After the titration period, patients continued treatment with their randomised dose during a 12-week maintenance period. At the end of the maintenance period (or at early discontinuation), patients underwent a two-week blinded taper or transition period, depending on whether they exited the study or were enrolled in the subsequent long-term open-label extension study. For patients who completed the full titration and maintenance period (T+M), the total treatment duration was 15 weeks.

A total of 115 patients were screened for eligibility to participate in Study 1504 Cohort 2 and comprised the enrolled population. 28 patients (24.3%) were screen failures (18 patients due to ECHO findings). 87 patients (75.7%) were randomised to study treatments (44 patients to placebo and 43 patients to fenfluramine 0.4 mg/kg/day). All randomised patients received at least one dose of fenfluramine or placebo and had at least one week of diary data; therefore, the ITT, safety and mITT populations were identical (2).

A total of 77 patients (88.5%) completed the study (41 patients in the placebo arm and 36 patients in the fenfluramine arm). 10 patients did not complete the study: three patients in the placebo arm and seven patients in the fenfluramine 0.4 mg/kg/day arm. An overview of the patient disposition is presented in Figure 5.

Figure 5: Overview of the patient disposition in Study 1504 (Nabbout et al. 2020)

5.2.3 STICLO-France

STICLO-France was a randomised, placebo-controlled, double-blinded add-on trial, assessing the efficacy of STP in patients with SMEI. The trial was conducted in France. After a one-month baseline period, patients were randomised to either STP or placebo as add-on to clobazam and valproate. Patients were assessed every month during the double-blind period of 2 months, and in subsequent open treatment for at least 1 month (8).

The study consisted of two arms:

- STP administered as capsules at the dose of 50 mg/kg a day, twice or three times daily (N=22); and
- placebo (N=20).

The maximum dose of valproate was 30 mg/kg per day and 0.5 mg/kg per day for clobazam. The dose of STP could be increased from 50 to 100 mg/kg per day and the comedication could be changed if seizures persisted. During the double-blind period, the daily dose of STP was 49.3 mg/kg per day (95% CI: 47.4, 51.2) on average.

A total of 47 patients were eligible to participate in the study. 42 were randomised to treatment with either STP or placebo (20 patients were allocated to placebo and 22 patients were allocated to stiripentol). One patient in the STP arm was not compliant and was excluded from the study. Five patients were withdrawn during the double-blind period (one on STP and four on placebo), which resulted in a total of 36 patients completing the trial (20 on STP and 16 on placebo). An overview of the patient disposition is presented in Figure 6.

Overall, the STP and placebo groups in STICLO-France were similar in terms of demographic and clinical characteristics before recruitment (see Table 30, Appendix 10.2).

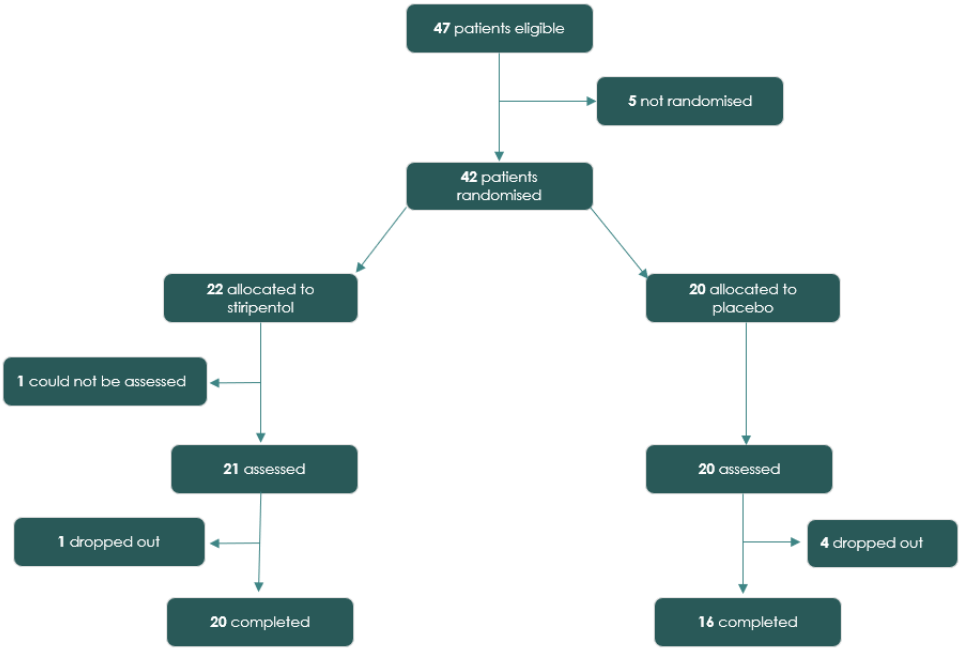

Figure 6: Overview of the patient disposition in STICLO-France (Chiron et al. 2000)

6. Clinical questions

To address the specific questions outlined in the DMC protocol we have provided the published data that supported the registration of fenfluramine (Lagae et al 2019 and Nabbout et al 2020), and additional data on file.

6.1 Clinical question 1: What is the value of fenfluramine compared to stiripentol for patients with Dravet syndrome (≥2 years of age) who receive combination therapy that does not include stiripentol?

A detailed discussion of the head-to-head comparative data of fenfluramine vs placebo added on to continued SoC AEDs that excludes STP (Study 1, Lagae et al 2019) and of the STICLO-France study of stiripentol vs placebo added on to continued SoC AEDs (Chiron et al 2000) is provided in the Appendix. No comparative analysis of fenfluramine and STP was conducted for clinical question 1, as this comparison is not relevant to the proposed positioning of fenfluramine and due to differences between Study 1 and STICLO-France which made it technically unfeasible to conduct a comparison, as described in the Appendix.

In the subpopulation of patients who are STP naïve and for whom STP is not considered to be a treatment option, continued SoC AED without STP (as in the placebo arm of Study 1) would be the relevant comparator. It is not feasible to conduct a subgroup analysis of Study 1 specifically in this subpopulation. We therefore refer the DMC to the results of the whole of Study 1 (presented in the Appendix) as an indication of the results that may be anticipated in this subpopulation.

The rationale behind not presenting a comparative analysis in this section was that STP is not a relevant comparator for the proposed clinical positioning of fenfluramine, and an indirect comparison of Study 1 and STICLO-France is not feasible, as shown in a feasibility assessment of an indirect comparison conducted for the NICE submission on fenfluramine. In the fenfluramine NICE submission, a feasibility assessment of an indirect comparison was conducted, and the highlights from this assessment are presented in the following. Information on the fenfluramine Study 1 and stiripentol STICLO-France can be found in section 5.2.1 and 5.2.3, respectively.

The fenfluramine and stiripentol trial designs and eligibility criteria appeared to be similar. Both are placebo controlled RCTs that assess the intervention as an add-on to standard of care AEDs. Both trials recruited patients experiencing four or more convulsive seizures per month during their baseline assessment periods. Notably, the stiripentol trial was conducted several years earlier than the fenfluramine trial. The fenfluramine trial was completed two to five years ago and may therefore more accurately reflect the contemporary clinical management of Dravet syndrome patients.

As convulsive seizures are associated with the most severe outcomes for patients with Dravet syndrome assessment of comparability of the convulsive seizure reduction endpoints used as primary and key secondary endpoints in the trials was conducted. These included percentage reduction from baseline in convulsive seizure frequency compared with placebo and 50% responder rates (i.e., proportion of patients achieving at least a 50% reduction from baseline in convulsive seizure frequency). In fenfluramine and stiripentol trials, convulsive seizures were assessed and recorded by caregivers of Dravet syndrome patients, which inevitably involves a degree of subjectivity; however, it seems reasonable to assume that the occurrence of convulsive seizures will have been recorded to a comparable extent in both trials. However, there are important differences in the assessment of convulsive seizure endpoints. All trials included tonic-clonic and clonic seizures but the fenfluramine trials also included focal seizures with a significant motor component among the included convulsive seizure types

In the fenfluramine trials, reduction in convulsive seizures were measured as the percentage change in CSF between baseline and T+M periods (per 28 days) and a parametric assessment of % reduction from baseline in convulsive seizure frequency per 28 days compared with placebo (i.e., the additional reduction over placebo) was performed. In STICLO-France, the reduction in convulsive seizures was measured as the percentage change from baseline in CSF after 1st month and after 2nd month of treatment period compared with baseline and was a secondary endpoint. Moreover, no assessment through whole treatment period and no parametric assessment of percentage reduction from baseline in convulsive seizure frequency per 28 days compared with placebo (i.e., the additional reduction over placebo) were conducted. In terms of 50% responder rates (proportion achieving at least 50% reduction in convulsive seizure frequency, the fenfluramine trials reported on CSF over combined T+M period (per 28 days) as a secondary endpoint and the stiripentol trial reported on CSF for 2nd month of treatment period compared with baseline (per 30 days) as a primary endpoint and no assessment through whole treatment period was conducted. Whilst the fenfluramine trial assessed convulsive seizure endpoints over the whole 14-15-week treatment period, the stiripentol trial assessed convulsive seizure endpoints for only the last four weeks of an only eight-week treatment period. In addition, for the reduction in seizure frequency endpoint, the reported analyses in the stiripentol trial do not adjust for placebo. The stiripentol trial endpoint assessment is therefore not comparable with the endpoint assessments in the trial of fenfluramine, and any attempt to compare their outcomes would require strong assumptions in favor of stiripentol that would lead to biased results. These limitations in the stiripentol trial data therefore preclude a robust assessment of the convulsive seizure endpoints for fenfluramine compared with stiripentol.

The fenfluramine trials (Study 1 and Study 1504) have demonstrated to be at a low risk of bias and provide high-quality evidence of the benefits of fenfluramine. Quality assessment of the stiripentol trial indicates that these trials had an unclear risk of bias. The STICLO-France study has been published in full (Chiron et al. 2000) but lacks complete details on allocation concealment and patient withdrawal. STICLO-France included a small number of patients (21 patients treated with stiripentol), and therefore, minor changes in patient numbers can amplify the relative treatment effects observed. The evidence supporting stiripentol is of low to moderate quality due to an unclear risk of bias.

Due to substantial differences in the assessment of convulsive seizure reduction endpoints in the stiripentol trial compared to the fenfluramine trial, as well as the unclear risk of bias that limits the quality of the stiripentol trial evidence, it is not feasible to conduct an indirect treatment comparison comparing fenfluramine and stiripentol.

Zogenix therefore does not believe a comparison of fenfluramine and STP is meaningful from a clinical point of view. As suggested in the preliminary application, and as explained in the Summary, fenfluramine is proposed for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older as add-on therapy to other SoC AED regimens that include STP, or after being treated with STP, or if ineligible to receive STP. Since fenfluramine is not intended to replace STP we do not find it clinically relevant to do a head-to-head comparison of fenfluramine versus STP and have therefore not presented a comparison.

6.2 Clinical question 1a: What is the value of fenfluramine compared to placebo for patients with Dravet syndrome (≥2 years of age) who receive combination therapy that does not include stiripentol, who are stiripentol-experienced?

6.2.1 Presentation of relevant studies

In the patient population who do not receive STP, we present results from the stiripentol-experienced subpopulation from Study 1 (6). This analysis was conducted to show the value of fenfluramine in patients who have previously received STP and where STP was discontinued due intolerance or lack of effect. The baseline characteristics of the stiripentol-experienced subpopulation is presented in Table 28 below the baseline characteristics of the overall patient population from Study 1. The data applied in the analyses is data on file. Currently, a published poster by Wirrell et al. 2018 (5) is available for the analysis on the subpopulation of stiripentol-experienced patients. The comparative analyses on fenfluramine and placebo in STP-experienced patients are presented in section 6.2.3.

6.2.2 Results from Study 1 on stiripentol-experienced patients

Convulsive seizures - mean percentage change in the number of convulsive seizures per 28 days

The primary efficacy endpoint in Study 1 was the change in the mean convulsive seizure frequency per 28 days during the T+M periods compared with the baseline period. The primary endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment group (3 levels) and age group (< 6 years, ≥ 6 years) as factors, and with baseline MCSF as a covariate. Based on an ANCOVA model that adjusts for age and baseline CSF, the percentage reduction in mean monthly (28 days) CSF in subjects randomised to fenfluramine 0.7 mg/kg/day was 60.8% greater than in placebo subjects during the 14-week T+M (5) [redacted]

[redacted]

Source: data on file.

Convulsive seizures - proportion of patients who achieved a 50% reduction in the number of convulsive seizures

A key secondary outcome in Study 1 was the proportion of patients with a ≥50% reduction from baseline in CSF. The comparison between fenfluramine and placebo was made using a logistic regression model that incorporated the following factors: treatment group (3 levels, but we do not report results for the fenfluramine 0.2 mg/kg/day arm) and age group (<6 years, ≥6 years, i.e., the generated odds ratio (OR) was adjusted for age). The logistic regression model modeled a

categorical response variable (achieved 50% reduction, yes or no) as a function of treatment group (fenfluramine 0.7 mg/kg and placebo), age group (<6 years, ≥6 years), and baseline CSF (2). The CIs around proportions were estimated with clopper-pearsons exact method.

Source: data on file.

Need for rescue medication – mean number of days per 28 days where rescue medication was used

The mean number of days per 28 days where rescue medication was used was not analysed in Study 1 for the subpopulation of stiripentol-experienced patients. Therefore, we conducted an analysis on patient level data on the mean days per 28 days where rescue medication was used from Study 1 to provide data on this outcome in the subpopulation. The method for extracting the information from the patient level data is presented in Appendix 0. Patients with zero rescue medication use at baseline was included in the analysis.

Source: data on file.

Need for rescue medication – proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used

The proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used was not analysed in Study 1. Therefore, we conducted an analysis on patient level data from Study 1 to provide data on this outcome. The method for extracting the information from the patient level data is presented in Appendix 0.

Source: data on file. Note: CIs rely on a normality assumption.

Quality of life – mean change in PedsQL

Not assessed due to lack of data in this subgroup.

Quality of life – proportion of patients with a score of 1 or 2 on CGI-I

Improvements in the patients QoL assessed with the Clinical Global Impression – Improvement (CGI-I) scale was a secondary outcome in Study 1. CGI-I measures improvement in the subject's clinical status from the baseline period. Both the parent/caregiver and the investigator rated their global impression of the patient's condition throughout the study at the end of titration period (visit 6), during the maintenance period (visit 8 and 10), and at the end of the study (visit 12). The severity of a patient's condition was rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The proportions of stiripentol-experienced patients with a score of 1 or 2 on CGI-I in the fenfluramine arm and placebo arm are available from the poster by Wirrell et al. 2018 (5) and CIs were estimated with the clopper-pearsons exact method.

In the parent/caregiver rating, 9 patients out of 22 in the fenfluramine arm (40.9%, 95% CI: 20.71%, 63.65%) had a clinically meaningful score (score of 1 or 2). In the placebo arm, 1 patient out of 16 (6.3%, 95% CI: 0.16%, 30.23%) had a clinically meaningful score.

In the investigator rated analysis, 14 out of 22 patients in the fenfluramine arm (63.6%, 95% CI: 40.66%, 82.80%) had a clinically meaningful score. In the placebo arm, 1 patient out of 16 (6.3%, 95% CI: 0.16%, 30.23%) had a clinically meaningful score.

Table 9: Proportion of patients with a score of 1 or 2 in CGI-I (stiripentol-experienced parent/caregiver ratings and investigator rating, mITT population from Study 1)

	Fenfluramine 0.7 mg/kg (N=22)	Placebo (N=16)
Investigator: Much improved or very much improved (1,2)	63.6% (95% CI: 40.66%, 82.80%)	6.3% (95% CI: 0.16%, 30.23%)

Source: Wirrell et al. 2018.

Adverse events – proportion of patients with at least one serious adverse event

All AEs experienced by stiripentol-experienced patients were tolerable and manageable. 22 out of 22 patients (100%, 95% CI: 84.56%, 100%) in the fenfluramine arm experienced at least one TEAE. In the placebo arm, it was 8 out of 16 patients (50%, 95% CI: 24.65%, 75.35%). At least one serious TEAEs were experienced by 4 out of 22 patients (18.2%, 95% CI: 5.19%, 40.28%) in the fenfluramine arm compared to 0 out of 16 patients (0%, 95% CI: 0.0%, 20.59%in the placebo arm. Results are presented in Table 10.

Table 10: Number of patients with at least one TEAE and one serious TEAE (stiripentol-experienced safety population from Study 1)

	Fenfluramine 0.7 mg/kg (N=22)	Placebo (N=16)
At least one TEAE, n (%; 95% CI)	22 (100%; 95% CI: 84.56%, 100%)	8 (50%; 95% CI: 24.65%, 75.35%)
At least one serious TEAE, n (%; 95% CI)	4 (18.2%; 95% CI: 5.19%, 40.28%)	0 (0%; 95% CI: 0.0%, 20.59%)

Source: Wirrell et al. 2018 poster (5). Note: 95% CIs estimated with clopper-pearsons exact method.

Adverse events – qualitative description of adverse event data

In the following, we present the summary of the safety profile of fenfluramine from the SPC. In the SPC, the following AEs are reported as the most commonly observed with fenfluramine treatment: decreased appetite (44.2%), diarrhoea (30.8%), pyrexia (25.6%), fatigue (25.6%), upper respiratory tract infection (20.5%), lethargy (17.5%), somnolence (15.4%), and bronchitis (11.6%) (1).

Clinical trials of children and young adults have shown that fenfluramine can cause decreased appetite and weight loss. However, decreases in weight and appetite seemed to be related to dose, and patients resumed weight gain over time during treatment with fenfluramine. 34.4% of children and young adults with Dravet syndrome treated with fenfluramine experienced decreased appetite, and 18.9% had a decrease in weight ≥7% from their baseline weight. In comparison, 8.3% of children and young adults on placebo had a decreased appetite, and 2.4% had a decrease in weight ≥7% from their baseline weight (1).

Status epilepticus was accessed in phase III clinical trials. The frequency was 6.6% in the fenfluramine group compared to 2.4% in the placebo group. Status epilepticus did not cause any discontinuations (1).

In double-blind studies and during an open-label extension study, patients did not develop any valvular heart disease. The non-pathologic findings: trace and mild mitral regurgitation as well as trace aortic regurgitation were also accessed. Among the 0.2 mg/kg/day group, trace mitral valve regurgitation was reported in 17.9% of the subjects (n=7/39). The same condition was reported in 22.5% of the 0.7 mg/kg/day group (n=9/40), in 20.9% of the 0.4 mg/kg/day group (n=9/43), and in 9.5% of the placebo group (n=8/84). Mild mitral regurgitation was reported in 2.3% of the subjects in the 0.4 mg/kg/day group (n=1/43), and trace aortic regurgitation was found in 7.9% of subjects in the 0.7 mg/kg/day group (n=3/40). All reported incidences were transient (1).

The long-term safety of fenfluramine was accessed in an open-label trial. Fenfluramine was used by 330 patients for up to 3 years, and the most frequently reported AEs were decreased appetite (18.8%), echocardiogram abnormal (trace regurgitation) (8.2%), weight decrease (6.1%), and abnormal behaviour (5.2%) (1).

6.2.3 Comparative analyses

The protocol on fenfluramine outlines two critical outcomes: convulsive seizures (measured as mean percentage change in the number of convulsive seizures per 28 days and the proportion of patients who achieved a 50% reduction in the number of convulsive seizures) and QoL (measured as mean change in PedsQL and proportion of patients with a score of 1 or 2 on CGI-I). Two important outcomes are outlined in the protocol: need for rescue medication (measured as mean number of days per 28 days where rescue medication was used and proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used) and AEs (measured as proportion of patients with at least one SAE and a qualitative description of the safety profile of the respective drug). The comparative analyses of each outcome were all direct comparative analyses based on results on the stiripentol-experienced subpopulation from Study 1. The comparative analyses are described in the following subsections. An overview of the results of the comparative analyses is presented in Appendix 10.5 (Table 47).

Comparative analysis on convulsive seizures - mean percentage change in the number of convulsive seizures per 28 days

[redacted]

As mentioned, the primary endpoint in Study 1, change in CSF was analysed using an analysis of covariance (ANCOVA) model with treatment group (3 levels) and age group (<6 years, ≥6 years) as factors, and with baseline mean CSF as a covariate. Based on that primary analysis method, fenfluramine 0.7 mg/kg per day showed a reduction of 60.8% compared to placebo (p-value: 0.002) during the combined T+M period (5).

Comparative analysis on convulsive seizures - proportion of patients who achieved a ≥50% reduction in the number of convulsive seizures

[redacted]

Source: own calculations and data on file

Comparative analysis on need for rescue medication – mean number of days per 28 days where rescue medication was used

[redacted]

Comparative analysis on need for rescue medication – proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used

[redacted]

Comparative analysis on quality of life – mean change in PedsQL

Not assessed due to lack of data in this subgroup.

Comparative analysis on quality of life – proportion of patients with a score of 1 or 2 on CGI-I

The absolute difference in the proportion of patients with a clinically meaningful score in the parent/caregiver rating was 34.66 percentage points (95% CI: 10.9, 58.4). The relative risk (RR) was 6.545 (95% CI: 0.919, 46.612). In the investigator rating, the absolute difference was 57.39 percentage points (95% CI: 34.0, 80.7) and the relative difference (RR) was 10.182 (95% CI: 1.487, 69.719). Results are presented in Table 12.

Table 12: Direct comparative analysis of the proportion of patients with a score of 1 or 2 in CGI-I (stiripentol-experienced mITT population from Study 1)

	Fenfluramine 0.7 mg/kg (N=22)	Placebo (N=16)
Parent/caregiver absolute difference	34.66 percentage points (95% CI: 10.9, 58.4)	
Parent/caregiver relative risk	6.545 (95% CI: 0.919, 46.612)	
Investigator absolute difference	57.39 percentage points (95% CI: 34.0, 80.7)	
Investigator relative risk	10.182 (95% CI: 1.487, 69.719)	

Source: own calculations and Wirrell et al. 2018 poster.

Adverse events – proportion of patients with at least one serious adverse event

At least one serious TEAEs were experienced by 4 out of 22 patients (18.2%, 95% CI: 5.19%, 40.28%) in the fenfluramine arm compared to 0 out of 16 patients (0%, 95% CI: 0.0%, 20.59%) in the placebo arm. The absolute difference in the proportions was 18.2 percentage points (95% CI: 2.1, 34.3). To estimate the relative risk, we applied the Haldane-Anscombe correction where we added 0.5 to all cells. With the correction, the relative difference (risk ratio) was 6.652 (95% CI: 0.0383, 115.433).

6.3 Clinical question 2: What is the value of fenfluramine compared to placebo for patients with Dravet syndrome (≥2 years of age) who receive combination therapy that includes stiripentol?

6.3.1 Presentation of relevant studies

To answer clinical question 2, we applied Study 1504, published in Nabbout et al. 2020 (7). Information on Study 1504 came primarily from the CSR (data on file), but the EPAR and the Nabbout et al. 2020 publication were also consulted.

6.3.2 Results from Study 1504

Convulsive seizures – mean percentage change in the number of convulsive seizures per 28 days

In the DMC protocol, convulsive seizures are a critical outcome and should be measured in two ways: 1) as mean percentage change in the number of convulsive seizures per 28 days, and 2) as the proportion of patients who achieved a 50% reduction in the number of convulsive seizures.

The primary efficacy end point in Study 1504 was a comparison of the difference between fenfluramine and placebo on the change in mean monthly CSF from baseline to the combined titration and maintenance (T + M) periods. Seizure types contributing to the primary endpoint were GTC, secondarily GTC, clonic, drop seizures (tonic-atonic), hemiclonic, and focal seizures with a clear and observable motor component. Parents/caregivers of patients in Cohort 2 had to

use an electronic diary daily to record the number/type of seizures, dosing, and use of rescue medication. Seizure frequency by type and duration (<2 minutes, 2 to 10 minutes, >10 minutes) was recorded daily by the parent/caregiver in the diary and was used to assess the number of convulsive seizures per 28 days.

For the primary endpoint, change in CSF was analysed using an analysis of covariance (ANCOVA) model with treatment group (3 levels) and age group (<6 years, ≥6 years) as factors, and with baseline mean CSF as a covariate. The primary analysis incorporated a log transformation to satisfy the underlying assumptions of the ANCOVA model. Based on that primary analysis, which supported the registration of fenfluramine with the EMA, fenfluramine 0.4 mg/kg per day showed a 54.0% (95%CI, 35.6%-67.2%; p < 0.001) greater reduction in mean monthly CSF compared with placebo. As Nabbout et al 2020 only reports the median percentage change in CSF for fenfluramine 0.4mg/kg/day vs placebo (-63.1 [-100.0 to 115.0) vs -1.1 [-82.8 to 435.1]; p<0.001), we have provided the mean number and percentage change from baseline in CSF, as requested in the DMC protocol, in Table 13.

Source: CSR on Study 1504 (data on file)

Convulsive seizures - proportion of patients who achieved a 50% reduction in the number of convulsive seizures

The proportion of patients who achieved a 50% reduction in CSF from baseline to the T+M period was a key secondary endpoint in Study 1504. The endpoint was analysed with a logistic regression model that included a categorical response variable (achieved 50% percentage point reduction, yes or no) as a function of treatment arm (fenfluramine or placebo), age group (<6 years, ≥6 years), and baseline CSF.

Significantly more patients in the fenfluramine arm than in the placebo arm achieved a ≥50% reduction in CSF during the T+M period compared with the baseline period (P <0.001). The number of patients with a ≥50% reduction in the placebo arm was 2 out of 44 patients (4.5%, 95% Cl: 0.56%, 15.47%) compared with 23 out of 43 patients (53.5%, 95% Cl: 37.65%, 68.82%) in the fenfluramine arm. The OR from the logistic regression model for achieving a ≥50% reduction

in CSF was 26.037 (95% CI: 5.502, 123.214) for the fenfluramine arm compared to the placebo arm (p-value < 0.001). Results are presented in Table 14.

Table 14: Proportion of patients with a ≥50% reduction in the number of convulsive seizures in Study 1504 Cohort 2 (mITT population from Study 1504)

	Fenfluramine 0.4 mg/kg (N=43)	Placebo (N=44)
Change from baseline in CSF ≥50%, n (%; 95% CI)	23 (53.5%; 95% CI: 37.65%, 68.82%)	2 (4.5%; 95% CI: 0.56%, 15.47%)
OR (95% CI)	26.037 (5.502, 123.214)	
P-value	<0.001	

Source: Nabbout et al. 2020. Note: the 95% CIs on proportions were estimated with the clopper-pearsons exact method.

Need for rescue medication – mean number of days per 28 days where rescue medication was used

In the DMC protocol, the need for rescue medication is an important outcome and should be measured in two ways: 1) as mean number of days per 28 days where rescue medication was used, and 2) the proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used.

The use of rescue medication was recorded in the diary each day. Rescue medications were summarised by treatment arm (fenfluramine versus placebo). The number of days where rescue medication was used (normalised to 28 days) was summarised for the T+M period in Study 1504 by the mean, SD, median and range.

The mean number of days where rescue medication was used per 28 days during baseline in the fenfluramine arm was 2.1 days (SD: 2.59) compared to 1.4 days (SD: 2.47) in the placebo arm. The mean number of days where rescue medication was used per 28 days during the T+M period was 1.4 days (SD: 2.15) in the fenfluramine arm compared to 1.2 days (SD: 2.64) in the placebo arm. Results are presented in Table 15.

Table 15: Mean number of days per 28 days where rescue medication was used during baseline and during T+M period (mITT population from Study 1504)

	Fenfluramine 0.4 mg/kg (N=43)	Placebo (N=44)
During baseline		
Mean (SD)	2.1 (2.59)	1.4 (2.47)
95% CI	1.326, 2.874	0.670, 2.130
During T+M periods		
Mean (SD)	1.4 (2.15)	1.2 (2.64)
95% CI	0.757, 2.043	0.420, 1.980

Source: Nabbout et al. 2020

Need for rescue medication – proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used

The proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used was not analysed in Study 1504. Therefore, we conducted an analysis on patient-level data from Study 1504 to provide data on this outcome. The method for extracting the information from the patient-level data is presented in Appendix 0.

[redacted]

[redacted]

Source: data on file.

Quality of life – mean change in PedsQL

The QoL was assessed in Study 1504 with the PedsQL measure completed by the parent/caregiver on behalf of the patient. The PedsQL consists of 4 core scales that measure physical, emotional, social and school functioning. The psychosocial health summary score is comprised from the emotional, social and school functioning scales. The physical health summary score is comprised of the physical functioning scale. The total score is the sum of all the items over the number of items answered on all the scales. Higher scores are better and indicate improved QoL.

The change from baseline in the total score was calculated for each patient by subtracting the total score measured at baseline from the total score measured at EOS. The change from baseline was summarised with descriptive statistics. The physical health summary and psychosocial health summary scores were also summarised. Scale scores were not computed if more than 50% of the items in the scale were missing. If 50% or more of the items in the scale were completed, the mean of the completed items in a scale was substituted for the missing scores. The scaled results were combined across age categories to produce a single score for each functional area.

[redacted]

Table 17: Mean change in PedsQL (mITT population from Study 1504). Higher values indicate improved QoL

[redacted]

[redacted]

Quality of life – proportion of patients with a score of 1 or 2 on CGI-I

The proportion of patients with improvement in clinical status as assessed by the parent/caregiver or investigator using the CGI-I score was a secondary endpoint in Study 1504. Each assessment time point also included a comparison between each active treatment and the placebo arm, using the Cochran-Mantel-Haenszel test stratified by age group, and a frequency distribution of the number and percentage of subjects in each category in the scale. The Mantel-Haenszel odds ratio was adjusting for age group.

[redacted] 14 out of 43 patients had a score of either 1 or 2 (32.6%, 95% CI: 18.6%, 46.6%) in the fenfluramine arm compared to 9 out of 44 patients (20.5%, 95% CI: 8.5%, 32.4%) in the placebo arm. [redacted] Results are presented in Table 18.

[redacted] 19 patients out of 43 (44.2%, 95% CI: 29.3%, 59.0%) had a score of either 1 or 2 compared to 7 patients out of 44 (15.9%, 95% CI: 5.1%, 26.7%) in the placebo arm. Results are summarised in Table 19.

Table 18: Proportion of patients with a score of 1 or 2 in CGI-I (Parent/caregiver ratings, mITT population from Study 1504)

	Fenfluramine 0.4 mg/kg (N=43)	Placebo (N=44)
Much improved or very much improved (1, 2), n (%; 95% CI)	14 (32.6%; 95% CI: 18.6%, 46.6%)	9 (20.5%; 95% CI: 8.5%, 32.4%)
[redacted]	[redacted]	
[redacted]	[redacted]	

Source: Much improved or very much improved (1, 2) from Nabbout et al. 2020. EOS: end of study. Mantel-Haenszel odds ratio adjusting for age group.

Table 19: Proportion of patients with a score of 1 or 2 in CGI-I (Investigator ratings, mITT population from Study 1504)

	Fenfluramine 0.4 mg/kg (N=43)	Placebo (N=44)
Much improved or very much improved (1, 2), n (%; 95% CI)	19 (44.2%; 95% CI: 29.3%, 59.0%)	7 (15.9%; 95% CI: 5.1%, 26.7%)

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

Source: Much improved or very much improved (1, 2) from Nabbout et al. 2020. *Mantel-Haenszel odds ratio adjusting for age group.

Adverse events – proportion of patients with at least one serious adverse event

The number and percentage of patients with at least one serious TEAE were reported in Study 1504. Overall, 13 patients in Study 1504 reported one or more serious TEAEs: 7 out of 44 patients (15.9%) in the placebo arm and 6 out of 43 patients (14.0%) in the fenfluramine arm. Serious TEAEs were due to seizures in 6 patients in the placebo arm and 4 patients in the fenfluramine arm (3 patients with status epilepticus and 1 patient with repeated seizures). In the placebo arm, other serious TEAEs included abdominal pain and pyrexia in 1 patient each and infections in 3 patients. In the fenfluramine arm, other serious TEAEs included osteochondritis and lethargy in 1 patient each. Results are presented in Table 20.

Table 20: Number of patients with at least one TEAE and one serious TEAE in Study 1504 Cohort 2 (safety population from Study 1504)

	Fenfluramine 0.4 mg/kg (N=43)	Placebo (N=44)
At least one TEAE, n (%; 95% CI)	42 (97.7%; 95% CI: 93.2%, 102.2%)	42 (95.5%; 95% CI: 89.3%, 101.6%)
At least one serious TEAE, n (%; 95% CI)	6 (14.0%; 95% CI: 3.6%, 24.3%)	7 (15.9%; 95% CI: 5.1%, 26.7%)

Source: Nabbout et al. 2020

Adverse events – qualitative description of adverse event data

A qualitative description of the adverse event data available on fenfluramine was presented in section 6.2.2.

6.3.3 Comparative analyses

The protocol on fenfluramine outlines two critical outcomes: convulsive seizures (measured as mean percentage change in the number of convulsive seizures per 28 days and the proportion of patients who achieved a ≥50% reduction in the number of convulsive seizures) and QoL (measured as mean change in PedsQL and proportion of patients with a score of 1 or 2 on CGI-I). Two important outcomes are outlined in the protocol: the need for rescue medication (measured as mean number of days per 28 days where rescue medication was used and proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used) and AEs (measured as proportion of patients with at least one SAE and a qualitative description of the safety profile of the respective drug). We conducted direct comparisons and the direct comparative analyses of each outcome are described in the following subsections. An overview of the results of the comparative analyses is presented in Appendix 10.5, Table 48.

Comparative analysis on convulsive seizures – mean percentage change in the number of convulsive seizures per 28 days

As presented in section 6.3.2, the percentage change in CSF per 28 days from baseline and during the entire T+M period was a reduction of [redacted] Based on the prespecified, adjusted primary analysis, which supported the registration of fenfluramine with the EMA, fenfluramine 0.4 mg/kg per day

showed a 54.0% (95%CI: 35.6%-67.2%; p < 0.001) greater reduction in mean monthly CSF compared with placebo.

Comparative analysis on convulsive seizures – proportion of patients who achieved a ≥50% reduction in the number of convulsive seizures

The OR for achieving a ≥ 50% reduction in CSF was 26.037 (95% CI: 5.502, 123.214) for the fenfluramine arm than for the placebo arm (P < 0.001). Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10).

The relative risk was calculated to be 12.178 (95% CI: 3.056, 48.525), which was significant (p-value = 0.0004). The absolute difference was calculated to 50.8 percentage points (95% CI: 9.35, 216.02). These results show a substantially higher proportion of patients in the fenfluramine arm who achieved a 50% reduction in the number of convulsive seizures compared to the placebo arm. Results are presented in Table 21.

Table 21: Direct comparative analysis of the proportion of patients who achieved a 50% reduction in the number of convulsive seizures (mITT population from Study 1504)

	Fenfluramine 0.4 mg/kg (N=43)	Placebo (N=44)
Relative risk (95% CI)	12.178 (3.056, 48.525)	
p-value on relative risk	0.0004	
Absolute difference (95% CI)	50.8 percentage points (9.35, 216.02)	

Source: own calculations

Comparative analysis on need for rescue medication – mean number of days per 28 days where rescue medication was used

The mean number of days where rescue medication was used per 28 days during baseline in the fenfluramine arm were 2.1 days (SD: 2.59) compared to 1.4 days (SD: 2.47) in the placebo arm. The mean number of days where rescue medication was used per 28 days during the T+M period was 1.4 days (SD: 2.15, 95% CI: 0.757, 2.043) in the fenfluramine arm compared to 1.2 days (SD: 2.64, 95% CI: 0.420, 1.980) in the placebo arm. The difference in means was 0.2 days (95% CI: -0.8107, 1.2107).

Comparative analysis on need for rescue medication – proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used

[redacted]

Comparative analysis on quality of life – mean change in PedsQL

[redacted]

Comparative analysis on quality of life – proportion of patients with a score of 1 or 2 on CGI-I

The OR between fenfluramine and placebo on the outcome 'Much improved or very much improved' in parent/caregiver ratings was 2.104, and the p-value was 0.142. Based on the

reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10).

The relative risk was calculated to be 1.716 (95% CI: 0.832, 3.541), and the p-value was 0.1441. The absolute difference was calculated to 14.7 percentage points (95% CI: 12.83, 68.25). These results show a higher proportion of patients scoring much improved or very much improved on CGI-I in the fenfluramine arm compared to the placebo arm. Results from the parent/caregiver ratings are presented in Table 22.

Table 22: Direct comparative analysis of the proportion of patients with a score of 1 or 2 on CGI-I (Parent/caregiver ratings, mITT population from Study 1504)

	Fenfluramine 0.4 mg/kg (N=43)	Placebo (N=44)
OR*	2.104	
Relative risk (95% CI)	1.716 (0.832, 3.541)	
p-value on relative risk	0.1441	
Absolute difference (95% CI)	14.7 percentage points (-3.44, 51.98)	

Source: own calculations and OR from CSR on Study 1504. *Mantel-Haenszel odds ratio adjusting for age group

The OR between fenfluramine and placebo on the outcome 'Much improved or very much improved' in investigator ratings was 3.858, and the p-value was 0.008. Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10).

The relative risk was calculated to be 2.652 (95% CI: 1.243, 5.659), and the p-value was 0.0118. The absolute difference was calculated to 26.3 percentage points (95% CI: 17.24, 87.50). These results show a higher proportion of patients scoring much improved or very much improved on CGI-I in the fenfluramine arm compared to the placebo arm. Results from the investigator ratings are presented in Table 23.

Table 23: Direct comparative analysis of the proportion of patients with a score of 1 or 2 on CGI-I (Investigator ratings, mITT population from Study 1504)

	Fenfluramine 0.4 mg/kg (N=43)	Placebo (N=44)
OR*	3.858	
Relative risk (95% CI)	2.652 (1.243, 5.659)	
p-value on relative risk	0.0118	
Absolute difference (95% CI)	26.3 percentage points (3.87, 74.12)	

Source: own calculations and OR from CSR on Study 1504. *Mantel-Haenszel odds ratio adjusting for age group

Comparative analysis on adverse events – proportion of patients with at least one serious adverse event

7 out of 44 patients (15.9%, 95% CI: 5.1%, 26.7%) in the placebo arm and 6 out of 43 patients (14.0%, 95% CI: 3.6%, 24.3%) in the fenfluramine arm experienced at least one serious TEAE. The absolute difference in the proportions was -1.96% (95% CI: -16.9%, 13.0%) in the fenfluramine arm compared to placebo. The relative difference, expressed as a risk ratio, was 0.877 (95% CI: 0.321, 2.399).

7. Other considerations

In the DMC protocol on fenfluramine, the expert committee has requested some additional information which we have provided in the following.

Fenfluramine in adult patients with Dravet syndrome

Dravet syndrome typically develops in early infancy and the patient populations in the two pivotal studies Study 1 and Study 1504 were children aged 2-18 years of age. The expert committee requested data from adult patients with Dravet syndrome. From the age of 2 years, there is no evidence of significant differential effects on seizure reduction by age with fenfluramine therapy and access to fenfluramine therapy in patients aged 2 years and older should not be determined by age. To evaluate the potential efficacy of fenfluramine on convulsive seizures in older children and young adults with Dravet syndrome, a sub-group analysis on all patients ≥12 years of age across both Study 1 and Study 1504 [redacted] was performed. Patients receiving fenfluramine (all doses combined) achieved a reduction in mean CSF [redacted] compared with placebo, which is highly consistent with the effects seen in all patients in the trials. This indicates that fenfluramine has comparable effects across all age groups (11). In addition to the RCTs and the OLE extension studies, which provide robust prospective evidence of efficacy in children and young adults for up to 3 years, the findings from real-world evidence studies points towards significant and sustained seizure reduction and improvements in clinical status observed in the RCT and OLE studies. The EMA did not limit the fenfluramine licensed indication to patients aged <18 years (1) and NICE in the UK has accepted that the evidence from the fenfluramine RCTs is applicable to adults based on clinical expert opinion, which noted that there is no reason to expect adult seizures to respond differently to fenfluramine (3). Addition of fenfluramine to standard of care AED regimens can provide profound reductions in seizure frequency in high proportions of patients with Dravet syndrome, which are sustained over many years with daily treatment, irrespective of age.

Fenfluramine in stiripentol-naïve patients

It was not possible to present data from the stiripentol-naïve subpopulation from Study 1 on the outcomes requested by the DMC in the protocol. Study 1 enrolled patients who were either stiripentol-naïve or stiripentol-experienced but excluded patients who were taking STP or had taken STP within 3 weeks of screening. In a post hoc analysis of patients in Study 1 that had previously failed on STP treatment (48.7% of trial population), the addition of fenfluramine 0.7mg/kg/day to standard of care AEDs statistically significantly reduced CSF compared to placebo (60.8% reduction from baseline over placebo; p=0.002 in the T+M period) (5), and to a similar magnitude to that observed in the whole trial population (62.3% reduction from baseline over placebo; p<0.0001) (6) . This indicates that fenfluramine is equally effective in patients who are stiripentol-naïve or who are stiripentol-experienced. These data therefore support the use of fenfluramine in patients irrespective of their concomitant AEDs or prior treatment with STP, which supports the proposed positioning by Zogenix for use of fenfluramine.).

Data on patients in concomitant treatment with AED clobazam and valproate

The addressing of this consideration was based on Study 1. First-line treatment choices for Dravet syndrome in Denmark are AEDs such as valproate and clobazam. In Study 1, 62% of patients and 60% of patients received concomitant treatment with valproate or clobazam, respectively, in the fenfluramine 0.7 mg/kg/day arm. In the total population, patients were at baseline being treated with a mean of 2.4 AEDs (SD: 1), which mostly included valproate and clobazam. Therefore, the clinical effect of fenfluramine in this patient population is assumed to be represented by the results of Study 1 presented in section 10.3. Post hoc analyses presented results that showed that results are consistent irrespective of concomitant AEDs (with or without clobazam or valproate) (11,12).

Evaluation of the risk of pulmonary hypertension and valvular heart disease in patients with Dravet syndrome

Because of reported cases of valvular heart disease that may have been caused by fenfluramine at higher doses used to treat adult obesity, cardiac monitoring must be performed using echocardiography. Prior to starting treatment with fenfluramine, patients must undergo an echocardiogram to establish a baseline prior to initiating treatment and exclude any pre-existing valvular heart disease or pulmonary hypertension. Echocardiogram monitoring should be conducted every 6 months for the first 2 years and annually thereafter. There were no cases of mitral valve incompetence, valvular heart disease or pulmonary arterial hypertension (AEs of special interest) in the RCTs, or the OLE study in which 330 patients were treated for up to 3 years, or the prospective observational study of up to 5 years of treatment. Moreover, fenfluramine has been well tolerated in the European Expanded access program (EAP). [redacted]

Fenfluramine has been well tolerated in the EAP. No patient in the EAP in either age group has developed valvular heart disease or pulmonary arterial hypertension. In the prospective real-world observational study in Belgium, there was no evidence of change in cardiac valve structure or function nor were there any echocardiogram findings suggestive of pulmonary arterial hypertension in any patient during up to 5 years of treatment (13). In the US Expanded access program no patient developed valvular heart disease or pulmonary arterial hypertension during up to 180 days of treatment (14). Collectively, these data support the general and cardiovascular safety of long-term treatment with fenfluramine.

Impact on patient weight with concomitant treatment with topiramate/zonisamide and fenfluramine

In Study 1, 25% of patients received concomitant treatment with topiramate and in Study 1504, 24% of patients received topiramate. In the phase 3 RCTs, the most common AEs (of any severity) with fenfluramine were decreased appetite, diarrhoea, and weight loss >7%. Of note, weight loss was often regained with continued treatment. [redacted] Interpretation of these data is complicated by the fact that other AEDs list weight loss amongst their AEs, including STP (very common) (16), and there is some evidence to suggest that Dravet syndrome may be associated with reduced weight growth independently of AED therapy (17). [redacted]

Survival data for treatment with fenfluramine

Patients with Dravet syndrome have a greater risk of premature mortality compared to the wider population and the general epilepsy population (18,19). This is primarily due to Sudden Unexpected Death in Epilepsy (SUDEP) which is when a person with epilepsy during or following a seizure for no obvious reason dies (20) and SE which is a prolonged seizure episode of >5 minutes. SUDEP and SE are estimated to account for around a half and a third of premature deaths, respectively. Accidental deaths, such as drowning or fatal injury following a seizure are also an important contributor to Dravet syndrome mortality (18,19). Cooper et al. 2016 (18) is a

published review of deaths observed in 100 consecutive patients with Dravet syndrome. Patients were followed for a median of 10 years and the review estimated a Dravet-specific death rate of 15.84 per 1000 person years (approximately 15-16% of the cohort per 10 years), and a Dravet-specific SUDEP rate of 9.32 per 1000 person-years (9-10% of the cohort per 10 years) (18). This would suggest that the other remaining Dravet syndrome deaths, primarily due to SE, occur at a rate of around 5-6% per 10 years.

A recent publication by Cross et al. 2021 (21) assessed the impact of fenfluramine on the expected mortality incidence, including SUDEP in patients with Dravet syndrome. A total of 732 patients with DS were treated with fenfluramine, representing a total of 1185.3 person-years of exposure. Three deaths occurred, all in the phase 3 program: one during placebo treatment (probable SUDEP) and two during treatment with fenfluramine (one probable SUDEP and one definite SUDEP). The all-cause and SUDEP mortality rates during treatment with fenfluramine was 1.7 per 1000 person-years (95% CI: 0.4, 6.7), a value lower than the all-cause estimate of 15.8 per 1000 person-years (95% CI: 9.9, 25.4) and SUDEP estimate of 9.3 (95% CI: 5.0, 17.3) reported by Cooper et al. 2016 (18) for persons with DS receiving standard-of-care.

Considerations on treatment duration and potential dose adjustments prior to discontinuation of fenfluramine

In the Study 1503 OLE study, which was prospectively designed to evaluate the long-term safety of fenfluramine, 330 patients have been exposed to target doses of fenfluramine for up to 3 years; the median duration of treatment exposure at the Day 120 Safety update cut-off (14 October 2019) was 631 days (range 7 to 1086) (22). In observational real-world settings, exposure to daily treatment with fenfluramine ranged 1-27 years (13,23–25) and in the cohort with the longest follow-up the mean total fenfluramine treatment duration was 16.1 years (range 6 to 27 years) (23). Updated analyses in 330 patients, with treatment duration up to 3 years (data cut-off 19 October 2019) (1), and real world observational analyses with fenfluramine treatment in some patients for up to 27 years, provide consistent conclusions that response to treatment with fenfluramine is durable and long-lasting, with no evidence of a waning of effect over time (13,23). The real-world observational studies include both children and adult initiators of fenfluramine, supporting the initiation and continued use of fenfluramine in all age groups, including adults. In terms of discontinuation of fenfluramine, the dose should be gradually decreased before patients discontinue treatment. According to the SPC on fenfluramine, the dose should be gradually decreased following the same titration scheme as when initially beginning fenfluramine treatment. Abrupt discontinuation should be avoided when possible to minimise the risk of increased seizure frequency and status epilepticus (1).

8. Discussion

Dravet syndrome is a rare and severe epilepsy syndrome that begins in the first year of life with recurrent seizures that are typically prolonged and hemiclonic. The epilepsy is highly drug resistant. Over time, most patients develop moderate-to-severe intellectual disability, behaviour disorders, and a characteristic crouch gait. There is a significant mortality, predominantly owing to SUDEP and SE (5,7). Available medications are inefficacious in many patients and very few

patients achieve seizure control. A more effective treatment for Dravet syndrome is therefore needed that will abolish or significantly reduce seizure activity in a higher proportion of patients, decrease seizure frequency and provide periods of seizure freedom.

Based on the findings from the two completed double-blind, randomised, placebo-controlled trials (Study 1 and Study 1504) and the interim analysis of the long-term OLE study, fenfluramine has demonstrated a profound, differentiated treatment response profile relative to currently available treatment options when comparing the: (i) magnitude of response; (ii) proportion of patients achieving clinically meaningful and profound levels of seizure frequency reduction; and (iii) durability of effect.

Significant anti-seizure effects were apparent from the first observation in the double-blind studies and were sustained through the entire 14- or 15-week treatment periods in both studies, as well as into the first 24 months of the OLE study and in the EAP. The magnitude of the anti-seizure response was large. In Study 1 patients treated with fenfluramine 0.7 mg/kg/day who were stiripentol-experienced had a mean percentage change from baseline in the entire T+M period in CSFs of [redacted]% and in Study 1504 (cohort 2) patients treated with 0.4 mg/kg/day added to an AED regimen with STP had a mean percentage change in CSF per 28 days from baseline and during the entire T+M period of -38.94%.

Clinically meaningful (≥50% reduction in seizure frequency) response was noted in 67.5% of patients receiving 0.7 mg/kg/day of fenfluramine in Study 1, and in 53.5% of patients receiving 0.4 mg/kg/day of fenfluramine in combination with STP (Study 1504 cohort 2). Importantly, treatment response has been durable and sustained through the first 2 years of the OLE study. In clinical trials, the OLE study and the EAP, fenfluramine was well-tolerated and the frequency of withdrawals for TEAEs was low. Importantly, no patient demonstrated pulmonary arterial hypertension or valvular heart disease during treatment with fenfluramine.

Given the clear relationships between convulsive seizure frequency, patient morbidity and mortality, as well as patient and caregiver quality of life, the significant and often profound reductions in convulsive seizure frequency demonstrated with fenfluramine as an add-on therapy are potentially life-changing for a high proportion of patients, their families and caregivers. In the context of this devastating, rare disease, with few effective and tolerable treatment options, fenfluramine should be considered to provide a modest budgetary investment for an innovative therapy that provides a step change in the treatment of Dravet syndrome patients in Denmark.

9. References

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10. Appendices

10.1 Literature search

We conducted the literature search on 29 July 2021, applying the search terms defined in the DMC protocol on fenfluramine. Table 24 presents the search terms and number of hits found in PubMed, and Table 25 presents the search terms and number of hits found in CENTRAL.

Table 24: Search terms and hits in PubMed (29 July 2021)

#	Search terms	Comment	Hits
#1	Dravet*[tiab] OR severe myoclonic epilepsy of infancy[tiab] OR severe myoclonic epilepsy in infancy[tiab] OR SMEI[tiab]	Population	1,427
#2	Fenfluramine[tw] OR Fintepla*[tiab]	Intervention and comparator	3,720
#3	stiripentol[tw] OR Diacomit*[tiab]		310
#4	placebo*[tw] OR sham[tiab] OR dummy[tiab]		333,184
#5	#2 OR #3 OR #4		336,744
#6	#1 AND #5		227
#7	English[la] AND hasabstract	Limitation to English references that have abstracts	20,589,003
#8	#6 AND #7		207
#9	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti]	Exclusion criteria	6,959,669
#10	#8 NOT #9	Final search for both clinical questions	106

Table 25: Search terms and hits in CENTRAL (29 July 2021)

#	Search terms	Comment	Hits
#1	(Dravet* or "severe myoclonic epilepsy of infancy" or "severe myoclonic epilepsy in infancy"):ti,ab,kw	Population	142
#2	(fenfluramine or Fintepla*):ti,ab,kw	Intervention and comparator	532
#3	(stiripentol or Diacomit*):ti,ab,kw		68
#4	(placebo* OR sham or dummy):ti,ab,kw		346,825
#5	#2 or #3 or #4		347,019
#6	#1 and #5		114
#7	("conference abstract" or review):ti,pt	Exclusion criteria	200,609
#8	(clinicaltrials.gov or trialsearch):so		369,117
#9	(meeting or conference or proceedings):so		44,663
#10	nct*:au		210,348
#11	#7 or #8 or #9 or #10		599,256
#12	#6 not #11		43

#13	#12 not pubmed:an	Final search for both clinical questions with exclusion of references from Pubmed. Limited to trials.	16

We applied the inclusion and exclusion criteria defined in the DMC protocol on fenfluramine. Table 26 presents the inclusion and exclusion criteria used in the search for relevant literature for clinical question 1 and 2.

Table 26: Inclusion and exclusion criteria used in the literature search

Inclusion criteria	**Population:** Patients with Dravet syndrome (or severe myoclonic epilepsy of infancy) ≥2 years of age with unsatisfactory response to treatment with clobazam and/or valproate (for clinical question 1) or with unsatisfactory response to treatment with clobazam and/or valproate and stiripentol (for clinical question 2). **Intervention(s):** Fenfluramine max 0.7 mg/kg per day as add-on therapy (for clinical question 1), fenfluramine max 0.4 mg/kg per day as add-on therapy (for clinical question 2), or stiripentol 40-50 mg/kg per day as add-on therapy (for clinical question 1). **Comparator(s):** Stiripentol 40-50 mg/kg per day as add-on therapy (for clinical question 1) or placebo as add-on therapy (for clinical question 2). **Outcomes:** Reporting one or more of the clinical outcome measures reported in the DMC protocol, i.e.: • convulsive seizures measured as the mean percentage change in number of convulsive seizures per 28 days and/or proportion of patients who achieve at least a 50% reduction in the number of convulsive seizures; • need for rescue medication measured as the mean number of days per 28 days where rescue medication is needed and/or the proportion of patients who achieve at least a 50% reduction in number of days per 28 days where rescue medication is needed; • QoL measured as the mean change in PedsQL and/or the proportion of patients with a score of 1 or 2 in CGI-I; and • AEs measured as the proportion of patients with at least one SAE. **Language restrictions:** English
Exclusion criteria	**Population:** Patients with other types of epilepsy **Intervention(s):** Unlicensed doses of fenfluramine or stiripentol **Comparator(s):** Unlicensed doses of stiripentol **Study design:** Case reports or case studies

Table 27 lists all articles excluded after full-text assessment. We have indicated for which clinical question the article was potentially relevant and an explanation as to why the article was excluded.

Table 27: List of excluded articles after full-text assessment and an explanation as to why the article was excluded

Reference	Potentially relevant for clinical question	Reason for exclusion
Bishop KI et al. (2021): Improved everyday executive functioning following profound reduction in seizure frequency with fenfluramine: Analysis from a phase 3 long-term extension study in children/young adults with Dravet syndrome. Epilepsy & behavior. 121: 108024.	Clinical question 2	No comparator arm and not relevant outcomes
Ceulemans B et al. (2016): Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine. Epilepsia. 57(7): e129-34.	Clinical question 1 or 2	No comparator arm and other available study with higher quality
Chiron C et al. (1999): Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled trial. Epilepsia. 40(Suppl 2): 180	Clinical question 1	Conference abstract later published in full article (8)
Devinsky O et al. (2017): Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. The New England journal of medicine. 376(21): 2011-20.	Clinical question 2	SAE data for placebo, but excluded because of no comparable fenfluramine studies on SAE
Devinsky O et al. (2018): Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 90(14): e1204-11.	Clinical question 2	SAE data for placebo, but excluded because of no comparable fenfluramine studies on SAE
Inoue Y and Ohtsuka Y (2014): Effectiveness of add-on stiripentol to clobazam and valproate in Japanese patients with Dravet syndrome: additional supportive evidence. Epilepsy research. 108(4): 725-31.	Clinical question 1	No comparator arm and other available study with higher quality
Inoue Y and Ohtsuka Y (2015): Long-term safety and efficacy of stiripentol for the treatment of Dravet syndrome: A multicenter, open-label study in Japan. Epilepsy research. 113: 90-97.	Clinical question 1	No comparator arm and other available study with higher quality
Lai WW et al. (2020): Cardiovascular safety of fenfluramine in the treatment of Dravet syndrome: Analysis of an ongoing long-term open-label safety extension study. Epilepsia. 61(11). 2386-95.	Clinical question 1 or 2	No comparator arm and not relevant outcomes
Miller I et al. (2020): Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA neurology. 77(5): 613-621.	Clinical question 2	SAE data for placebo, but excluded because of no comparable fenfluramine studies on SAE
Myers KA et al. (2018): Stiripentol efficacy and safety in Dravet syndrome: a 12-year observational study. Developmental medicine and child neurology. 60(6): 574-78.	Clinical question 1	No comparator arm and not relevant outcomes
Perez J et al. (1999): Stiripentol: efficacy and tolerability in children with epilepsy. Epilepsia. 40(11): 1618-26.	Clinical question 1	Not relevant study population (refractory epilepsy) and not relevant stiripentol dose
Perry MS (2020): You Can Teach an Old Drug New Tricks. Epilepsy currents. 20(4): 193-95.	Clinical question 1 or 2	Commentary on already published trials
Schoonjans A et al. (2017): Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients. European journal of neurology. 24(2): 309-14.	Clinical question 1 or 2	No comparator arm and other available study with higher quality

Specchio N et al. (2020): Efficacy and safety of Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: A real-world study. Epilepsia. 61(11): 2405-14.	Clinical question 1 or 2	No comparator arm and not relevant outcomes
Sullivan J et al. (2020): Fenfluramine HCl (Fintepla®) provides long-term clinically meaningful reduction in seizure frequency: Analysis of an ongoing open-label extension study. Epilepsia. 61(11): 2396-2404.	Clinical question 1 or 2	No comparator arm and not relevant outcomes
Thanh TN et al. (2002): Long-term efficacy and tolerance of stiripentol in severe myoclonic epilepsy of infancy (Dravet's syndrome). Epilepsy. 9(11): 1120-27.	Clinical question 1	Not in English (French)
Wirrell EC et al. (2013): Stiripentol in Dravet syndrome: results of a retrospective U.S. study. Epilepsia. 54(9): 1595-604.	Clinical question 1	No comparator arm and not relevant outcomes
Yamada M et al. (2021): Long-term safety and effectiveness of stiripentol in patients with Dravet syndrome: Interim report of a post-marketing surveillance study in Japan. Epilepsy research. 170: 106535.	Clinical question 1	No comparator arm and not relevant outcomes
Yıldız EP et al. (2019): Efficacy of Stiripentol and the Clinical Outcome in Dravet Syndrome. Journal of child neurology. 34(1): 33-37.	Clinical question 1	Not relevant stiripentol dose, no comparator arm and not relevant outcomes

10.2 Main characteristics of included studies

Table 28, Table 29 and Table 30 present the main characteristics of Study 1, Study 1504 and STICLO-France, respectively.

Table 28: Main characteristics of Study 1

Trial name	A multicenter, randomised, double-blinded, parallel-group, placebo-controlled trial of two fixed doses of ZX008 (fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome
NCT number	Study 1 is registered with clinicaltrials.gov with two identical protocols: NCT02682927 and NCT02826863.
Objective	The primary objective of Study 1 was to demonstrate that fenfluramine 0.7 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome in children and young adults, based on change in frequency of convulsive seizures between the baseline period and combined titration and maintenance (T+M) period.
Publications – title, author, journal, year	Lagae L et al. (2019): Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 394(10216): 2243-54 (6).
Study type and design	The Study 1 was a prospective merged analysis of two identical phase III, randomised, double-blinded, placebo-controlled studies (ZX008-1501 and ZX008-1502).
Follow-up time	The trial comprised of a six-week observational baseline period followed by a two-week titration period, which was followed by a 12-week maintenance period. The maintenance period was followed by a two-week taper/transition period. I.e., the total follow-up time was 16 weeks. The treatment period was 14 weeks.

Population (inclusion and exclusion criteria)	**Inclusion criteria** (2)**:** • Males and females between 2-18 years of age. Female patients of childbearing potential must not have been pregnant or breast-feeding and must have had a negative urine pregnancy test. Patients of childbearing or child-fathering potential must have been willing to use medically acceptable forms of birth control, which included abstinence, while being treated on this study and for 90 days after the last dose of study drug. • Patient had documented medical history to support a clinical diagnosis of Dravet syndrome, where convulsive seizures were not completely controlled by current antiepileptic drugs (AEDs). • Patients met all the following five criteria: o onset of seizures in the first year of life in an otherwise healthy infant; o a history of seizures that were either generalised tonic-clonic, unilateral clonic, or bilateral clonic, and were prolonged; o initial development was normal; o history of normal brain magnetic resonance imaging (MRI) without cortical brain malformation; and o lack of alternative diagnosis. • Patients met at least one of the following three criteria: o emergence of another seizure type, including myoclonic, generalised tonic-clonic, tonic, atonic, absence, and/or focal developed after the first seizure type; o prolonged exposure to warm temperatures induced seizures and/or seizures were associated with fevers due to illness or vaccines, hot baths, high levels of activity, and sudden temperature changes, and/or seizures were induced by strong natural and/or fluorescent lighting, as well as certain visual patterns; and o genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis). • Patients had ≥4 convulsive seizures (tonic, tonic-atonic, tonic-clonic, or clonic) per four-week period for the past 12 weeks prior to screening, reported by parent/guardian to investigator or investigator medical notes. • All medications or interventions for epilepsy (including ketogenic diet (KD) and vagal nerve stimulator/stimulation (VNS) were stable for at least four weeks prior to screening and were expected to remain stable throughout the study. • Patients was informed of the nature of the study and informed consent was obtained from the legally responsible parent/guardian. • Patients provided assent in accordance with IRB/IEC requirements, if capable. • Patient's parent/caregiver was willing and able to be compliant with diary completion, visit schedule, and study drug accountability. **Exclusion criteria** (2)**:** • Subject had a known hypersensitivity to fenfluramine hydrochloride or any of the excipients in the study medication. • Subject had pulmonary arterial hypertension. • Subject had current or history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, or stroke. • Subject had current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration of >1 month. • Subject was at imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview and/or responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must have been excluded if they reported suicidal behavior in the past six months, as measured by the C-SSRS at screening or baseline, which included

	suicidal ideation with intent and plan (Item 5). If a subject reported suicidal ideation on Item 4 without specific plan, and the investigator felt that the subject was appropriate for the study considering the potential risks, the investigator must have documented appropriateness for inclusion, and discussed with the parent/caregiver to be alert to mood or behavioural changes, especially around times of dose adjustment. • Subject had a current or history of glaucoma. • Subjects with moderate or severe hepatic impairment were excluded. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes <3 x upper limit of normal (ULN) and/or elevated bilirubin <2 x ULN) may have been entered into the study, after review and approval by the Medical Monitor in conjunction with the sponsor, with consideration of potential cause, concomitant medications, and other risk factors. • Subject was receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally acting noradrenergic agonist; or cyproheptadine (note: Short-term medication requirements were handled on a per-case basis by the Medical Monitor). • Subject was currently receiving or had received stiripentol in the past 21 days prior to screening. • Subject was currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or had taken any of these within the past 30 days, as maintenance therapy. • Subject was unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges and their juices beginning with the baseline period and throughout the study. • Subject had positive results on the urine tetrahydrocannabinol (THC) Panel or the whole blood cannabidiol (CBD) at the screening visit. • Subject had participated in another clinical trial within the past 30 days. • Subject was currently receiving an investigational product. • Subject was unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions. • Subject had a clinically significant condition or had had clinically relevant symptoms or a clinically significant illness in the four weeks prior to the screening visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject. **Randomisation inclusion criteria** (2)**:** • Subject was approved for study inclusion by the Epilepsy Study Consortium. • Subject did not have a cardiovascular or cardiopulmonary abnormality based on screening ECHO, ECG, or physical examination, including but not limited to trace mitral or aortic valve regurgitation or signs of pulmonary hypertension, and was approved for entry by the central cardiac reader. • Subject demonstrated a stable baseline with ≥ six convulsive seizures during the six-week baseline period, with a minimum of two in the first three weeks and two in the second three weeks. • Subject's parent/caregiver had been compliant with diary completion during the Baseline period, in the opinion of the investigator (e.g., at least 90% compliant).
Intervention	Two doses of fenfluramine were assessed: • 0.7 mg/kg per day orally twice daily • 0.2 mg/kg per day orally twice daily The doses had to be titrated according to an algorithm presented below. The maximum daily dose was 30 mg fenfluramine.

Randomised group	Titration step 1 Study day 1-4	Titration step 2 Study day 5-8	Titration step 3 Study day 9-14
Fenfluramine 0.2 mg/kg/day	0.2 mg/kg/day	0.2 mg/kg/day	0.2 mg/kg/day
Fenfluramine 0.7 mg/kg/day	0.2 mg/kg/day	0.4 mg/kg/day	0.7 mg/kg/day
Placebo	Placebo	Placebo	Placebo

Baseline characteristics

The baseline characteristics from the overall population and the subpopulation of stiripentol-experienced patients in Lagae et al. 2019 (6) are presented in the tables below.

Data is number of participants (%) unless otherwise specified.	Fenfluramine 0.7 mg/kg/day (N=40)	Fenfluramine 0.2 mg/kg/day (N=39)	Placebo (N=40)	Total (N=119)
Age, years				
Mean (SD)	8.8 (4.4)	9.0 (4.5)	9.2 (5.1)	9.0 (4.7)
Range	2–18	2–17	2–18	2–18
Patients younger than 6 years	11 (28)	9 (23)	11 (28)	31 (26)
Male	21 (52)	22 (56)	21 (52)	64 (54)
Race				
White	34 (85)	33 (85)	31 (78)	98 (82)
Asian	1 (3)	2 (5)	4 (10)	7 (6)
Other or not reported*	5 (12)	4 (10)	5 (12)	14 (12)
Bodyweight (kg), mean (SD)	31.8 (13.5)	35.1 (19.6)	31.7 (16.2)	32.9 (16.5)
BMI (kg/m^2), mean (SD)	18.5 (3.5)	19.3 (5.7)	18.0 (3.8)	18.6 (4.4)
SCN1A mutations	33 (82)	31 (80)	31 (78)	95 (80)
Region				
USA and Canada	24 (60)	24 (61)	24 (60)	72 (60)
Rest of world	16 (40)	15 (39)	16 (40)	47 (40)
Number of concomitant antiepileptic drugs, mean (SD)	2.3 (0.9)	2.5 (1.1)	2.5 (0.9)	2.4 (1.0)
Concomitant antiepileptic drugs				
Valproate (all forms)	25 (62)	24 (62)	22 (55)	71 (60)
Clobazam	24 (60)	24 (62)	22 (55)	70 (59)
Topiramate	11 (28)	10 (26)	9 (22)	30 (25)
Levetiracetam	4 (10)	11 (28)	11 (28)	11 (28)
Patients given maximum dose of fenfluramine (26 mg per day)	12 (30)	0	0	12 (10)
Baseline CSF per 28 days				
Mean (SD)	31.4 (30.6)	45.5 (99.8)	44.2 (40.2)	40.3 (64.0)
Median (range)	20.7 (4.8–124)	17.5 (4.7–623.5)	27.3 (3.3–147.3)	24.1 (3.3–623.5)

*Privacy laws in some regions preclude disclosure of particular personal information.

In the table below, the baseline characteristics of the stiripentol-experienced subpopulation is presented. Source: Poster by Wirrell et al. 2018 (5)

	Placebo (N=16)	Fenfluramine 0.2 mg (N=20)	Fenfluramine 0.7 mg (N=22)	Total (N=58)
Age (years)				
n	16	20	22	58
Mean	10.3	9.3	9.7	9.7
SD	4.76	4.33	4.13	4.32
Median	9.5	9.5	9.5	9.5
Min	3	2	3	2
Max	18	16	18	18
Age Group, n (%)				
<6 years	2 (12.5%)	5 (25.0%)	3 (13.6%)	10 (17.2%)
≥6 years	14 (87.5%)	15 (75.0%)	19 (86.4%)	48 (82.8%)
Sex				
Male	11 (68.8%)	10 (50.0%)	13 (59.1%)	34 (58.6%)
Female	5 (31.3%)	10 (50.0%)	9 (40.9%)	24 (41.4%)
Race				
White	13 (81.3%)	17 (85.0%)	21 (95.5%)	51 (87.9%)
Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	3 (18.8%)	1 (5.0%)	0 (0.0%)	4 (6.9%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported [*]	0 (0.0%)	2 (10.0%)	1 (4.5%)	3 (5.2%)
Unknown [*]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnic Group				
Hispanic or Latino	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (1.7%)
Not Hispanic or Latino	10 (62.5%)	17 (85.0%)	18 (81.8%)	45 (77.6%)
Not Reported [*]	6 (37.5%)	2 (10.0%)	3 (13.6%)	11 (19.0%)
Unknown [*]	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (1.7%)
Region/Country				
North America	5 (31.3%)	8 (40.0%)	9 (40.9%)	22 (37.9%)
Canada	1 (6.3%)	0 (0.0%)	1 (4.5%)	2 (3.4%)
United States	4 (25.0%)	8 (40.0%)	8 (36.4%)	20 (34.5%)
ROW	11 (68.8%)	12 (60.0%)	13 (59.1%)	36 (62.1%)
Australia	0 (0.0%)	1 (5.0%)	1 (4.5%)	2 (3.4%)

Belgium	0 (0.0%)	2 (10.0%)	2 (9.1%)	4 (6.9%)
Denmark	6 (37.5%)	0 (0.0%)	1 (4.5%)	7 (12.1%)
France	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Germany	2 (12.5%)	3 (15.0%)	4 (18.2%)	9 (15.5%)
Italy	1 (6.3%)	2 (10.0%)	1 (4.5%)	4 (6.9%)
Spain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline Height (m)				
n	16	20	22	58
Mean	1.33	1.32	1.34	1.33
SD	0.173	0.198	0.199	0.189
Median	1.32	1.33	1.35	1.33
Min	1.0	1.0	1.0	1.0
Max	1.6	1.6	1.7	1.7
Baseline Weight (kg)				
n	16	20	22	58
Mean	33.4	32.1	35.4	33.7
SD	16.37	11.33	14.19	13.77
Median	28.7	32.3	32.1	30.5
Min	16	17	18	16
Max	81	53	60	81
Baseline BMI (kg/m^2)				
n	16	20	22	58
Mean	17.76	17.75	19.14	18.28
SD	4.462	2.488	3.790	3.614
Median	16.43	17.13	18.92	17.74
Min	11.6	14.1	12.5	11.6
Max	31.6	23.0	27.4	31.6

*Not reported or missing: Privacy laws in some regions/countries preclude disclosure of certain personal information.

BMI=Body Mass Index, where BMI = weight (kg)/height (m2).

Note: Percentages are calculated based on the number of subjects with non-missing data in the Safety population.

Primary and secondary endpoints

Primary endpoint (2)**:**

- Change in CSF (mean number of convulsive seizures per 28 days) from baseline to the T+M period

Key Secondary endpoints (2)**:**

- Proportion of patients in each fenfluramine treatment arm compared with placebo who were considered treatment responders, defined as those with ≥50% reduction in convulsive seizures from baseline (Time frame: 0-14 weeks)
- Comparison of patients' longest seizure-free interval in each fenfluramine treatment arm compared with placebo (Time frame: 0-14 weeks)
- A comparison of each patient's longest convulsive seizure-free interval, and longest interval without any seizures, during the 14-week T+M period, calculated independently for the fenfluramine 0.7 and 0.2 mg/kg/day treatment groups versus placebo from seizure diary records

Additional secondary outcomes:

	• The number of convulsive seizure-free days • The proportion of patients that achieved ≥75% reductions from baseline in CSF • The change from baseline in non-convulsive seizure frequency and all seizure frequency • The incidence of rescue medication usage, and medical utilisation • The incidence of status epilepticus • Clinical Global Impression (CGI) - Improvement rating, as assessed by the parent/caregiver • The change from baseline in Quality of Life (as assessed by Quality of Life in Childhood Epilepsy (QOLCE) Scale and Paediatric Quality of Life Inventory (PedsQL)); • The change from baseline in affective symptoms of the parent/caregiver. **Safety and tolerability of fenfluramine 0.2 and 0.7 mg/kg/day compared to placebo:** • Compare safety and tolerability of fenfluramine 0.2 and 0.7 mg/kg/day and placebo with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate, temperature, and respiratory rate), ECG, ECHO, body weight and cognitive function.
Method of analysis	The primary efficacy endpoint was the change from baseline in the mean CSF per 28 days during the T+M periods. The mean CSF was calculated from all available data collected during the baseline and treatment periods. The primary endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment arm (3 levels) and age group (<6 years, ≥6 years) as factors, and with baseline mean CSF as a covariate. The primary analysis compared the fenfluramine 0.7 mg/kg/day arm to the placebo arm using a 2-sided test at the alpha=0.05 level of significance. The primary endpoint was also analysed using a nonparametric method and if normality assumptions were not met, the results of the nonparametric analysis were used for evaluation of the primary endpoint. An additional analysis was performed to assess the sensitivity of the primary analysis to changes in concomitant AED medications that could occur during the trial. Specifically, the primary analysis was repeated with a factor added to indicate whether a subject had a change in concomitant AED medication during the T+M period. Proportion of Subjects with ≥50% reduction from baseline in CSF was compared between treatment groups using a logistic regression model that incorporated the same factors as the ANCOVA used in the primary analysis. Two separate logistic regression models were used for comparing fenfluramine 0.7 mg/kg with placebo and fenfluramine 0.2 mg/kg with placebo. This modelled a categorical response variable (achieved 50 percentage point reduction, yes or no) as a function of treatment group (fenfluramine and placebo), age group (<6 years, ≥6 years), and baseline CSF. Descriptive statistics are presented by treatment group and include the number and proportion of subjects <6 years, ≥6 years, and overall achieving the reduction, along with the model-estimated OR (including 95% CI) and p-values for the separate comparisons of fenfluramine 0.7 mg/kg/day to placebo and fenfluramine 0.2 mg/kg/day to placebo. For each type of assessor (parent/caregiver and investigator), the mean (SD) CGI-I score, and the number and percentage of subjects who showed improvement (i.e., had a score of 3 or lower), and the number and percentage who did not improve (i.e., had a score of 4 or higher) were presented by treatment group at each assessment time point. Each assessment time point also included a comparison between each active treatment and the placebo group, using the Cochran-Mantel-Haenszel test stratified by age group, and a frequency distribution of the number and percentage of subjects in each category in the scale. A histogram of the frequency distribution was provided. The number and percentage of subjects who showed good or very good improvement (i.e., had a score of 2 or lower), and the number and percentage who did not improve (i.e., had a score of 3 or higher) were summarised by treatment group at each assessment time point, as an exploratory analysis. For the PedsQL 4.0 Generic Core Scale, the change from baseline for the Total Score was calculated for each subject by subtracting the Total Score measured at baseline from the Total Score measured at EOS. The change from baseline was summarised with descriptive statistics, and treatment groups were compared using pairwise Wilcoxon rank sum tests. The Physical

	Health Summary and Psychosocial Health Summary scores were likewise summarised and compared between each active group and placebo. Scale scores were not computed if more than 50% of the items in the scale were missing. If more than 50% or more of the items in the scale were completed, the mean of the completed items in a scale was imputed. The scaled results were combined across age categories to produce a single score for each functional area. All safety data was appropriately analysed by treatment arm. The number and percentage of subjects with AEs were displayed by System Organ Class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA Version 18.1). Summaries in terms of severity and relationship to study drug were also be provided. Adverse Events of Special Interest (AESI) and serious AEs were summarised separately in a similar manner. Laboratory tests, vital signs, physical examinations, neurological examinations, ECG, Doppler echocardiogram, C-SSRS, Tanner Staging results, etc, were summarised appropriately, by treatment. All safety summaries were based on the safety population.
Subgroup analyses	None.

Table 29: Main characteristics of Study 1504

Trial name	A Multicenter, Randomised, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 (Fenfluramine Hydrochloride) Oral Solution, as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome: Study ZX008-1504 Cohort 2 (2).
NCT number	NCT02926898
Objective	The primary objective was to demonstrate that fenfluramine is superior to placebo for the treatment of Dravet syndrome in children and young adults optimised on a STP regimen based on the change in CSF from baseline to the combined titration and maintenance periods (T+M periods).
Publications – title, author, journal, year	Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, Stephani U, Laux L, Wirrell E, Knupp K, Chiron C, Farfel G, Galer BS, Morrison G, Lock M, Agarwal A, Auvin S; FAiRE, DS Study Group. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 2020 Mar 1;77(3):300-308. doi: 10.1001/jamaneurol.2019.4113. (26) Sullivan J, Perry MS, Wheless JW, Galer B, Gammaitoni A. Fenfluramine responder analyses and numbers needed to treat: Translating epilepsy trial data into clinical practice. Eur J Paediatr Neurol. 2021 Jan 22;31:10-14. doi: 10.1016/j.ejpn.2021.01.005. (27)
Study type and design	Multicenter, two-cohort, randomised, double-blind, placebo-controlled parallel-group trial.
Follow-up time	The treatment period in the trial was 15 weeks (T+M).
Population (inclusion and exclusion criteria)	**Inclusion criteria** (28)**:** • Subject must be male or non-pregnant, non-lactating female, age two to 18 years (inclusive). • Subject must have documented medical history to support a clinical diagnosis of Dravet syndrome, where convulsive seizures are not completely controlled by current antiepileptic drugs.

- Subject must be receiving a therapeutically relevant and stable dose of CLB, VP, and STP for at least four weeks prior to screening and expected to remain stable throughout the study (Cohort 2 only).
- Subject must be receiving a stable dose of CLB and VPA, administered twice daily, to be eligible for dose regimen one and two or subject must be receiving a stable dose of CLB, VPA, and STP, administered twice daily, to be eligible for dose regimen 3 (Cohort 1 only).

Exclusion criteria (28)**:**

- Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.
- Subject has pulmonary arterial hypertension.
- Subject has a current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvopathy, myocardial infarction or stroke.
- Subject has a current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than one month.
- Subject has a current or past history of glaucoma.
- Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin re-uptake inhibition; triptans, atomoxetine, or other centrally-acting noradrenergic agonist: cyproheptadine, and/or CYP 2D6/3A4/2B6 inhibitors/substrates.
- Subject is currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.
- Subject has a positive result on urine THC Panel or whole blood CBD at the screening visit.
- Subject has a clinically significant condition or has had clinically relevant symptoms or a clinically significant illness in the four weeks prior to the Screening Visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

Intervention

The intervention was fenfluramine 0.5 mg/kg/day orally administrated and divided into two doses, with a maximum daily dose of 20 mg. The fenfluramine dose had to be gradually up-titrated in three steps over 21 days. The up-titration algorithm is presented in the table below. Placebo was given to match the fenfluramine dose (2)

	Study day 1-7	Study day 8-14	Study day 15-21
Fenfluramine dose	0.2 mg/kg/day	0.4 mg/kg/day	0.5 mg/kg/day

Baseline characteristics

The baseline characteristics from Nabbout et al. 2019 is presented in the table below.

Characteristics	Patient numbers (%)			P-value[1]
	Fenfluramine	Placebo	Total	
Numbers	43	44	87	NA
Age, mean (SD) [range], y	8.8 (4.6) [2-18]	9.4 (5.1) [2-19]	9.1 (4.8) [2-19]	0.57
Patients < 6 years	12 (28)	12 (27)	24 (28)	>0.99
Male	23 (53)	27 (61)	50 (57)	0.52
Race				
White	23 (53)	29 (66)	52 (60)	0.66
Black/African American	1 (2)	2 (5)	3 (3)	

	Asian	2 (5)	1 (2)	3 (3)	
	Other	3 (7)	1 (2)	4 (5)	
	Not reported or missing[2]	13 (30)	11 (25)	24 (28)	
	Unknown	1 (2)	0 (0)	1 (1)	
	BMI, mean (SD)	17.3 (2.7)	19.1 (4.9)	18.2 (4.0)	0.11
	CSF per 28 days				
	Median (range)	14.0 (3-213)	10.7 (3-163)	NA	0.62
	Mean (SD)	27.9 (36.9)	21.6 (27.6)	NA	
	Number of concomitant AEDs at baseline				
	2	1 (2)	1 (2)	2 (2)	0.10
	3	19 (44)	26 (59)	45 (52)	
	4	16 (37)	16 (36)	32 (37)	
	5	7 (16)	1 (2)	8 (9)	
	Other antiepileptic treatments in ≥10% of subgroup[3,4]				
	Stiripentol	43 (100)	44 (100)	87 (100)	NC
	Clobazam	40 (93)	42 (96)	82 (94)	
	Valproate	38 (88)	39 (89)	77 (89)	
	Topiramate	14 (33)	7 (16)	21 (24)	
	Levetiracetam	6 (14)	5 (11)	11 (13)	
	Baseline weight (kg)				
	Mean (SD)	31.3 (14.85)	36.2 (21.08)	33.8 (18.32)	
	Median	27.9	30.5	28.6	
	Baseline BMI (kg/m^2)				
	Mean (SD)	17.32 (2.715)	19.14 (4.890)	18.24 (4.049)	
	Median	16.58	17.51	17.13	

1: P-values (fenfluramine vs placebo) were calculated by Wilcoxon rank sum test (age, BMI, and baseline CSF per 28 days), Fisher exact test (age group and sex), and Freeman-Halton test (race and number of concomitant AEDs) with statistical significance set at P less than 0.05.
2: Not reported or missing: privacy laws in some regions and countries preclude disclosure of certain personal information.
3: Concomitant medications in less than 10% of patients included acetazolamide, clonazepam, diazepam, ethosuximide, felbamate, gamma-aminobutyric acid, lorazepam, phenobarbital, pregabalin, and zonisamide.
4: The number of patients following a ketogenic diet was 4 (5%) in the overall population. The number of patients with vagal nerve stimulator implantation was 5 (6%) overall.

Primary and secondary endpoints

Primary endpoint (2):

- Change from baseline in CSF to the T+M periods.

Key secondary endpoints (2):

- Proportion of subjects (n (%)) who achieve a ≥ 50% reduction in CSF from baseline to the T+M period
- Duration of the longest convulsive seizure-free interval during the T+M period (in days)

Additional secondary endpoints (2,29):

- Mean number of CSF days during the T+M period
- Number (%) of subjects with ≥ 25% and ≥ 75% reduction in CSF from Baseline to the T+M period
- Number (%) of subjects with complete or nearly complete convulsive seizure freedom during the T+M period
- Change in mean number of nonconvulsive seizures from Baseline to the T+M period
- Change in mean number of nonconvulsive seizures by type from Baseline to the T+M period

	• Change in mean total seizure frequency (convulsive + nonconvulsive) from Baseline to the T+M period • Change in number of instances of rescue medication used and number of doses from Baseline to the T+M period • Number of hospital admissions, hospital and healthcare service visits to seizures and number of subjects who utilized additional healthcare resources • Mean number of episodes of SE • Change in frequency of prolonged seizures from Baseline to the T+M period (i.e., proportion of a subject's seizures lasting < 2 minutes, 2 to 10 minutes, or > 10 minutes) • Proportion of subjects with improvement in clinical status as assessed by the parent/caregiver using the CGI-I score • Proportion of subjects with improvement in clinical status as assessed by the Principal Investigator using the CGI-I score • QOLCE to measure changes in quality of life of the subject • HRQOL based on the PedQL Generic Core Scale • HRQOL of the parent/caregiver using the EQ-5D-5L scale • Impact of the condition on parents and the family using the PedsQL Family Impact Module (this was not assessed in the Netherlands) • Safety endpoints included: AEs, clinical laboratories, vital signs, physical examinations, neurologic examination, Doppler ECHO, 12-lead ECG, body weight and cognitive function was assessed using the cognition domain score on the QOLCE and age-appropriate versions of the Behavior Rating Inventory for Executive Function (BRIEF).
Method of analysis	The primary endpoint (CSF during the T+M period) was analysed using a parametric analysis of covariance (ANCOVA) model with treatment arm (fenfluramine or placebo) and age group (< 6 years, ≥ 6 years) as factors, log Baseline frequency (CSFB) as a covariate, and log CSF T+M + 1 as response. Treatment arm means and difference from placebo were estimated with least squares means from the analysis model along with 95% confidence intervals (CIs) and associated 2-sided P values. Estimated treatment arm means and CI endpoints were exponentiated for presentation. If distributional assumptions of the ANCOVA were not met, a nonparametric analysis was to be performed in its stead. The primary analysis described above was repeated with baseline seizure frequency as a categorical variable, rather than a covariate. Baseline seizure frequency per 28 days was categorised as either <10; 10 to 50; or >50. In addition, the primary analysis described above was repeated using data from the maintenance period only as response. For subjects who did not reach the maintenance period, data from the transition were used to represent their maintenance period data. A similar ANCOVA model was used, and if distributional assumptions were not met, a nonparametric analysis was performed.
Subgroup analyses	None.

Table 30: Main characteristics of STICLO-France. Source:

Trial name	STICLO-France
NCT number	Not identified
Objective	To assess the efficacy and safety of stiripentol as an add-on to clobazam and valproate in children with SMEI.

Publications – title, author, journal, year	C Chiron, M C Marchand, A Tran, E Rey, P d'Athis, J Vincent, O Dulac, G Pons. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial, The Lancet 2000 Nov, 11;356(9242):1638-42.
Study type and design	Randomised, placebo-controlled double-blinded add-on trial
Follow-up time	The study had a baseline period of one month and hereafter placebo and stiripentol was added to valproate/clobazam. Patients were assessed every month during the double-blind period of two months, and in subsequent open treatment for at least one month.
Population (inclusion and exclusion criteria)	The study protocol included patients from 15 French centres with the following criteria of inclusion: • 3 years and older • SMEI, defined as onset of the epilepsy in the first year of life with clonic (or tonic-clonic) generalised seizures but normal psychomotor development and normal electroencephalogram (EEG) • Appearance of myoclonia after 1 year of age • Atypical absences • Generalised spikes and waves on EEG • Mental delay • At least four clonic (or tonic-clonic) generalised seizures a month • Valproate and clobazam as ongoing antiepileptic drugs Patients receiving other drugs (except progabide) and those whose parents were unable to comply regularly with drug delivery and daily seizure diary were not included. Written informed consent was obtained from the parents or guardian of all patients.
Intervention	Stiripentol was administered as capsules at the dose of 50 mg/kg a day, twice or three times daily. Patients received stiripentol as an add-on to valproate/clobazam (30 mg/kg a day for valproate and 0·5 mg/kg a day for clobazam). The dose of stiripentol could be increased from 50 to 100 mg/kg a day, and the comedication changed if seizures persisted. The mean daily dose of stiripentol during the double-blind period was 49.3 mg/kg a day (95% CI: 47.4–51.2 mg/kg day).
Baseline characteristics	The baseline characteristics from Chiron et al. 2000 is presented in the table below.

	Stiripentol (n=21)	Placebo (n=20)
Mean age (years) (IQR)	9.4 (3–16.7)	9.3 (3.2–20.7)
Male	6	11
Mean weight (kg) (IQR)	32 (14–60)	31 (15–70)
Median (IQR) number of monthly seizures	18 (4–73)	19 (4–76)
Mean dose valproate (mg/kg a day) (IQR)	23.7 (10–46.4)	24 (13.8–50)
Mean dose clobazam (mg/kg a day (IQR)	0.53 (0.05–1.04)	0.55 (0.14–1.18)
Patients on progabide*	5	2

*Progabide has been used in SMEI, with unsatisfactory effects, and was in the process of being removed from the market.

Primary and secondary endpoints	Primary outcome was the percentage of responders on stiripentol and on placebo, defined as having experienced at least a 50% reduction of clonic (or tonic-clonic) seizure frequency during the second month of the double-blind period compared with baseline. Patients who presented with status epilepticus during the double-blind period were regarded as non-responders. Secondary outcomes were the absolute count of clonic (or tonic-clonic) seizures during the second month of the double-blind period (normalised to 30 days by dividing the raw count by the exact number of days of observation and multiplying by 30) and the percentage of change from baseline.

Method of analysis	A difference of at least 25% was requested between stiripentol and placebo for the percentage of responders. Because no data were published for this criterion in a reference population with the same epilepsy syndrome, it was decided to include 40 patients (balanced between stiripentol and placebo) and to compute from their data (but without awareness of the treatments) a 95% CI for the difference between the percentages of responders. Since this interval agreed with the request, the sample size was computed and found that 20 patients per arm were sufficient. All statistical analyses were done on an intention-to-treat basis. The percentages of responders were estimated by an exact 95% CI and compared between arms by Fisher's exact test. A 95% CI was also computed for the between-groups difference of the percentages of responders. Stiripentol and placebo arms were finally compared by the Mann-Whitney test.
Subgroup analyses	None.

10.3 Presentation of results from Study 1 and STICLO-France

The proposed positioning of fenfluramine in the treatment of seizures associated with Dravet syndrome is as an add-on therapy to SoC AED regimens that include STP, or in patients after being treated with STP, or in patients who are ineligible to receive STP. We therefore do not believe a comparison of fenfluramine against STP is relevant to the proposed positioning of fenfluramine. In addition, it is not technically feasible to conduct a robust indirect comparison of fenfluramine versus STP due to the differences in the trial designs and endpoints.

We applied Study 1 to inform the fenfluramine 0.7 mg/kg arm and STICLO-France to inform the STP arm. Information on Study 1 came from data on file (CSR), Lagae et al. 2019 (6) and the EPAR, while information on STICLO-France came from the publication by Chiron et al. 2000 (8). The study design in the two studies were similar, as both studies were randomised, placebo-controlled double-blinded studies. STICLO-France named the disease SMEI, while Study 1 named the disease Dravet syndrome. SMEI is an older name for Dravet syndrome; thus, the two studies include patients with the same disease. The patient population in the two studies were similar: the mean age of included patients was 9.4 years in the STP arm of STICLO-France and 8.8 years in the fenfluramine arm of Study 1. Study 1 included slightly more males, but the mean body weight was similar in the two studies (31.8 kg in the 0.7 mg/kg fenfluramine arm in Study 1, and 32 kg in the STP arm of STICLO-France). Moreover, at baseline, the median number of monthly seizures was similar in the two studies: 20.7 seizures in Study 1 and 18 seizures in STICLO-France. Information on patients included in the two trials is provided in Table 28 (Study 1) and Table 30 (STICLO-France), Appendix 10.2.

10.3.1 Results from Study 1

Convulsive seizures - mean percentage change in the number of convulsive seizures per 28 days

In the DMC protocol, convulsive seizures are a critical outcome and should be measured in two ways: 1) as mean percentage change in the number of convulsive seizures per 28 days, and 2) as the proportion of patients who achieve a 50% reduction in the number of convulsive seizures.

The primary efficacy endpoint in Study 1 was the change in the mean convulsive seizure frequency (CSF) per 28 days during the T+M period compared to the baseline period for fenfluramine 0.7mg/kg/day vs placebo. Seizure types contributing to the primary endpoint were generalised tonic clonic (GCT), tonic, clonic, drop seizures (tonic-atonic), hemiclonic, and focal seizures with an observable motor component. Monthly (28-day) CSF was based on electronic diary data obtained for each patient. For each patient, the CSF was calculated from all available

data collected during the baseline and T+M periods, and the treatment group mean CSF per 28 days was calculated for the baseline and T+M periods. The baseline period included the 42 days immediately preceding the randomisation visit and the T+M period was 14 weeks (including two weeks titration) (2).

CSF was counted from the daily diary records provided by the patient or parent/caregiver. For any individual subject, CSF per 28 days during the baseline period was calculated as: (28 x total number of convulsive seizures during the baseline period) / total number of days in the baseline period with non-missing diary data. In both the fenfluramine and placebo arms, means were obtained by averaging over the subjects in the treatment group (2). CSF per 28 days for the T+M period was derived the same way. The percentage change from baseline for all subjects was estimated by: $(CSF_{T+M} - CSF_B) * 100 / CSF_B$. The difference from baseline was estimated by $CSF_{T+M} - CSF_B$, where CSF_{T+M} is the T+M period CSF, and CSF_B is the baseline period CSF (2).

For the primary endpoint, change in CSF was analysed using an analysis of covariance (ANCOVA) model with treatment group (3 levels) and age group (<6 years, ≥6 years) as factors, and with baseline mean CSF as a covariate. The primary analysis incorporated a log transformation to satisfy the underlying assumptions of the ANCOVA model; Baseline, M, and T+M period values were log transformed prior to analysis. Based on that primary analysis, which supported the registration of fenfluramine with the EMA, fenfluramine 0.7 mg/kg per day showed a 62.3% greater reduction in mean MCSF compared with placebo (95% CI 47.7, 72.8, p<0·0001) (6), As Lagae et al 2019 only reports the median percentage change in CSF for fenfluramine 0.7mg/kg/day vs placebo (-74.9% [range –100 to 196.4] vs –19·%2 [–76.1 to 51.8]; p<0.0001) (6), we have provided the mean number and percentage change from baseline in CSF, as requested in the DMC protocol, in Table 5.

As seen in Table 31, the mean number of CSF per 28 days at baseline was 31.35 (SD: 30.562, 95% CI: 21.879, 40.821) in the fenfluramine arm[redacted]

[redacted]

[redacted]

Source: CSR on Study 1 (data on file) and Lagae et al. 2019. Note: these analyses are based on unadjusted summary statistics.

Convulsive seizures - the proportion of patients who achieved a 50% reduction in the number of convulsive seizures

A key secondary outcome in Study 1 was the proportion of patients with a ≥50% reduction from baseline in CSF. The comparison between fenfluramine and placebo was made using a logistic regression model that incorporated the following factors: treatment group (3 levels, but we did not include fenfluramine 0.2 mg/kg/day in our analysis, and age group (<6 years, ≥6 years, i.e., the generated odds ratio (OR) was adjusted for age). The logistic regression model modeled a categorical response variable (achieved 50 %-point reduction, yes or no) as a function of treatment group (fenfluramine 0.7 mg/kg and placebo), age group (<6 years, ≥6 years), and baseline CSF (2). Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10).

As seen in Table 32, 27 out of 40 patients (67.5%, 95% CI: 53%, 82%) achieved a ≥50% reduction from baseline in CSF in the fenfluramine arm compared to 5 out of 40 patients (12.5%, 95% CI: 2.3%, 22.7%) in the placebo arm. The OR from the logistic regression was 14.960 (95% CI: 4.484, 49.915) and the result was statistically significant (p-value: <0.001) in favor of fenfluramine.

Table 32: Proportion of patients who achieved a ≥50% reduction in the number of convulsive seizures (mITT population from Study 1)

	Fenfluramine 0.7 mg/kg (N=40)	Placebo (N=40)
Change from baseline in CSF ≥50%, n (%; 95% CI)	27 (67.5%, 95% CI: 53%, 82%)	5 (12.5%, 95% CI: 2.3%, 22.7%)
OR (95% CI)	14.960 (4.484, 49.915)	
P-value	<0.001	
Relative difference	5.450 (95% CI: 2.335, 12.721)	
Absolute difference	55.6 percentage points (95% CI: 16.69, 146.51)	

Note: Data from the T+M period (2 weeks + 12 weeks) presented. Source: Lagae et al. 2019. Relative difference and absolute difference were own calculations.

Need for rescue medication – mean number of days per 28 days where rescue medication is used

The use of rescue medication was recorded in the daily diary. Rescue medication was administered according to each subject's personalised regimen consisting of one or more medications. The number of days rescue medication was taken (normalised to 28 days) was calculated for each subject. Multiple medications taken on the same day were counted once for that day. The number of medications used per episode was calculated and summarised for each subject. Rescue medications related to an episode of status epilepticus (SE) were considered to be all rescue medications administered on the day of the SE (or seizure lasting >10 min). If more than one episode of SE or a seizure lasting >10 min occurred in a single day, the rescue medication for that episode is all rescue administered after the seizure until the start time of the next prolonged seizure.

[redacted]

During the T+M period, the mean number of days were 0.9 (95% CI: 0.320, 1.480) days in the fenfluramine arm compared to 3.1 (95% CI: 1.659, 4.541) days in the placebo arm. The mean difference was -2.2 days (95% CI: -3.8 days, -0.65 days). Results are summarised in Table 33.

Table 33: Mean number of days per 28 days where rescue medication was used. Baseline values and values during the T+M period are presented (mITT population from Study 1)

	Fenfluramine 0.7 mg/kg (N=40)	Placebo (N=40)
During baseline		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
During T+M periods		
Mean (SD)	0.9 (1.87)	3.1 (4.65)
95% CI	0.320, 1.480	1.659, 4.541
Mean difference during the T+M period	-2.2 days	
95% CI of difference	-3.8 days, -0.65 days	

Note: T+M period was 2 weeks + 12 weeks. Source: Baseline values from CSR on Study 1 (data on file) and values during T+M period from Lagae et al. 2019

Need for rescue medication – proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used

[redacted]

[redacted]

[redacted]

Quality of life – Mean change in PedsQL

The change from baseline in the Pediatric Quality of Life Inventory (PedsQL) score was a secondary outcome in Study 1. The PedsQL measures 4 functional areas (physical, emotional, social, and school functioning) and was completed by the parent/caregiver as a proxy for the patient. The PedsQL is not a disease-specific quality of life measure. The PedsQL uses responses from the functional areas to generate 2 summary scores and a total score: the Psychosocial Health Summary score is comprised from the emotional, social, and school functioning scales; the Physical Health Summary score is comprised of the physical functioning scale; the Total Score is the sum of all the items over the number of items answered on all the scales. The trial did not stratify patients based on their QoL, and differences by treatment group may be seen due other influential covariates of QoL such as: Age and number of underlying comorbidities.

The mean (SD) total score at baseline in the PedsQL generic core for placebo and fenfluramine 0.7 mg/kg was 45.6 (17.07) and 48.7 (18.12), respectively. The mean (SD) change from baseline in the total score at the end of study (EOS) visit for the placebo was -1.6 (10.43), while there was an increase for fenfluramine of 5.9 (15.11). [redacted] Results are summarised in Table 35.

Table 35: Mean change in PedsQL (mITT population from Study 1). Higher values indicate improved QoL

	Fenfluramine 0.7 mg/kg (N=40)	Placebo (N=40)
[redacted]		
Total Score		
Baseline, mean (SD)	48.7 (18.12)	45.6 (17.07)
EOS, mean (SD)	55.7 (19.55)	45.6 (13.83)
Change from baseline, mean (SD; 95% CI)	5.9 (SD: 15.11; 95% CI: 1.217, 10.583)	-1.6 (SD: 10.43; 95% CI: -4.832, 1.632)
Difference in means	7.50	
95% CI of difference	1.81, 13.19	

Source: Physical Health Summary and Psychosocial Health Summary data only available from CSR on Study 1 (data on file). Total score from Lagae et al. 2019. Differences in mean change from baseline were own calculations. EOS: end of study

Quality of life – Proportion of patients with a score of 1 or 2 on CGI-I

Improvements in the patients QoL assessed with the Clinical Global Impression – Improvement (CGI-I) scale was a secondary outcome in Study 1. CGI-I measures improvement in the subject's clinical status from the baseline period. Both the parent/caregiver and the investigator rated their global impression of the patient's condition throughout the study at the end of titration period (visit 6), during the maintenance period (visit 8 and 10), and at the end of the study (visit 12). The severity of a patient's condition was rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

. Each assessment time point also included a comparison between fenfluramine and placebo, using the Cochran-Mantel Haenszel test stratified by age group, and a frequency distribution of the number and percentage of patients in each category in the scale. The OR estimated in both the parent/caregiver assessment and the investigator assessment was adjusted for age group. To accommodate the DMC protocol on fenfluramine, we present the proportion of patients with a score of 1 or 2.

[redacted]

[redacted]25 patients (62.5%, 95% CI: 47.5%, 77.5%)[redacted]
[redacted]4 patients (10.0%, 95% CI: 0.7%, 19.3%)[redacted]
[redacted]Results are summarised in Table 36 and Table 37.

Table 36: Proportion of patients with a score of 1 or 2 in CGI-I (Parent/caregiver ratings, mITT population from Study 1)

	Fenfluramine 0.7 mg/kg (N=40)	Placebo (N=40)
Number and percentage of subjects with a clinically meaningful improvement CGI scale (1 or 2) at visit 12 (EOS visit)		
Much improved or very much improved (1, 2), n (%; 95% CI)	22 (55.0%; 95% CI: 39.6%, 70.4%)	4 (10.0%; 95% CI: 0.7%, 19.3%)
OR	12.0	
P-value	<0.001	
Relative difference	5.714 (95% CI: 2.164, 15.09)	
Absolute difference	47.1 percentage points (95% CI: 11.64, 140.90)	

EOS: end of study. Source: Clinically meaningful improvement from Lagae et al. 2019.

Table 37: Proportion of patients with a score of 1 or 2 in CGI-I (Investigator ratings, mITT population from Study 1)

	Fenfluramine 0.7 mg/kg (N=40)	Placebo (N=40)
Number and percentage of subjects with a clinically meaningful improvement CGI scale (1 or 2) at visit 12 (EOS visit)		

Much improved or very much improved (1, 2), n (%; 95% CI)	25 (62.5%, 95% CI: 47.5%, 77.5%)	4 (10.0%, 95% CI: 0.7%, 19.3%)
OR	19.6	
P-value	<0.001	
Relative difference	6.853 (95% CI: 2.623, 17.902)	
Absolute difference	58.5 percentage points (95% CI: 16.23, 169.02)	

EOS: end of study. Source: separate scores of 1 or 2 from CSR on Study 1 (data on file). Summary of clinically meaningful improvement from Lagae et al. 2019. Note: if the lower limit of the confidence interval had a negative value, we replaced it with 0.

Adverse events – proportion of patients with at least one serious adverse event

[redacted] Results are summarised in Table 38.

Table 38: Number of patients with at least one TEAE and one serious TEAE (safety population from Study 1)

	Fenfluramine 0.7 mg/kg (N=40)	Placebo (N=40)
At least one TEAE, n (%; 95% CI)	38 (95.0%; 95% CI: 88.2%, 101.8%)	26 (65.0%; 95% CI: 50.2%, 79.8%)
Difference in proportions	30 percentage points	
95% CI	13.7, 46.3	
[redacted]		
[redacted]		
[redacted]		

Source: At least one serious TEAE from CSR on Study 1 (data on file), values on at least one TEAE from Lagae et al. 2019

Adverse events – qualitative description of adverse event data

A qualitative description of adverse event data on fenfluramine was provided in section 6.2.2.

10.3.2 Results from STICLO-France

Convulsive seizures - mean percentage change in the number of convulsive seizures per 28 days

Mean change from baseline in the number of convulsive seizures, normalised to 30 days, was a secondary outcome in STICLO-France. The mean change from baseline in percentage of seizure frequency was -69% (95% CI: -50%, -88%) in the STP arm and 7% (95% CI: 25%, -11%) in the placebo arm. Results are presented in Table 39.

Table 39: Mean change from baseline in percentage of seizure frequency in STICLO-France (responders, ITT population)

	Stiripentol (N=21)	Placebo (N=20)

Mean change from baseline in percentage of seizure frequency (95% CI)	-69% (-50%, -88%)	7% (25%, -11%)

Source: Chiron et al. 2000

Convulsive seizures - the proportion of patients who achieve a 50% reduction in the number of convulsive seizures

The primary outcome in STICLO-France was the percentage of responders on STP and on placebo, defined as having experienced at least a 50% reduction of clonic (or tonic-clonic) seizure frequency during the second month of the double-blind period compared with baseline. Patients who achieved at least a 50% reduction in their seizure frequency was regarded as responders. Out of 21 patients, 15 (71%, 95% CI: 52.1%, 90.7%) achieved at least a 50% reduction in seizures from baseline in the STP arm compared to 1 (5%, 95% CI: 0%, 14.6%) in the placebo arm. Results are presented in Table 40.

Table 40: Number of patients who achieved at least a 50% reduction in seizures from baseline in STICLO-France (responders, ITT population)

	STP (N=21)	Placebo (N=20)
Responders, n (%, 95% CI)	15 (71%, 95% CI: 52.1%, 90.7%)	1 (5%, 95% CI: 0%, 14.6%)

Source: Chiron et al. 2000

Need for rescue medication – mean number of days per 28 days where rescue medication is used

The need for rescue medication was not assessed in STICLO-France. Therefore, we cannot present any data on this outcome.

Need for rescue medication – proportion of patients who achieve 50% reduction in the number of days per 28 days where rescue medication is used

The need for rescue medication was not assessed in STICLO-France. Therefore, we cannot present any data on this outcome.

Quality of life – Mean change in PedsQL

Quality of life was not assessed in STICLO-France. Therefore, we cannot present any data on this outcome.

Quality of life – Proportion of patients with a score of 1 or 2 on CGI-I

Quality of life was not assessed in STICLO-France. Therefore, we cannot present any data on this outcome.

Adverse events – proportion of patients with at least one serious adverse event

Drug-related adverse events were observed in the 21 (100%) patients on STP compared to five (25%) on placebo (p=0.0009). The AEs most frequently observed on STP were drowsiness and loss of appetite, which could result in loss of weight, whereas weight gain was equally reported for STP and placebo. SAEs were reported in five patients (23.8%, 95% CI: 5.6%, 42.0%) on STP (drowsiness in three, loss of weight in two patients) and in 1 patient (5%, 95% CI: 0%, 14-6%) on placebo (drowsiness). Results are presented in Table 41.

Table 41: Number serious AEs observed in STICLO-France

	STP (N=21)	Placebo (N=20)
Serious AEs, n (%; 95% CI)	5 (23.8%; 95% CI: 5.6%, 42.0%)	1 (5%; 95% CI: 0%, 14.6%)

Source: Chiron et al. 2000

Adverse events – qualitative description of adverse event data

The following section is based on the SPC on STP (16). The most common side effects with STP are anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia and dystonia. In Table 42, we present an overview of the very common, common, uncommon, and rare AEs by MedDRA terminology (very common: ≥1/10, common: ≥1/100 to <1/10, uncommon: ≥1/1,000 to <1/100, rare: ≥1/10,000 to <1/1,000). Within each frequency grouping inTable 42, undesirable effects are presented in order of decreasing severity.

Table 42: Summary of safety profile of STP from SPC on STP (Diacomit)

System Organ Class (MedDRA terminology)	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders		Neutropenia		Thrombocytopenia *
Metabolism and nutrition disorders	Anorexia, loss of appetite, weight loss			
Psychiatric disorders	Insomnia	Aggressiveness, irritability, behaviour disorders, opposing behaviour, hyperexcitability, sleep disorders		
Nervous system disorders	Drowsiness, ataxia, hypotonia, dystonia	Hyperkinesia		
Eye disorders			Diplopia	
Gastrointestinal disorders		Nausea, vomiting		
Skin and subcutaneous tissue disorders			Photosensitivity, rash, cutaneous allergy, urticaria	
General disorders and administration site conditions			Fatigue	
Investigations		Raised γ-GT		Liver function test abnormal

*Thrombocytopenia data are derived from both clinical trials and post-marketing experience.
Source: SPC on STP

Many of the above adverse reactions are often due to an increase in plasma levels of other anticonvulsant medicinal products and may regress when the dose of these medicinal products is reduced.

10.4 Results per study

Results per study are presented in the following tables.

Table 43: Results per study from Study 1 on overall population

Trial name:	A multicenter, randomised, double-blinded, parallel-group, placebo-controlled trial of two fixed doses of ZX008 (fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome (Study 1)
NCT number:	Study 1 is registered with clinicaltrials.gov with two identical protocols: NCT02682927 and NCT02826863

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean percentage change in CSF per 28 days (unadjusted)	Fenfluramine	40	[redacted]	[redacted]	[redacted]	Not reported.	NA	NA	NA	Mean difference presented	CSR on Study 1 (data on file)
	Placebo	40	[redacted]								CSR on Study 1 (data on file)

Mean percentage change in the number of convulsive seizures per 28 days (ANCOVA model)	Fenfluramine	40	Not reported	Not reported	Not reported	Not reported	62.3%	47.7, 72.8	p<0.0001	Results are based on an analysis of covariance model with treatment group and age group.	Lagae et al. 2019
	Placebo	40	Not reported								
Proportion of patients who	Fenfluramine	40	27 (67.5%, 95% CI: 53%, 82%)			Not reported	RR: 5.450	(95% CI: 2.335, 12.721	0.00009	Logistic regression that incorporated the factors such as treatment group (3 levels, but	Lagae et al. 2019

achieved a 50% reduction in the number of convulsive seizures						we did not consider fenfluramine 0.2 mg/kg/day in our analysis) and age group (<6 years, ≥6 years)). The logistic regression model modeled a categorical response variable (achieved 50 %-point reduction, yes or no) as a function of treatment group (fenfluramine 0.7 mg/kg and placebo), age group (<6 years, ≥6 years), and baseline CSF. Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10).	#
	Placebo	40	5 (12.5%, 95% CI: 2.3%, 22.7%)	55.6 percentage points	(95% CI: 16.69, 146.51)		

	Fenfluramine	40	0.9 (95% CI: 0.320, 1.480)						Mean difference is presented	Baseline values from CSR on Study 1 (data on file) and values during T+M period from Lagae et al. 2019
Mean number of days per 28 days where rescue medication is used				-2.2 days	(95% CI: -3.8 days, -0.65 days)	NA		NA	NA	
	Placebo	40	3.1 (95% CI: 1.659, 4.541)							Baseline values from CSR on Study 1 (data on file) and values during T+M period from Lagae et al. 2019
[redacted]									Mean difference is presented	Patient analysis (data on file)

[redacted]										
										Patient analysis (data on file)
	Fenfluramine	40	5.9 (95% CI: 1.217, 10.583)						Mean difference presented	
Mean change in PedsQ (total score)	Placebo	40	-1.6 (95% CI: -4.832, 1.632)	7.50	(95% CI: 1.81, 13.19)	NA	NA	NA	NA	Total score from Lagae et al. 2019. Differences in mean change from baseline were own calculations

Proportion of patients with a score of 1 or 2 on CGI-I (parent/care giver rating)	Fenfluramine	40	Much improved or very much improved (1, 2), n (%; 95% CI): 22 (55.0%; 95% CI: 39.6%, 70.4%)	47.1 percentage points	(95% CI: 11.64, 140.90)	Not reported.	RR: 5.724	(95% CI: 2.164, 15.09)	0.00045	OR estimated with the Mantel-Haenszel adjusting for age group. Relative difference estimated with Haldane-Anscombe correction. The applied methods were based on the DMC guideline (10).	Separate scores of 1 or 2 from CSR on Study 1 (data on file). Summary of clinically meaningful improvement from Lagae et al. 2019
	Placebo	40	Much improved or very much improved (1, 2): 4 (10.0%; 95% CI: 0.7%, 19.3%)							
Proportion of patients with a score of 1 or 2 on CGI-I	Fenfluramine	40	Much improved or very much improved (1, 2): 25 (62.5%, 95% CI: 47.5%, 77.5%)	58.5 percentage points	(95% CI: 16.23, 169.02)	NA	RR: 6.853	(95% CI: 2.623, 17.902)	0.00009	OR estimated with the Mantel-Haenszel adjusting for age group. Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied	Separate scores of 1 or 2 from CSR on Study 1 (data on file). Summary

(investigator rating)	Placebo	40	Much improved or very much improved (1, 2), n (%; 95% CI): 4 (10.0%, 95% CI: 0.7%, 19.3%)							methods were based on the DMC guideline (10).	of clinically meaningful improvement from Lagae et al. 2019
Proportion of patients with at least one TEAE	Fenfluramine	40	95.0% (95% CI: 88.2%, 101.8%)	30 percentage points	(95% CI: 13.7%, 46.3%)	NA	1.462	(95% CI: 1.152, 1855)	NA	Absolute and relative differences presented.	Lagae et al. 2019
	Placebo	40	65.0% (95% CI: 50.2%, 79.8%)								
Proportion of patients with at	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	Absolute and relative differences presented.	CSR on Study 1 (data on file)

least one serious AE	[redacted]		

Table 44: Results per study from Study 1 on STP-experienced patients

Trial name:	A multicenter, randomised, double-blinded, parallel-group, placebo-controlled trial of two fixed doses of ZX008 (fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome (Study 1)
NCT number:	Study 1 is registered with clinicaltrials.gov with two identical protocols: NCT02682927 and NCT02826863

	Estimated absolute difference in effect	Estimated relative difference in effect	Description of methods used for estimation	References

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Mean percentage change in CSF per 28 days (unadjusted)	Fenfluramine	22	[redacted]	[redacted]	[redacted]	Not reported.	NA	NA	NA	Mean difference presented	Data on file
	Placebo	16	[redacted]								Data on file
Mean percentage change in the number of convulsive seizures per 28	Fenfluramine	22	Not reported	Not reported	Not reported	Not reported	60.8%	Not reported	P=0.002	Results are based on an analysis of covariance model with	Wirrell et al. 2018

days (ANCOVA model)								treatment group and age group.	
	Placebo	16	Not reported						
Proportion of patients who achieved a 50%	Fenfluramine	22	[redacted]	[redacted]	[redacted]	Not reported	RR: [redacted]	Logistic regression that	Data on file

reduction in the number of convulsive seizures					incorporated the factors such as **treatment group (3 levels, but we did not consider fenfluramine 0.2 mg/kg/day in our analysis) and age group (<6 years, ≥6 years))**. The logistic regression model modeled a categorical response variable (achieved 50 %-point reduction, yes or no) as a function of treatment group	#
	Placebo	16	[redacted]	[redacted]		

(fenflurami ne 0.7 mg/kg and placebo), age group (<6 years, ≥6 years), and baseline CSF. Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10).

Mean number of days per 28 days where rescue medication is used	Fenfluramine	22	[redacted]95% CI: [redacted]	[redacted]	[redacted]	NA	NA	NA	NA	Mean difference is presented	Patient level analysis (data on file)
	Placebo	16	[redacted](95% CI: [redacted],								
Proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used	Fenfluramine	22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Mean difference is presented	Patient analysis (data on file)
	Placebo	16	[redacted]								Patient analysis (data on file)
Mean change in PedsQL (total score)	-										
	-										

Proportion of patients with a score of 1 or 2 on CGI-I (parent/caregiver rating)	Fenfluramine	22	Much improved or very much improved: 40.9% (95% CI: 20.71%, 63.65%)	34.66 percentage points	(95% CI: 10.9, 58.4)	Not reported.	6.545	(95% CI: 0.919, 46.612)	Not reported.	Absolute and relative differences presented.	Data on file
	Placebo	16	Much improved or very much improved: 6.3% (95% CI: 0.16%, 30.23%)								
Proportion of patients with a score of 1 or 2 on CGI-I (investigator rating)	Fenfluramine	22	Much improved or very much improved: 63.6% (95% CI: 40.66%, 82.80%)	57.39 percentage points	(95% CI: 34.0, 80.7)	Not reported.	10.182	(95% CI: 1.487, 69.719)	Not reported.	Absolute and relative differences presented.	Data on file
	Placebo	16	Much improved or very much improved: 6.3% (95% CI: 0.16%, 30.23%)								
Proportion of patients with at least one serious AE	Fenfluramine	22	18.2%; 95% CI: 5.19%, 40.28%)	18.2 percentage points	(95% CI: 2.1, 34.3)	NA	6.652	(95% CI: 0.0383, 115.433)	NA	Absolute and relative differences presented.	Data on file

	Placebo	16	0%; 95% CI: 0.0%, 20.59%)								

Table 45: Results per study from STICLO-France

Trial name:	A Multicenter, Randomised, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 (Fenfluramine Hydrochloride) Oral Solution, as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome: Study ZX008-1504 Cohort 2										
NCT number:	NCT02926898										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Results (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean percentage change in	STP	21	-69% (-50%, -88%)	-76 percentage points	Not reported.	NA	NA	NA	NA	Mean difference presented.	Chiron et al. 2000

the number of convulsive seizures per 28 days	Placebo	20	7% (25%, -11%)							Chiron et al. 2000
The proportion of patients who achieve a 50% reduction in the number of convulsive seizures	STP	21	71% (95% CI: 52.1%, 90.7%)	66 percentage points	Not reported.	NA	NA	NA	NA	Difference in proportions presented.	Chiron et al. 2000 Chiron et al. 2000
	Placebo	20	5% (95% CI: 0%, 14.6%)								
Mean number of days per 28 days where rescue medication is used	STP									The need for rescue medication was not assessed in STICLO-France.	
	Placebo										

*P*roportion of patients who achieve 50% reduction in the number of days per 28 days where rescue medication is used	STP Placebo			The need for rescue medication was not assessed in STICLO-France.	
Mean change in PedsQL	STP Placebo			Quality of life was not assessed in STICLO-France.	
Proportion of patients with a score of 1 or 2 on CGI-I				Quality of life was not assessed in STICLO-France	

Proportion of patients with at least one serious adverse event	STP	21	23.8% (95% CI: 5.6%, 42.0%)	18.8 percentage points	NA	NA	NA	NA	NA	Difference in proportions presented	Chiron et al. 2000
	Placebo	20	5% (95% CI: 0%, 14.6%)							

Table 46: Results per study from Study 1504

Trial name:	A Multicenter, Randomised, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 (Fenfluramine Hydrochloride) Oral Solution, as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome: Study ZX008-1504 Cohort 2
NCT number:	NCT02926898

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean percentage change in the number of convulsive seizures per 28 days (unadjusted)	Fenfluramine	43	[redacted]	[redacted]	[redacted]	Not reported	NA	NA	NA	Mean difference presented	[redacted]

	Placebo	44	[redacted]							[redacted]
Mean percentage change in the number of convulsive seizures per 28 days (ANCOVA model)	Fenfluramine	43	15.1	Not reported	Not reported	Not reported	54.04	35.55, 67.23	<0.001	Estimated with an ANCOVA model. The difference from placebo and the 95% CI was obtained from the LS Means on the log scale as follows: 100 × [1-exp (ls mean active – ls mean placebo)].	Nabbout et al. 2020
	Placebo	44	7.0							

Proportion of patients who achieved a 50% reduction in the number of convulsive seizures	Fenfluramine	43	53.5% (95% CI: 37.65%, 68.82%)	50.8 percentage points	(95% CI: 9.35, 216.02)	Not reported.	12.178	(95% CI: 3.056, 48.525)	0.0004	Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10).	Nabbout et al. 2020 and own calculations
	Placebo	44	4.5% (95% CI: 0.56%, 15.47%)								

Mean number of days per 28 days where rescue medication was used	Fenfluramine	43	1.4 (0.757, 2.043)	0.2 days	(95% CI: -0.8107, 1.2107	Not reported	NA	NA	NA	Mean difference presented	Nabbout et al. 2020 and own calculations
	Placebo	44	1.2 (0.420, 1.980)								
Proportion of patients who achieved a 50% reduction in the number of days per 28 days where	Fenfluramine	28	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	NA	Absolute and relative difference in proportions presented.	Patient analysis on Study 1504 data (data on file)

rescue medication was used										
	Placebo	19	[redacted]							
									Mean difference presented.	CSR on study 1 (data on file)
	Fenfluramine	43	[redacted]							
Mean change in PedsQL				[redacted]	[redacted]	NA	NA	NA	NA	
	Placebo	44	[redacted]							CSR on study 1 (data on file)

Proportion of patients with a score of 1 or 2 on CGI-I (parent/caregiver)	Fenfluramine	43	32.6% (95% CI: 18.6%, 46.6%)	14.7 percentage points	(95% CI: -3.44, 51.98)	NA	1.716	(95% CI: 0.832, 3.541),	NA	Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10)	Much improved or very much improved (1, 2) from Nabbout et al. 2020 and own calculations.
	Placebo	44	20.5% (95% CI: 8.5%, 32.4%)							
Proportion of patients with a score of 1 or 2 on CGI-I (investigator)	Fenfluramine	43	44.2% (95% CI: 29.3%, 59.0%)	26.3 percentage points	(95% CI: 3.87, 74.12)	NA	RR: 2.652	(95% CI: 1.243, 5.659),	0.0118	Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference. The applied methods were based on the DMC guideline (10)	Much improved or very much improved (1, 2) from Nabbout et al. 2020 and own calculations.
	Placebo	44	15.9% (95% CI: 5.1%, 26.7%)							

Proportion of patients with at least one serious adverse event	Fenfluramine	43	14.0% (95% CI: 3.6%, 24.3%)	-1.96 percentage points	(95% CI: -16.9, 13.0)	NA	RR: 0.877	(95% CI: 0.321, 2.399)	NA	Absolute and relative difference in proportions presented.	Own calculations
	Placebo	44	15.9% (95% CI: 5.1%, 26.7%)								

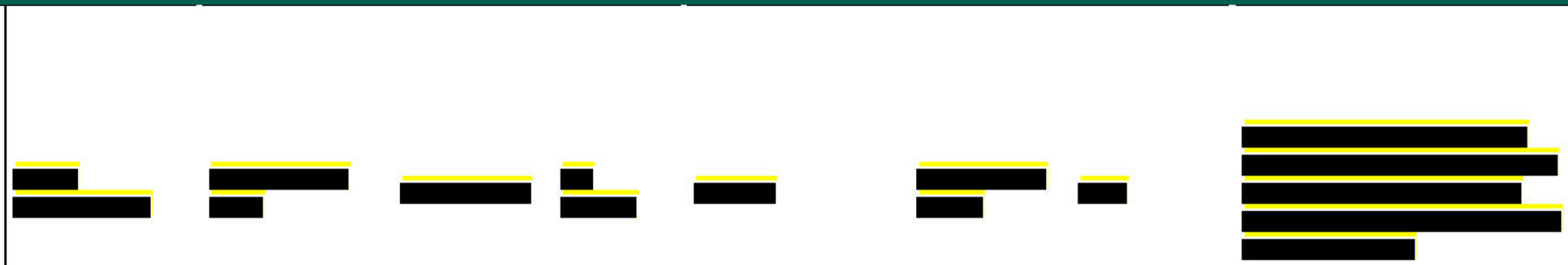
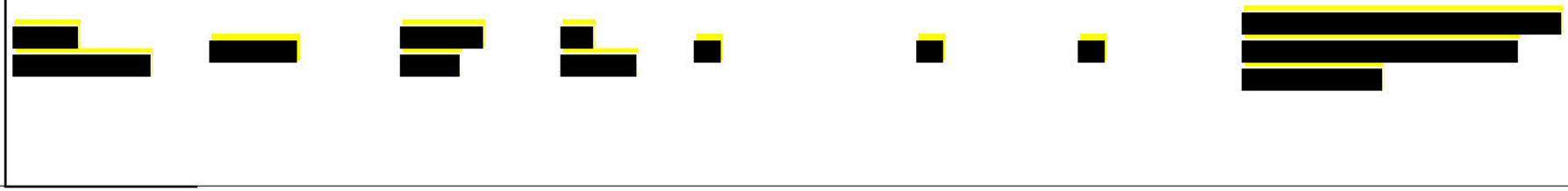
10.5 Results per PICO (clinical question)

In the following tables, we present results per PICO (the comparative analyses) conducted for clinical question 1a (Table 47) and 2 (Table 48). We will not present a table for clinical question 1, as we did not conduct a comparative analysis to answer clinical question 1. The rationale for this was presented in section 6.1.

Table 47: Comparative analysis on clinical question 1a

Results per outcome	

		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Mean percentage change in the number of convulsive seizures per 28 days (unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean percentage change in the number of convulsive seizures per 28 days (ANCOVA model)	Study 1 (subpopulation)	Not reported	Not reported	Not reported	60.8%	Not reported	P=0.002	Difference from placebo with ANCOVA model presented

Proportion of patients who achieved a 50% reduction in the number of convulsive seizures	
Mean number of days per 28 days where rescue medication was used	

Proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used								
Mean change in PedsQL								
Proportion of patients with a score of 1 on CGI-I (parent/caregiver)	Study 1 (subpopulation)	34.66 percentage points	(95% CI: 10.9, 58.4)	Not reported	RR: 6.545	(95% CI: 0.919, 46.612)	Not reported.	Absolute difference in proportions presented and relative difference

Proportion of patients with a score of 2 on CGI-I (investigator)	Study 1 (subpopulation)	57.39 percentage points	(95% CI: 34.0, 80.7)	Not reported	RR: 0.182	(95% CI: 1.487, 69.719)	Not reported	Absolute difference in proportions and risk ratio (RR) presented.
Proportion of patients with at least one serious adverse event	[redacted]							

Table 48: Comparative analysis on clinical question 2

Results per outcome:								
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	

Mean percentage change in the number of convulsive seizures per 28 days (unadjusted)	Study 1504	-51.82 percentage points	(95% CI: -80.2522, -23.3878)	Not reported	NA	NA	NA	Mean difference presented
Mean percentage change in the number of convulsive seizures per 28 days (ANCOVA model)	Study 1504	Not reported	Not reported	Not reported	54.04	35.55, 67.23	<0.001	Difference from placebo estimated with ANCOVA model

Proportion of patients who achieved a 50% reduction in the number of convulsive seizures	Study 1504	50.8 percentage points	(95% CI: 9.35, 216.02).	Not reported.	RR: 12.178	3.056, 48.525	0.0004	Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference.
Mean number of days per 28 days where rescue medication was used	Study 1504	0.2 days.	(95% CI: -0.8107, 1.2107)	Not reported.	NA	NA	NA	Mean difference presented.

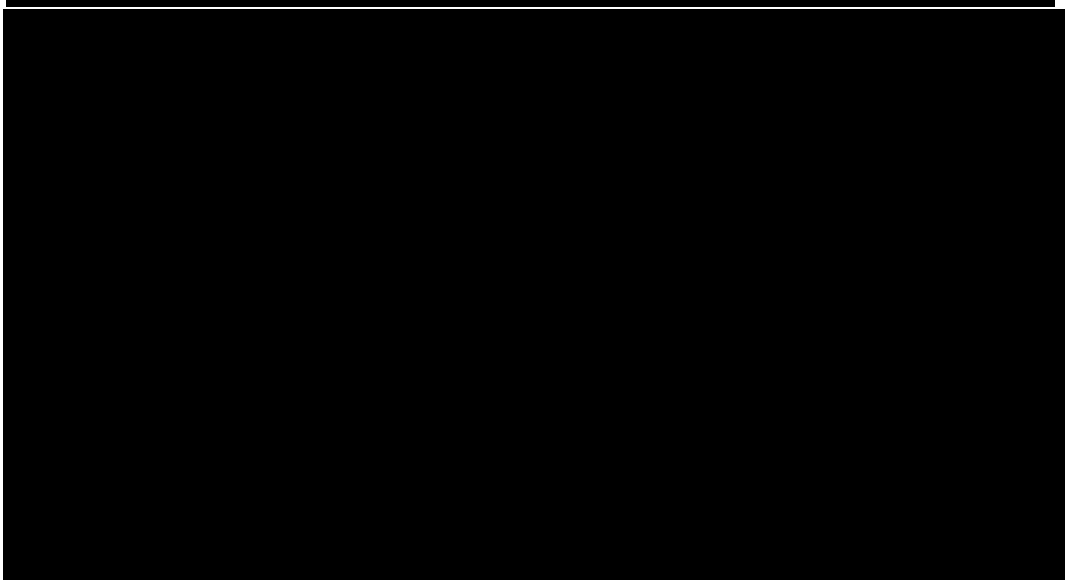
Proportion of patients who achieved a 50% reduction in the number of days per 28 days where rescue medication was used	[redacted]						
Mean change in PedsQL	Study 1504	-0.6	(95% CI: -5.6963, 4.4963)	Not reported	NA	NA	NA	Mean difference presented.
Proportion of patients with a score of 1 or 2 on CGI-I (parent/caregiver rating)	Study 1504	14.7 percentage points	(95% CI: -3.44, 51.98)	Not reported	RR: 1.716	95% CI: 0.832, 3.541)	0.1441	Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference.

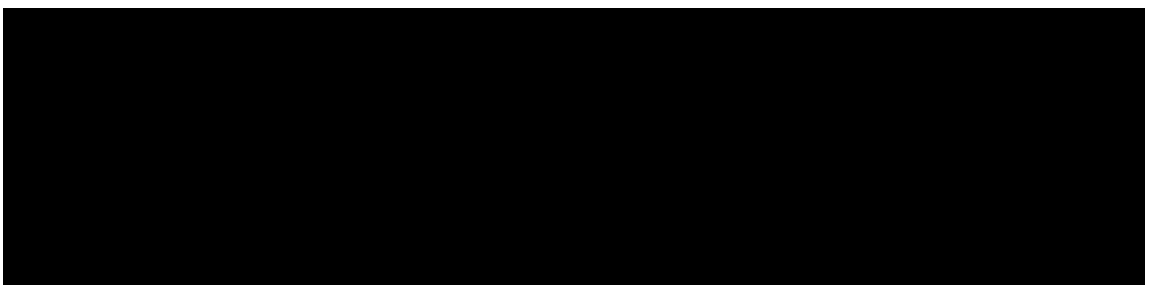
Proportion of patients with a score of 1 or 2 on CGI-I (investigator)	Study 1504	26.3 percentage points	(95% CI: 3.87, 74.12)	Not reported	RR: 2.652	(95% CI: 1.243, 5.659)	0.0118	Based on the reported OR, we calculated the relative difference. Based on the relative difference, we calculated the absolute difference.
Proportion of patients with at least one serious adverse event	Study 1504	-1.96 percentage points	(95% CI: -16.9, 13.0)	Not reported	RR: 0.877	(95% CI: 0.321, 2.399	Not reported	Absolute difference in proportions and risk ratio (RR) presented.

10.6 Patient analyses on proportion of patients who achieve 50% reduction in number of days where rescue medication is used and on mean change in the number of days of rescue medication use per 28 days

[redacted]

[redacted]





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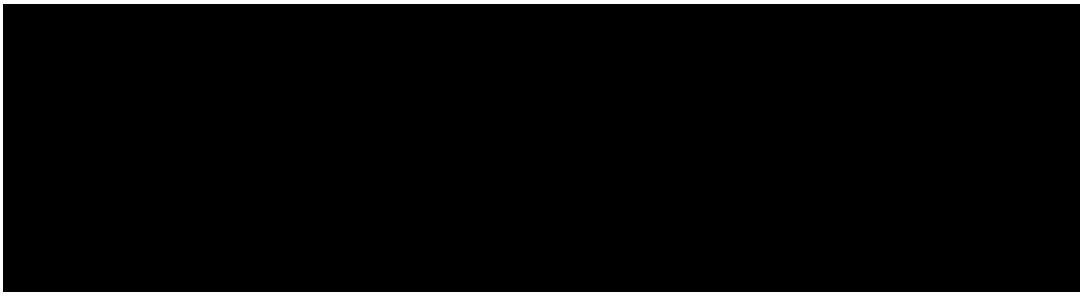

10.7 Feasibility assessment of an indirect comparison between fenfluramine and stiripentol

In the fenfluramine NICE submission, a feasibility assessment of an indirect comparison was conducted, and the highlights from this assessment are presented in the following. Information on the fenfluramine Study 1 and stiripentol STICLO-France can be found in section 5.2.1 and 5.2.3, respectively.

The fenfluramine and stiripentol trial designs and eligibility criteria appear to be similar. Both are placebo-controlled RCTs that assess the intervention as an add-on to standard of care AEDs. Both trials recruited patients experiencing four or more convulsive seizures per month during their baseline assessment periods. Notably, the stiripentol trials were conducted 15-20 years earlier than the fenfluramine trial. The fenfluramine trial was completed two to five years ago and may therefore more accurately reflect the contemporary clinical management of Dravet syndrome patients.

In fenfluramine and stiripentol trials, convulsive seizures were assessed and recorded by caregivers of Dravet syndrome patients, which inevitably involves a degree of subjectivity; however, it seems reasonable to assume that the occurrence of convulsive seizures will have been recorded to a comparable extent in both trials. However, there are important differences in the assessment of convulsive seizure endpoints. Whilst the fenfluramine trial assessed convulsive seizure endpoints over the whole 14-15-week treatment period, the stiripentol trial assessed convulsive seizure endpoints for only the last four weeks of an only eight-week treatment period. In addition, for the reduction in seizure frequency endpoint, the reported analyses in the stiripentol trials do not adjust for placebo. The stiripentol trial endpoint assessments are therefore not comparable with the endpoint assessments in the trial of fenfluramine, and any attempt to compare their outcomes would require strong assumptions in favor of stiripentol that would lead to biased results. These limitations in the stiripentol trial data therefore preclude a robust assessment of the convulsive seizure endpoints for fenfluramine compared with stiripentol.

The fenfluramine trials have demonstrated to be at a low risk of bias and provide high-quality evidence of the benefits of fenfluramine. Quality assessment of the stiripentol trials indicates that these trials had an unclear risk of bias. The STICLO-France study has been published in full (Chiron et al. 2000) but lacks complete details on allocation concealment and patient withdrawal. STICLO-France included a small number of patients (21 patients treated with stiripentol), and therefore, minor changes in patient numbers can amplify the relative treatment effects observed. The evidence supporting stiripentol is of low to moderate quality due to an unclear risk of bias.

Due to substantial differences in the assessment of convulsive seizure reduction endpoints in the stiripentol trial compared to the fenfluramine trial, as well as the unclear risk of bias that limits the quality of the stiripentol trial evidence, it is not feasible to conduct an indirect treatment comparison comparing fenfluramine and stiripentol.

Cost per patient and budget impact analysis of fenfluramine (Fintepla®) for the treatment of Dravet syndrome

Application to the Danish Medicines Council

November 2021

ZOGENIX

Company contacts information

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Text marked with yellow is strictly confidential and should be deleted before publication.

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List of abbreviations

AE	Adverse event
AED	Anti-epileptic drug
CLB	Clobazam
CS	convulsive seizures
DMC	Danish Medicines Council
DS	Dravet syndrome
EC	European Committee
EMA	European Medicines Agency
EPAR	European Public Assessment report
FDA	Food and drug administration
FFA	Fenfluramine
KOL	Key opinion leader
NICE	National Institute for Health and Care Excellence
PPP	Pharmacy purchasing price
SD	Standard deviations
SE	Status epilepticus
SPC	Summary of product characteristics
STP	Stiripentol
SUDEP	Sudden Unexpected Death in Epilepsy
QoL	Quality of life
UK	United Kingdom
VPA	Valproate

1 Background

Dravet syndrome (DS) is a rare, life-threating and treatment-resistant form of epilepsy, clinically considered to be one of the most severe forms of epileptic encephalopathy. Developing in early infancy, DS is characterised by convulsive seizures (CS) that are both frequent and severe, which increases the risk of death due to Sudden Unexpected Death in Epilepsy (SUDEP), status epilepticus (a state of continuous seizure that can cause permanent neurological damage), and accidents. DS patients experience convulsive seizures, often on a daily basis. It is estimated that 15-20% of children with DS die before reaching adulthood, and the risk remains elevated throughout life (1–3).

Patients suffering from DS also experience severe "comorbidities" such as: impaired physical development, effecting the ability to talk and walk; and significant behavioural, cognitive and learning difficulties. These comorbities are associated with the high seizure frequency experienced by DS patients. The burden of comorbities alongside often daily seizures profoundly impact the overall quality of life of patients from early childhood and onwards (4–6).

There is a substantial burden associated with caring for patients with DS, mainly due to their high (convulsive and non-convulsive) seizure frequency and the wide range of comorbidities. This has a significant implication for the quality of life of not just caregivers such as parents to DS patients, who are responsible for delivering daily care, but also the broader family unit that can be impacted by the consequences of DS (4–7).

Seizures in DS are often intractable, despite the use of combination anti-epileptic drug (AED) therapy. Complete seizure freedom is rarely possible; however, increasing the number of seizure-free days by reducing the frequency of seizures substantially reduces the daily risk of accidental injury and death and improves the quality of life of patients and their caregivers (1,6).

In Denmark, DS is identified when patients experience their first acute seizure and visit the emergency department at the hospital in their first years of life. Due to the age of the child and the rareness of DS, seizures are most often diagnosed and treated as febrile convulsions, as they may have been associated with a febrile illness or have followed a recent vaccination. A neuropediatric investigation is initiated after recurrent attacks, and diagnosed DS patients are referred to the specialist epilepsy hospital, Filadelfia, where they visit two or three times a year (8).

Treatment aims at reducing the number of seizures and happens in consultation with a multi-disciplinary support team of physicians and nurses. Complete seizure freedom is rarely possible for patients with DS; however, increasing the number of seizure-free days by reducing the frequency of seizures, substantially reduces the daily risk of accidental injury, hospitalisation and death, as well as improving quality of life (QoL) for the patient and their family. Reducing seizure frequency is therefore a primary aim of DS treatment. Unfortunately, there are limited treatment options available for patients with DS and consequently, most patients receive add-on therapies to existing treatments. Typically, DS patients receive an average of three AEDs based

on data from Europe and Danish register data, but some patients require as many as six different medications (6,9,10). Despite polytherapy with AEDs, seizures in DS are often pharmaco-resistant and remain intractable to existing therapies. There are limited therapeutic options, as many AEDs used in general epilepsies can exacerbate seizures in DS. Therefore, there is a significant unmet need for tolerable therapies that reduce the frequency of seizures and their wide impacts on patients and their families (6,9,10).

1.1 Fenfluramine

Fenfluramine is a serotonin-releasing agent that stimulates multiple 5-HT receptor sub-types through the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist of specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors, and by acting on the sigma-1 receptor. The precise mode of action of fenfluramine in DS is not known (11).

Fenfluramine comes in syringes of 3 mL and 6 mL for oral administration with 2.2 mg fenfluramine per mL. The dose depends on the patient's weight and whether they are on stiripentol (STP) treatment or not. The dose should be gradually up-titrated. If the calculated dose is ≤3.0 mL, the 3 mL syringe should be used. If the calculated dose is >3 mL, the 6 mL syringe should be used (11). The calculated dose should be rounded to the nearest graduated increment (11). The dose regimen is more thoroughly described in the following. Additional information on fenfluramine is provided in Table 4.

Fenfluramine dose for patients **not** concurrently receiving STP as part of the existing standard of care AEDs

For patients who are not taking STP, the starting dose is 0.1 mg/kg twice daily (0.2 mg/kg per day). After seven days, for patients who tolerate fenfluramine and require a further reduction of seizures, the dose can be increased to 0.2 mg/kg twice daily (0.4 mg/kg per day). After an additional seven days, for patients who tolerate fenfluramine and require a further reduction of seizures, the dose can be increased to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg per day). This is the recommended maintenance dose for patients not on STP treatment. If patients require a more rapid titration, the dose may be increased every four days. The maximum daily dose should not exceed 26 mg (13 mg twice daily, i.e., 6 mL twice daily). If patients discontinue treatment, the dose should be decreased gradually (similar pace as the up-titration) (11). Table 1 provides a summary of the dose according to weight for patients not on STP.

Table 1 **Recommended titration schedule for FFA when administered (without STP)**

	Twice-daily dose (mg/kg)	Weight in kg												
		10	15	20	25	30	35	40	45	50	55	60	65	70
Starting dose	0.1	0.5 mL	0.6 mL	0.8 mL	1.0 mL	1.3 mL	1.5 mL	1.7 mL	1.9 mL	2.1 mL	2.3 mL	2.5 mL	2.7 mL	2.9 mL
Day 7	0.2	0.8 mL	1.2 mL	1.6 mL	2.0 mL	2.4 mL	2.8 mL	3.2 mL	3.6 mL	4.0 mL	4.4 mL	4.8 mL	5.2 mL	5.6 mL
Day 14	0.35	1.6 mL	2.4 mL	3.2 mL	4.0 mL	4.8 mL	5.6 mL	6.0 mL	6.0 mL	6.0 mL	6.0 mL	6.0 mL	6.0 mL	6.0 mL

Source: Summary of product characteristics (SPC) of Fintepla® (11).
STP = stiripentol, FFA = fenfluramine

Fenfluramine dose for patients concurrently receiving STP as part of the existing standard of care AEDs

For patients on STP treatment, the starting dose is 0.1 mg/kg twice daily (0.2 mg/kg per day). After seven days, for patients who tolerate fenfluramine and require a further reduction of seizures, the dose can be increased to 0.2 mg/kg twice daily (0.4 mg/kg per day). This is the recommended maintenance dose for patients on STP treatment. If patients require a more rapid titration, the dose may be increased every four days. The maximum daily dose should not exceed 17 mg (8.6 mg twice daily, i.e., 4 mL twice daily). If patients discontinue treatment, the dose should be decreased gradually (similar pace as the up-titration) (11). Table 2 provides a summary of the dose according to weight for patients on STP.

Table 2 **Recommended titration schedule for FFA when administered with STP**

	Twice-daily dose (mg/kg)	Weight in kg												
		10	15	20	25	30	35	40	45	50	55	60	65	70
Starting dose	0.1	0.5 mL	0.6 mL	0.8 mL	1.0 mL	1.3 mL	1.5 mL	1.7 mL	1.9 mL	2.1 mL	2.3 mL	2.5 mL	2.7 mL	2.9 mL
Day 7	0.2	1.0 mL	1.5 mL	2.0 mL	2.5 mL	3.0 mL	3.6 mL	4.0 mL	4.0 mL	4.0 mL	4.0 mL	4.0 mL	4.0 mL	4.0 mL

Source: SPC on Fintepla® (11).
STP = stiripentol, FFA = fenfluramine

Following discussions with the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the dosing regimen of fenfluramine was stated based on its active fenfluramine moiety rather than its salt form. This has no impact on the results of the studies or study outcomes, but different dosing levels may be stated in early regulatory documents and publications related to the development programme. The dosing referred to in this document is based on the two phase III trials (Lagae et al. 2019 (12) and Nabbout et al. 2020 (13)). The SPC

and the European Public Assessment Report (EPAR) are aligned with the updated dosing nomenclature advised by the FDA and the EMA. The previous dose level terminology and the updated terminology are presented in Table 3.

Table 3 **Dose level terminology**

Previous terminology	Updated terminology	As twice-daily dose (updated)
0.8 mg/kg/day	0.7 mg/kg/day	0.35 mg/kg/day
0.5 mg/kg/day	0.4 mg/kg/day	0.2 mg/kg/day
0.2 mg/kg/day	0.2 mg/kg/day	0.1 mg/kg/day
Max daily dose for a patient >30kg not receiving stiripentol		
30 mg/kg/day	26 mg/kg/day	13 mg/kg/day
Max daily dose for a patient >30kg concomitantly receiving stiripentol		
20 mg/kg/day	17 mg/kg/day	8.5 mg/kg/day

Table 4 **Information on fenfluramine**

Brand name	Fintepla®
Active ingredient	Fenfluramine
Indication	Fenfluramine is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other antiepileptic medicines in children aged ≥2 years or older.
Strengths and dosing	Fenfluramine is administrated as an oral solution twice daily. The dose regimen is described in section 1.1.
ATC-code	N03AX26
Packages	Fenfluramine comes in 3 mL syringes and 6 mL syringes with 2.2 mg fenfluramine per mL.
EC approval date	18 December 2020

Source: SPC on fenfluramine (11).

1.2 Patient population

Given its rarity, the incidence and prevalence of Dravet syndrome in Denmark is not well known. The expert committee in the Danish Medicines Council (DMC) estimates that approximately 50 children and adolescents and 30-40 adults are diagnosed with DS in Denmark (14). Most of these patients are treated at the specialised hospital Filadelfia. The study by Bayat et al. 2015 was conducted at Filadelfia and proposes a Danish DS incidence of 1:22.000 infants, based on a six-

year birth cohort from 2004 to 2009 (15). The incidence presented in Bayat et al. 2015 suggests that approximately 2-3 infants are born with DS each year in Denmark.

The DMC expert committee estimates that approximately 55 out of the 85 Danish DS patients are not well-treated (insufficient response or unacceptable adverse events (AEs)) with current treatment options. The current treatment options include AEDs such as clobazam, valproate and stiripentol. According to the DMC expert committee, these patients have a need for supplementary treatment. Therefore, the total number of patients expected to be candidates for treatment with fenfluramine in Denmark is 55 patients.

1.3 Clinical questions

The cost per patient analyses and the budget impact analyses presented in the current application were conducted to answer the following clinical questions:

1) *What is the value of fenfluramine compared to stiripentol in patients with Dravet syndrome (≥2 years of age) who receive an existing combination AED therapy that does not include stiripentol?*
2) *What is the value of fenfluramine compared to placebo in patients with Dravet syndrome (≥2 years of age) who receive an existing combination AED therapy that includes stiripentol?*

Clinical question 2 includes patients that are currently receiving treatment with STP where fenfluramine is add-on therapy to STP. The comparator is the comparator in the randomised controlled trial, Study 1504, which was placebo. We present a cost per patient and budget impact analysis for patients in clinical question 2.

Clinical question 1 includes patients that are not receiving treatment with STP, and the outlined comparator in the DMC protocol on fenfluramine is STP. Two subpopulations exist in the overall population of patients not on STP in Study 1: STP-experienced and STP-naïve patients. In the following, we present a cost per patient and budget impact analysis focusing on STP-experienced patients, which we have named *clinical question 1a*. The comparator in this analysis is existing standard of care (without STP), or as investigated in the substantiating RCT (Study 1), placebo because STP is not a clinically appropriate or relevant comparator in this subpopulation due to intolerance to or lack of effect of STP in these patients. For the purposes of this analyses, we refer to this comparator arm to fenfluramine in this document as “placebo”.

This analysis was conducted to show the value of fenfluramine in patients who have previously received STP and/or where STP was undesirable due to contraindications, intolerance or lack of effect.

We do not present a cost per patient analysis or budget impact analysis on the overall population in clinical question 1, nor do we present these analyses specifically for the stiripentol-naïve subpopulation. [redacted] In addition, the studies available for a comparison of fenfluramine and STP are not comparable, and it is therefore not technically possible to conduct an indirect treatment comparison to inform this hypothetical comparison of fenfluramine versus STP.

As described in the clinical application, we anticipate that on a clinical basis fenfluramine would only be used without STP in STP-naïve patients where STP is not considered to be a treatment option (e.g. due to contraindication). Given that the vast majority of patients would be eligible to receive STP, this use of fenfluramine in STP-naïve patients is estimated to be negligible. Furthermore, as the efficacy of fenfluramine in the STP-experienced subpopulation of Study 1 is similar to that in the whole of Study 1 population (reduction from baseline in monthly convulsive seizure frequency versus placebo of 60.8% versus 62.3% in the whole Study 1 population), we would expect that the treatment efficacy and hence the cost per patient with fenfluramine in this minority use case would be similar to that in the STP-experienced subpopulation addressed in clinical question 1a. The cost per patient analysis provided for clinical question 1a therefore also reflects the cost per patient for the negligible use of fenfluramine in the STP-naïve patients. [redacted]

- Clinical question 1a: What is the value of fenfluramine compared to placebo for patients with Dravet syndrome (≥2 years of age) who receive an existing combination AED therapy that does not include stiripentol and who are stiripentol-experienced?
- Clinical question 2: What is the value of fenfluramine compared to placebo in patients with Dravet syndrome (≥2 years of age) who receive an existing combination AED therapy that includes stiripentol?

2 Methods: Cost per patient analyses

The purpose of these cost per patient analyses was to estimate the incremental cost of treating DS patients with add-on fenfluramine (compared to placebo); when added to a patient's existing standard of care AED therapy that includes STP (question 2), or excludes STP due to prior experience and failure of STP, intolerance to STP, or where STP is undesirable (Question 1a) .

To estimate the cost(s) per patient and answer clinical question 1a and clinical question 2, we built a health economic model in Excel. The Excel model was populated with inputs from the two registration phase III trials: Study 1 (clinical question 1a) and Study 1504 (clinical question 2) (12,13,16,17).

Study 1 comprised two identical phase III, randomised, multinational, double-blinded placebo-controlled trials (trial 1501 and 1502). The purpose of the two trials was to assess the efficacy and safety of two doses of fenfluramine (0.2 mg/kg per day and 0.7 mg/kg per day, with a maximum daily dose of 26 mg) compared to placebo, when used as adjunctive therapy in children and young adults with DS. One trial was done in the USA and Canada (NCT02682927), the other in western Europe and Australia (NCT02826863). DS is rare disease, with a high unmet medical need. Due to the urgency of enabling a licensable filing with the regulatory authorities alongside practical challenges with identifying and enrolling a rare disease population of patients in both trials, it was decided to merge the 1st half of the enrolled cohort from Study 1501 and Study 1502 before unblinding the results and undertaking the analysis (Study 1) to present to the regulatory agencies to facilitate an expedited licensing. The second cohort of patients in study 1501 and study 1502 (Study 3) has recently finished enrolling and is undergoing analyses to present to regulatory agencies.

In Study 1, the study duration comprised of a six-week baseline period followed by a two-week titration (T) period and a 12-week maintenance (M) period, resulting in a total treatment period (T+M) of 14 weeks. Patients could continue into an open-label extension study.

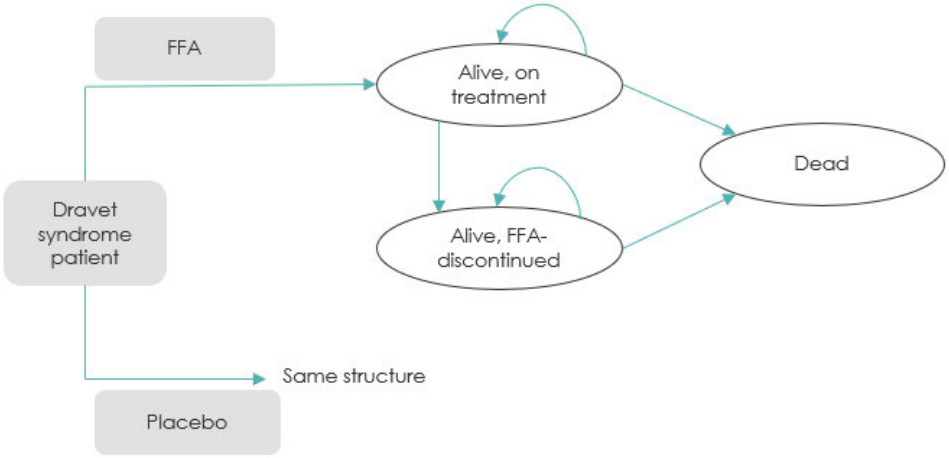
Study 1504 (NCT02926898) consisted of two parts: Cohort 1 and Cohort 2. The first part (Cohort 1) was an open-label study with 18 patients with DS. The purpose of the first part was to assess the pharmacokinetics and safety of fenfluramine and to define the therapeutic dose of fenfluramine to be used in Cohort 2. Cohort 2 was the second part of the trial and was a double-blinded, randomised, two-armed, phase III and placebo-controlled trial with the purpose of evaluating fenfluramine (0.4 mg/kg per day) in combination with STP, valproate (VPA), and/or clobazam (CLB).

We also interviewed the Danish key opinion leader (KOL) Marina Nikanorova, who is a physician at the specialised hospital Filadelfia and is highly experienced in treating DS patients. In the following sections, Marina Nikanorova will be referred to as the “clinical expert”. In the following sections, we describe the health economic model, developed to estimate the cost per patient and budget impact in the two clinical questions.

2.1 Applied model

To estimate the cost per patient and budget impact in the two clinical questions, we developed a health economic model in Excel. The model is a health state model where patients can transition between three health states. Figure 1 provides an overview of the model.

Figure 1 **Structure of the health state model**



FFA: fenfluramine

The cost per patient in both clinical questions and for both fenfluramine and placebo is estimated based on 1.0 patient, simulated over a chosen time horizon divided into cycles with a length of 28 days (described in section 2.6). As seen in Figure 1, the model consists of three health states: "Alive and on treatment", "Alive and discontinued", and "Dead" (section 2.1.1). Patients entered the model in the "Alive and on treatment" health state in cycle 0. In the subsequent cycles, patients could either remain in the "Alive and on treatment" health state or transition to the "Alive and discontinued" or "Dead" health states. Transitions between the health states are described in 2.1.1.

In the model, inputs and the underlying calculations for clinical question 1a and clinical question 2 are presented in the 'Cost per patient' sheet. In the same sheet, the results of the two cost per patient analysis for clinical question 1a and clinical question 2 are presented at the bottom. Given the inputs and the underlying calculations of drug costs, hospital costs etc. in the 'Cost per patient' sheet, the per-cycle calculations are presented in the 'Fenfluramine' and 'Placebo' sheets for clinical question 1a and in the 'FFA+STP' and 'Placebo+STP' sheets for clinical question 2.

In each cycle, monitoring costs, costs associated with the treatment of CS and status epilepticus (SE), AE costs (section 2.8); cross-sectional costs (section 2.8.4) and patient and transportation (section 2.8.5) cost are calculated for the proportion of 1.0 patient in the "Alive and on treatment" and the "Alive and discontinued" health states. No costs are calculated in the "Dead" health state.

This analysis reflects an incremental approach to costs. In clinical question 1a, the drug cost of fenfluramine is ascribed to patients in the fenfluramine arm in the "Alive and on treatment"

health state each cycle. For patients on placebo, no drug costs are ascribed in the "Alive and on treatment" because the drug cost of placebo is 0 DKK. Costs of the underlying concomitant AEDs are not included, as we assumed that the use of AEDs does not differ between patients treated with fenfluramine and placebo (12). Hence, patients who discontinue fenfluramine subsequently incur no drug costs (excl. rescue medication) and it is assumed that patients who discontinue fenfluramine or placebo will maintain or go back to their existing AED SoC, respectively.

For clinical question 2, the drug costs for fenfluramine and STP are ascribed in each cycle to patients in the "Alive and on treatment" health state with fenfluramine and STP. For patients on placebo and STP, the drug cost of STP is ascribed in each cycle to patients "Alive and on treatment". No drug cost associated with placebo was assumed. Costs of the underlying concomitant AEDs were not included in clinical question 2 because we also assumed there to be no differences in underlying AED treatment between patients treated with fenfluramine and STP, and placebo and STP (13). When patients discontinue fenfluramine or discontinue placebo in clinical question 2, they subsequently still incur the drug cost of STP because we assume that patients will not discontinue their existing AED SoC which includes STP in clinical question 2. Given treatment with FFA may reduce mortality (18), it was considered that a survival advantage of FFA treated patients, over otherwise maintaining a patients current standard of care (i.e. "placebo") in these patients, would mean patients may continue to receive STP (within their standard of care AED) treatment for longer and so it would be appropriate to capture these additional costs, as a consequence of preserving a longer life in FFA-treated patients.

This incremental approach to costs, potentially infers a conservative approach disfavouring fenfluramine, given that the full value of FFA may be underestimated. With an improved control of seizures, patients may look to simplify their regimen or reduce the doses of their existing concomitant AEDs. This would infer a cost-saving. However, given the tailored and individualised approach to treating DS patients on the basis of clinical priorities and their unmet needs at the time, this is difficult to quantify. It has therefore not been considered in these analyses. Other benefits to QoL to the patient and broader family unity are also not captured in a cost-analysis

2.1.1 Transitions between health states

Patients can leave the "Alive, on treatment" state due to treatment discontinuation or death (as illustrated in Figure 1).

Transition probability for discontinuation

For the two intervention arms (fenfluramine or Placebo) and for each of the two scenarios of patients concurrently receiving AEDs that exclude (question 1a) or include STP (Question 2) inputs regarding discontinuation came from the two phase III trials: Study 1 (clinical question 1a) and Study 1504 (clinical question 2) (13,17). The open-label extension (OLE) served as input on discontinuation beyond the trial study periods.

Table 5 **Treatment discontinuation probabilities**

	Clinical question 1a		Clinical question 2	
	Fenfluramine (SoC excl. STP)	Placebo (SoC excl. STP)	Fenfluramine (SoC incl. STP)	Placebo (SoC incl. ST
Discontinuation in study period	12.5%	2.5%	16.3%	6.8%
Study period	14 weeks		15 weeks	
Discontinuation per cycle, cycle 1-4	3.6%%	0.7%%	4.3%	1.8%
Discontinuation per cycle, cycle > 4*	[redacted]	[redacted]	[redacted]	[redacted]

Source: (13,17) and OLE data.
SoC = standard of care, STP = stiripentol, FFA = fenfluramine; SUDEP = sudden unexplained death in epilepsy.
* Calculated as -(28/365,25)*ln(1-9.06%).

Table 5 gives an overview of the applied discontinuation rates for fenfluramine and placebo. The table shows that in study 1504, 7 out of 43 patients (7/43=16.3%) discontinued on fenfluramine in the study period (15 weeks). Similarly, 3 out of 44 patients (3/44=6.8%) discontinued on placebo in the study period (13). Patients mainly discontinue due to AEs, tolerability, or lack of treatment effect, and we assumed that patients would discontinue relatively shortly after treatment start. Thus, in the model simulations, it is assumed that patients who discontinue will mainly discontinue in cycle 1-4. That is, the discontinuation rates observed in the clinical studies over the length of the study periods are converted to per-cycle transition probabilities for discontinuation for cycle 1-4. From cycles >4, a per-cycle transition probability for discontinuation of [redacted] was applied, estimated based on the discontinuation rate of [redacted] per year from the long-term extension trial OLE.

Transition probability for mortality

Patients with DS face an increased risk of death due to SUDEP, SE and accidents. Data on mortality in DS patients is limited, and no deaths were observed in the two clinical trials (12,13).

To take mortality into account, we used a study by Cooper et al. 2016 (2). Cooper et al. 2016 reports an all-cause mortality rate in DS patients of 15.84 per 1,000 person-years (98% CI: 9.01 to 27.85) and of it a SUDEP mortality rate of 9.32 per 1,000 person-years (98% CI: 4.46 to 19.45). The SUDEP mortality rate in DS patients while treated with fenfluramine (1.7 deaths per 1,000 person-years) was substantially lower than the rate reported in DS patients receiving standard of care (9.32 per 1,000 person-years). We used these data to estimate a mortality risk per cycle for patients treated with fenfluramine and for patients not treated with fenfluramine. Due to lack of more detailed data, we assumed the same mortality risk per cycle for patients treated with fenfluramine in addition to SoC that excluded (clinical question 1a), or included STP (clinical question 2), as well the same mortality risk per cycle for patients treated with placebo in addition to SoC that excluded (clinical question 1a) or included STP (clinical question 2), respectively.

In addition to the results from Cooper et al., the general Danish age-specific background mortality was additively included in the modelled survival. In the studies ((12,13)), the overall average age of the included patients were 9 years. Thus, in model year 1 the background mortality of a 9-year-old is applied, in model year 2, the background mortality of a 10-year-old is applied etc. Statistics Denmark's life tables were used to estimate the age-specific background mortality.

Table 6 **Mortality risks for patients with DS**

	Overall mortality (deaths per 1,000 person-years)	SUDEP mortality (deaths per 1,000 person-years)	Per-cycle mortality risk
Fenfluramine (Soc AEDs +/- STP)	8.22**	1.7*	0.06%***
Placebo (Soc AEDs +/- STP)	15.84*	9.32*	0.12%****

* Source: (2).
** Calculated as 15.84-9.32+1.7 = 8.22.
*** Calculated as -(28/365,25)*ln(1-(8.22/1000))
**** Calculated as -(28/365,25)*ln(1-(15.84/1000))
AEDs = antiepileptic drugs; FFA = fenfluramine; SoC = standard of care, STP = stiripentol, SUDEP = sudden unexplained death in epilepsy

Based on the overall mortality risks of 8.22 and 15.84 per 1,000 person-years from Cooper et al. 2016, we calculated a probability of transitioning to "dead" of 0.06% per cycle for patients receiving fenfluramine (Soc +/- STP) and a transition probability of 0.12% per cycle for patients treated with placebo (Soc +/-STP) (see Table 6). The calculation of these transition probabilities of death can been seen in the 'Background' sheet in the Excel model.

It should be noted that applying a constant mortality risk per cycle over the entire time horizon of the analysis is a very simple approach, but more detailed data on mortality in older patients is missing. As described previously, it is estimated that 15-20% of children with DS die before reaching adulthood, and the risk remains elevated throughout life (1-3). In the 'Placebo' and 'Placebo+STP' sheets it is shown that 21.1% of the patients are deceased by the end of year 15 (cycle 194). As treatment with fenfluramine is indicated for patients 2 years of age and older, the patient age at model-year 15 will be of a minimum age of 17-18 years, implying that it is modelled that 21.1% of the patients die before reaching adulthood. This estimate is in line with the 15-20% reported in the literature. Application of a constant mortality risk has previously been accepted by the clinical experts in NICE, UK.

2.2 Intervention

The intervention in clinical question 1a and clinical question 2 is fenfluramine. As mentioned in section 1.1, the dose depends on the patient's weight and whether they are on concomitant STP

treatment or not (up to a daily maximum of 17 mg or 26 mg, respectively). The dose should be gradually up titrated. In both clinical questions, patients had 28 treatment days per cycle because the cycle length in the model was 28 days (described in section 2.6). In the model, a maximum patient weight is implemented in the fenfluramine dosing calculations ensuring that the maximum dose is not exceeded.

In clinical question 1a, a maximum dose of fenfluramine 0.7 mg/kg per day was applied based on the intervention in the stiripentol-experienced subpopulation from Study 1. The dose was gradually titrated, starting with 0.2 mg/kg per day for seven days, titrated to 0.4 mg/kg per day for another seven days and titrated to 0.7 mg/kg per day after the 14 days. Patients were then assumed to receive the 0.7 mg/kg per day dose for the rest of the treatment period unless they had to discontinue treatment. The average weight at baseline for the total stiripentol-experienced subpopulation was 33.7 kg in Study 1 (see Table 9).

In clinical question 2, a maximum dose of fenfluramine 0.4 mg/kg per day was applied based on the intervention in Study 1504. The dose was gradually titrated, starting with 0.2 mg/kg per day for seven days, titrated to 0.4 mg/kg per day. Patients received the 0.4 mg/kg per day dose for the rest of the treatment period unless they had to discontinue treatment. The total patient population in Study 1504 had an average weight at baseline of 33.8 kg (see Table 10). Information on the titration scheme and the applied doses is presented in Table 7 and Table 8.

Table 7 **Titration scheme for fenfluramine in clinical question 1a and clinical question 2**

	Clinical question 1a	Clinical question 2
Days on starting dose	7	7
Days on titration 1 dose	7	7
Days on titration 2 dose	14	Only titrated once
Number of treatment days per cycle	28	28

Source: SPC on fenfluramine (11).

Table 8 **Dose regimen of fenfluramine clinical question 1a and clinical question 2**

	Clinical question 1a	Clinical question 2
Starting dose	0.2 mg/kg per day	0.2 mg/kg per day
Dose in titration 1 period	0.4 mg/kg per day	0.4 mg/kg per day
Dose in titration 2 period	0.7 mg/kg per day	0.4 mg/kg per day
Dose in the first 28 days	471.800 mg	331.240 mg
Dose in the subsequent cycles of 28 days	660.520 mg	378.560 mg

Source: SPC on fenfluramine (11).

The clinical expert informed that fenfluramine bottles are handed over to caregivers, who collect the amount of solution that corresponds to the necessary amount of mg fenfluramine in the syringes that comes with the bottle. Based on this information, we applied exact doses of fenfluramine and assumed no waste associated with fenfluramine administration.

2.3 Comparator

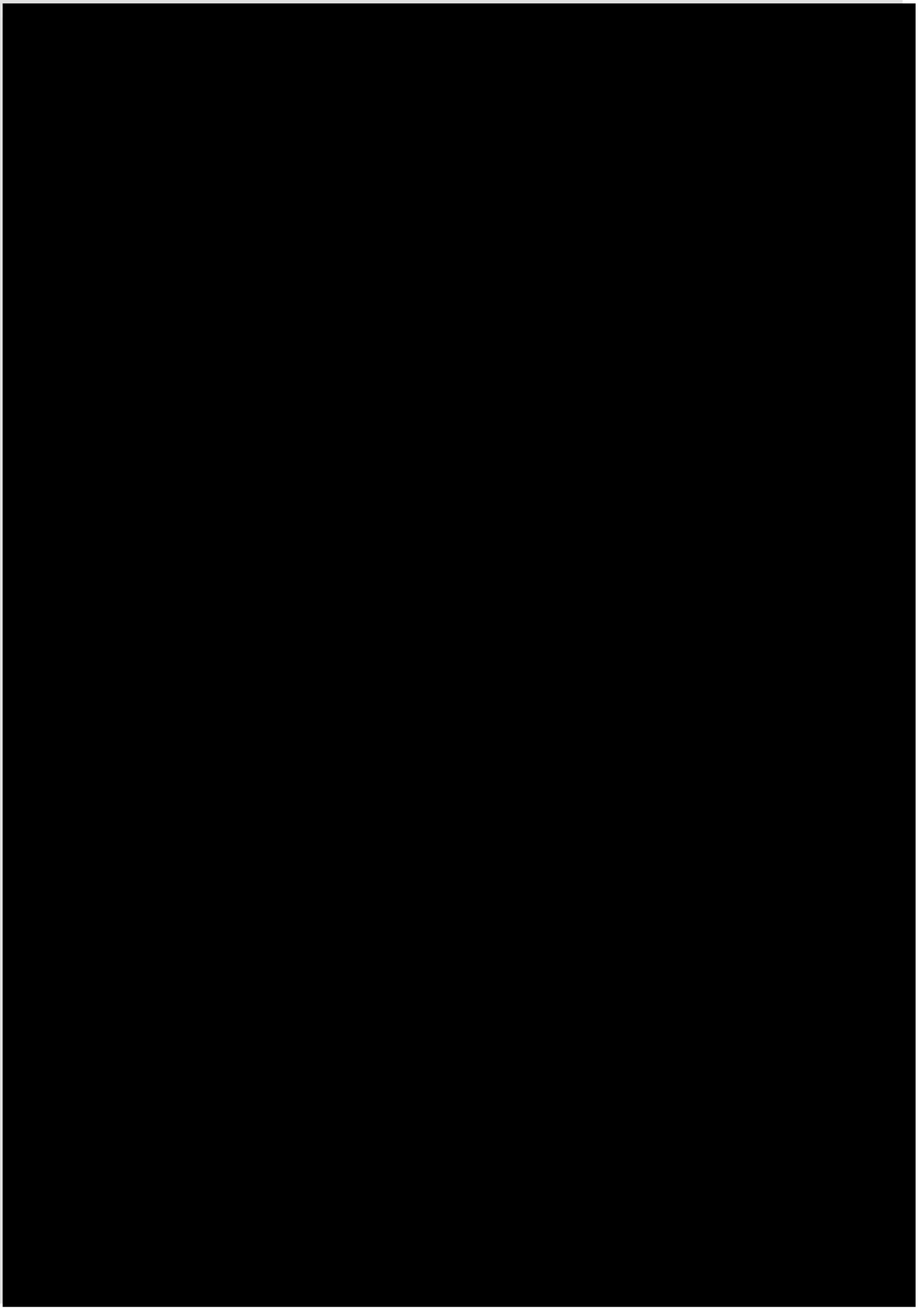
The comparator in both clinical question 1a and clinical question 2 was placebo as an add-on therapy to existing AED SoC. Placebo matching fenfluramine was administered in both Study 1 and Study 1504. Patients in clinical question 2 received concomitant STP in both the fenfluramine arm and placebo arm. The applied dose of STP was 40-50 mg/kg per day orally administered (19). The total STP dose per 28 days were 42,588 mg in both arms in clinical question 2 (based on the average weight at baseline in Study 1504 of 33.8 kg and 45 mg/kg per day STP).

2.4 Patient population in the model

The patient population in clinical question 1a was based on a subpopulation of stiripentol-experienced patients from Study 1. The baseline characteristics of the subpopulation is presented in Table 9. As seen in Table 9, patients in the fenfluramine arm of clinical question 1a had a mean age [redacted]

The patient population in clinical question 2 was based on the patient population in Study 1504. The baseline characteristics of the patient population in Study 1504 is presented in Table 10. As seen in the table, patients in the fenfluramine arm had a mean age of 8.8 years and a mean age of 31.3 kg. In the placebo arm of Study 1504, the mean age was 9.4 years and the mean weight was 36.2 kg.

Table 9 **Baseline characteristics of stiripentol-experienced patients from Study 1**



Source: Zogenix data on file.

Table 10 **Baseline characteristics of patients in Study 1504**

Characteristics	Patient numbers (%)			P-value[1]
	Fenfluramine	Placebo	Total	
Numbers	43	44	87	NA
Age, mean (SD) [range], y	8.8 (4.6) [2-18]	9.4 (5.1) [2-19]	9.1 (4.8) [2-19]	0.57
Patients < 6 years	12 (28)	12 (27)	24 (28)	>0.99
Male	23 (53)	27 (61)	50 (57)	0.52
Race				
White	23 (53)	29 (66)	52 (60)	
Black/African American	1 (2)	2 (5)	3 (3)	
Asian	2 (5)	1 (2)	3 (3)	0.66
Other	3 (7)	1 (2)	4 (5)	
Not reported or missing[2]	13 (30)	11 (25)	24 (28)	
Unknown	1 (2)	0 (0)	1 (1)	
BMI, mean (SD)	17.3 (2.7)	19.1 (4.9)	18.2 (4.0)	0.11
Convulsive seizure frequency per 28 days				
Median (range)	14.0 (3-213)	10.7 (3-163)	NA	0.62
Mean (SD)	27.9 (36.9)	21.6 (27.6)	NA	
Number of concomitant AEDs at baseline				
2	1 (2)	1 (2)	2 (2)	
3	19 (44)	26 (59)	45 (52)	0.10
4	16 (37)	16 (36)	32 (37)	
5	7 (16)	1 (2)	8 (9)	
Other antiepileptic treatments in ≥10% of subgroup[3,4]				
Stiripentol	43 (100)	44 (100)	87 (100)	
Clobazam	40 (93)	42 (96)	82 (94)	NC
Valproate	38 (88)	39 (89)	77 (89)	
Topiramate	14 (33)	7 (16)	21 (24)	

Levetiracetam	6 (14)	5 (11)	11 (13)
Baseline Weight (kg)			
Mean (SD)	31.3 (14.85)	36.2 (21.08)	33.8 (18.32)

Source: Nabbout et al. 2020.

1: P-values (fenfluramine vs placebo) were calculated by Wilcoxon rank sum test (age, BMI, and baseline CSF per 28 days), Fisher exact test (age group and sex), and Freeman-Halton test (race and number of concomitant AEDs) with statistical significance set at P less than 0.05.
2: Not reported or missing: privacy laws in some regions and countries preclude disclosure of certain personal information.
3: Concomitant medications in less than 10% of patients included acetazolamide, clonazepam, diazepam, ethosuximide, felbamate, gamma-aminobutyric acid, lorazepam, phenobarbital, pregabalin, and zonisamide.
4: The number of patients following a ketogenic diet was 4 (5%) in the overall population. The number of patients with vagal nerve stimulator implantation was 5 (6%) overall.

2.5 Applied perspective

A limited societal perspective was applied in the cost per patient analysis, in accordance with DMC guidelines (20).

2.6 Cycle length and time horizon

The model operates with a cycle length of 28 days (four weeks). The dosing of fenfluramine in the titration period changes every seven days implying that 28 days is a suitable cycle length. It is also consistent with the collected RCT data and analyses i.e., monthly change in seizures from baseline, over a 28 days period.

The time horizon of the analysis is flexible and can be varied between one and 91 years. In the base case, the time horizon was set to 10 years. Assuming a patient starts treatment with fenfluramine at the age of nine, a 91-year time horizon cover a lifetime horizon.

2.7 Discounting

Costs incurred after year 1 to year 35 are discounted by 3.5% per year. Costs incurred from year 36-70 are discounted by 2.5% per year and cost incurred from year 71 and thereafter are discounted by 1.5% per year, in accordance with the Danish Ministry of Finance's guidelines for economic analyses (21).

2.8 Resource use and unit costs

The cost per patient analysis of fenfluramine included the notable drug costs (cost of fenfluramine, rescue medications and STP), hospital costs (including monitoring costs, admission costs, telephone consultations, AE costs and echocardiograms), cross-sectional costs and patient and transportation costs. End-of-life costs were not included in the analysis because we assumed that most DS patients die as a consequence of a CS or SUDEP and will not die at the hospital or receive any palliative/terminal care prior to their death.

2.8.1 Drug costs

The included drug costs in clinical question 1a were the cost of fenfluramine and the cost of rescue medication. In clinical question 2, the included drug costs were the cost of fenfluramine, the cost of STP and the cost of rescue medication. We did not include any drug costs for other concomitant AEDs such as valproate and clobazam because we assumed no difference in the usage of other AEDs between the fenfluramine and placebo arms in the two clinical questions. The drug costs were based on the pharmacy purchasing prices (PPP) and obtained from www.medicinpriser.dk (October 2021). In the following, we describe how we estimated the costs of the included drugs in the cost per patient analysis. An overview of included drugs is provided in Table 11.

Table 11 **Drug information**

Treatment	Strength (mg)	Size	PPP (DKK)
Fenfluramine	2.2 mg per mL	360 mL bottle	[redacted]
STP	250 mg	60 tablets	1,340
Diazepam (rectal)	5.0 mg	5 x 2.5 mL rectal solution	244.0
Buccolam	5.0 mg	4 pre-filled oral syringes	775.0

Source: www.medicinpriser.dk (October 2021). Diazepam: rectal solution, 5 mg/dosis. Buccolam: oral solution, 5 mg/1mL.

Fenfluramine is available as bottle formats containing 60 mL, 120 mL and 360 mL for oral solution. Each bottle contains 2.2 mg fenfluramine per mL; a bottle with 360 mL contains 792 mg fenfluramine. With each 360 mL bottle follows two 3 mL syringes with 0.1 mL graduations, and two 6 mL syringes with 0.2 mL graduations. The cost per mg of fenfluramine derived from a 60 or 120mL bottle would be similar. [redacted] The amount of fenfluramine (mg) used in the first 28 days and the subsequent 28 days in both clinical questions were presented in Table 8.

Patients in the fenfluramine arm in clinical question 1a and 2 received rescue medication. Based on inputs from the clinical expert, we assumed that patients would be rescued with rectal diazepam or buccal midazolam (Buccolam). We applied the diazepam dose listed on

pro.medicin.dk for children experiencing convulsive (tonic-clonic) SE (22). The applied Buccolam dose was the average of the listed doses for children between 3-13 months, 1-5 years, and 5-10 years on pro.medicin.dk (23). The mean number of days on rescue medication per 28 days in the stiripentol-experienced subpopulation from Study 1 was [redacted] in the placebo arm. Based on the information provided in Table 12, we estimated a weighted cost of rescue medication per 28 days to be [redacted]

For clinical question 2, the mean number of days on rescue medication per 28 days was 1.4 days in the fenfluramine arm and 1.2 days in the placebo arm (13). We estimated a weighted cost of rescue medication per 28 days to be [redacted]

Table 12 **Rescue medication applied in clinical question 1a**

	Applied dose (mg)	PPP (DKK) per mg	Weighted cost in the fenfluramine arm, DKK	Weighted cost in the placebo arm, DKK
			Clinical question 1a	
Rectal diazepam	5	10	[redacted]	[redacted]
Buccal midazolam	5	39		
			Clinical question 2	
Rectal diazepam	5	10	[redacted]	[redacted]
Buccal midazolam	5	39		

Source: medicinprisør.dk (October 2021), choice of drugs from clinical expert interview.

Patients in clinical question 2 received concomitant treatment with STP. STP is sold under the brand name Diacomit and comes in packages of 60 tablets with 250 mg STP per tablet. The PPP of one package of 60 x 250 mg STP tablets is DKK 1,340: the PPP per mg is DKK 0.089. The total amount of STP (mg) used per 28 days was 42,588.

Table 13 presents the total fenfluramine drug costs in the first 28 days and in the subsequent cycles of 28 days in both clinical questions. The drug costs in the first 28 days and the drug costs in the subsequent cycles of 28 days for fenfluramine are for both clinical questions presented with the drug costs for rescue medication in clinical question 1a and STP in clinical question 2.

Table 14 presents the total drug costs per 28 days in the placebo arm in both clinical questions.

Table 13 **Drug costs in the fenfluramine arm in clinical question 1a and clinical question 2, DKK**

	Clinical question 1a	Clinical question 2
Fenfluramine drug cost first 28 days (cycle 1)	[redacted]	[redacted]
Fenfluramine drug cost in subsequent 28-day cycle	[redacted]	[redacted]
Rescue medication drug cost	[redacted]	[redacted]
STP drug cost	[redacted]	3,804
Total drug cost the first 28 days	[redacted]	[redacted]
Total drug cost per 28 days hereafter	[redacted]	[redacted]

Note: the drug costs in clinical question 1a consisted of the fenfluramine drug cost and the weighted cost of rescue medication. In clinical question 2, the drug costs consisted of the fenfluramine drug cost and the STP drug cost.

Table 14 **Drug costs in the placebo arm in clinical question 1a and clinical question 2, DKK**

	Clinical question 1a	Clinical question 2
Total drug costs in the placebo arm	534	[redacted]

Note: In clinical question 1a, the drug costs in the placebo arm were due to the cost of rescue medication. The drug costs in the placebo arm in clinical question 2 were due to the drug cost of STP.

2.8.2 Hospital costs

We included the following hospital costs:

- Monitoring costs
- Acute hospital admission costs due to CS and SE
- Hospital costs due to AEs
- Hospital costs associated with echocardiograms

Monitoring costs

According to the clinical expert, DS patients typically have two-three outpatient monitoring visits per year. In addition, the clinical expert informed that there are approx. six telephone consultations per year. The resource use and the applied unit costs are shown in Table 15.

Table 15 **Monitoring: resource use and unit costs**

	Per year	Per cycle	DKK	Source
Monitoring visits	2.5	0.2		Clinical expert
Telephone consultation	6	0.5		Clinical expert
Unit cost: Monitoring visits			3,122	DRG 01MA09
Unit cost: Telephone consultation			129	DRG 65TE01

Hospital costs: CS and SE

As described, DS is a rare and potentially life-threating disease characterised by frequent and severe convulsive seizures. SE is defined as a seizure lasting five or more minutes of either continuous seizure activity or repetitive seizures without regaining consciousness (24).

Some CS are handled by the caregivers without acute contact or admission to a hospital. However, some CS requires acute hospital admission. Input about the frequency of CS (and SE), the average number of days with 1 or more CS, and the average hospital admission days due to CS and SE came from the clinical trials. Table 16 provides an overview of the applied input data. For each admission day, a bed-day tariff of DKK 8,876 was applied (25).

Table 16 **Information on acute hospital contacts**

	Clinical question 1a		Clinical question 2	
	Fenfluramine (SoC excl. STP)	Placebo (SoC excl. STP)	Fenfluramine (SoC incl. STP)	Placebo (SoC incl. STP)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: (12,13,16,17).
Note: The average number of CS days per cycle is calculated as '28 days' minus 'Average number of CS free days'. 'Average number of CS free days' are data on file.

Hospital costs: AEs

In the clinical trials, different of AEs were observed for patients receiving fenfluramine, placebo, fenfluramine and STP, and placebo and STP. In the stiripentol-experienced subpopulation from Study 1, 8 out of 16 patients (50.0%) in the placebo arm and 22 out of 22 patients (100.0%) in the fenfluramine arm experienced at least 1 treatment-emergent AE. Serious TEAEs were experienced by 0 out of 16 patients (0.0%) in the placebo arm and 4 out of 22 patients (18.2%) in

the fenfluramine arm. In Study 1504, 42 out of 43 patients (97.7%) experienced at least one TEAE in the fenfluramine arm compared to 42 out of 44 patients (95.5%) in the placebo arm. Serious TEAEs were experienced by 6 out of 43 patients (14.0%) in the fenfluramine arm and 7 out of 44 patients (15.9%) (13).

In the cost per patient model, the AEs percentage reported in the trials are listed (see Table 17). However, according to the clinical expert, these AEs do not lead to extra resource use in the healthcare sector. Typically, AEs can lead to treatment discontinuation. We assumed that costs associated with managing AEs are included in the routine monitoring costs either at a visit or at a telephone consultation. Thus, costs associated with AEs are not included in the analysis. The model is flexible and AE costs can be included at the discretion of the user.

Table 17 **Adverse events**

Clinical question 1a			Clinical question 2		
	Risk			Risk	
AE	Fenflura-mine (SoC excl. STP)	Placebo (SoC excl. STP)	AE	Fenflura-mine (SoC incl. STP)	Placebo (SoC incl. STP)
Decreased appetite	59%	6%	Decreased appetite	44%	11%
Influenza	0%	19%	Pyrexia	26%	9%
Echocardiogram abnormal	23%	0%	Fatigue	26%	5%
Diarrhea	18%	6%	Diarrhea	23%	7%
Nasopharyngitis	9%	19%	Nasopharyngitis	16%	34%
Seizure	5%	13%	Blood glucose decreased	14%	5%
Lethargy	23%	0%	Lethargy	14%	5%
Somnolence	18%	6%	Bronchitis	12%	5%

Source: Data on file on stiripentol-experienced patient population and Table 3 in Nabbout et al (13).

Hospitals costs: echocardiograms

Due to historically reported cases of valvular heart disease associated with fenfluramine when used as an anti-obesity product in adults and at higher doses than for DS, cardiac monitoring must be performed using echocardiography (11). Based on the SPC, it is assumed that echocardiography is performed at the start of treatment; every 6 months for the first 2 years and annually thereafter, and at the end of treatment for patients treated with fenfluramine. A simplified assumption in the model is applied of undertaking an echo every 12 months in all fenfluramine treated patients whilst on treatment. The applied input data are shown in Table 18.

Table 18 **Resource use and unit costs, echocardiography (applied to FFA arm only)**

	Inputs	Source
Frequency (echo.), per 6 months	0.5	Assumption/SPC (11)
Frequency (echo)., per cycle	0.08	
Unit cost per echo. (DKK)	3,122	DRG 01MA09

Summary: Total hospital costs per cycle

The total hospital costs per cycle in each treatment arm are presented in Table 19. The total costs are based on the input data and underlying calculations presented in this section (2.8.2).

Table 19 **Total hospital costs per cycle**

	Clinical question 1a		Clinical question 2	
	Fenfluramine (SoC excl. STP)	Placebo (SoC excl. STP)	Fenfluramine (SoC incl. STP)	Placebo (SoC incl. STP)
Hospital costs per cycle (DKK)	[redacted]	[redacted]	[redacted]	[redacted]

2.8.3 End-of-life costs

As stated, DS is associated with a risk of premature death (increased mortality risk). In the analysis, we assumed that deaths occur suddenly (due to SUDEP or accidents). Therefore, we did not include extra costs associated with end-of-life. If death occurs during hospitalisation, it is implicitly assumed that end-of-life costs are included in the hospital costs associated with CS and SE (see section 2.8.2).

2.8.4 Cross-sectional costs

We interviewed the clinical expert on the cross-sectional resource utilisation associated with DS patients. According to the clinical expert, DS patients can suffer from motor deficits, such as decreased gait function, and they might receive physiotherapy. Moreover, the clinical expert informed that DS patients can have contacts to other specialists besides Filadelfia, mostly due to comorbidities or other health issues besides DS. Finally, there are also costs incurred by DS patients' use of municipal services.

However, no cross-sectional costs were included in the analysis due to lack of data supporting a difference between fenfluramine or placebo in the cross-sectional resource utilisation. But the model is flexible and cross-sectional costs can be included at the discretion of the user.

2.8.5 Patient and transportation costs

Patient and transportation costs were included in accordance with DMC guidelines. A unit cost of DKK 179 per hour was used in the estimation of the cost of patient time and a unit cost of DKK 3.52 per km was used in the estimation of transportation costs. An average driving distance of 50 km each way to the hospital was assumed, summarising to a total of 100 km. 60 minutes of patient time each way to the hospital was assumed, summarising to a total of two hours of patient time spent on transportation to the hospital. In the model, it is possible to change the average driving distance.

Patient and transportation costs were associated with patients' transport to and from the hospital and time spent at the hospital (Filadelfia) and private specialists during outpatient contacts and admissions.

Clinical question 1a

Based on inputs from the clinical expert, we assumed that patients in the fenfluramine arm have [redacted] hospital visits per 28 days and [redacted] visits to a private specialist (see section 2.8.2). Patients in the placebo arm were assumed to have [redacted] visits to the hospital and [redacted] private specialist visits per 28 days. The duration of a hospital visit was assumed to be 9 hours (including treatment and transportation time) and we assumed that if patients would visit a private specialist, the duration of a visit would be 2.5 hours (including transportation time). Total patient and transportation costs for clinical question 1a are presented in Table 20.

Table 20 **Patient and transportation costs in clinical question 1a, DKK**

	Fenfluramine	Placebo
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Clinical question 2

Based on input from the clinical expert, we assumed that patients in the fenfluramine arm have [redacted] hospital visits per 28 days and [redacted] visits to a private specialist (see section 2.8.2). Patients in the placebo arm were assumed to have [redacted] visits to the hospital and [redacted] private specialist visits per 28 days. The duration of a hospital visit was assumed to be 9 hours (including treatment and

transportation time), and we assumed that if patients would visit a private specialist, the duration of a visit would be 2.5 hours (including transportation time). Total patient and transportation costs for clinical question 1a are presented in Table 21.

Table 21 **Patient and transportation costs in clinical question 2, DKK**

	Fenfluramine	Placebo
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2.9 Sensitivity analyses

To assess the uncertainties associated with the assumptions and parameter values applied in the cost per patient analysis in the two clinical questions, we conducted various one-way sensitivity analyses. Beside the sensitivity analyses conducted on the time horizon, we conducted deterministic sensitivity analyses where we changed the base case value +/- 20%[1]. The sensitivity analysis for clinical question 1a is presented in Table 22, with the alternative scenarios/values and values applied in the base case. The sensitivity analysis on clinical question 2 is presented in Table 23.

[1] For fenfluramine dosing the +20% analysis is set to the max. dose per day if the +20% dose exceeds the max dose per day.

Table 22 **Overview of the sensitivity analyses conducted on assumptions and parameters in the cost per patient analysis for clinical question 1a**

Parameter	Base case analysis	Sensitivity analysis	
		Lower	Upper
Time horizon	10 years	1 year	Life time
Fenfluramine dose	First 28 days: 471.8000 mg Subsequent cycles: 660.5200 mg	First 28 days: 377.440 mg Subsequent cycles: 528.416 mg	First 28 days: 566.160 mg Subsequent cycles: 728 mg
Probability of death (yearly rate)	[redacted]		
Probability of discontinuation			
Number of hospital visits			
Number of inpatient days			

Table 23 **Overview of the sensitivity analyses conducted on assumptions and parameters in the cost per patient analysis in clinical question 2**

Parameter	Base case analysis	Sensitivity analysis	
		Lower	Upper
Time horizon	10 years	1 year	Lifetime
Fenfluramine dose	First 28 days: 331.2400 Subsequent cycles: 378.5600	First 28 days: 264.992 mg Subsequent cycles: 302.848 mg	First 28 days: 397.488 mg Subsequent cycles: 454.272 mg
Probability of death	[redacted]		
Probability of discontinuation			
Number of hospital visits			
Number of inpatient days			

2.10 Overview of base case settings in the model

Table 24 **Overview of the base case settings and possible alternative settings in the model**

	Base case setting	Alternative setting options
Cost per patient analysis		
Applied model	Health state model	None
Patient population	DS patients	None
Intervention	Fenfluramine	None
Comparator(s)	Placebo	
Time horizon	10 years	Flexible
Discount rate	Year 1-35: 3.5% Year 36: 2%	Flexible
Perspective	Limited societal	None
Included costs	Drug cost Hospital costs Cross-sectional costs Adverse events Patient and transportation costs	None
Subsequent treatments	No	None
Inclusion of waste	Assumed no waste due to the packaging of fenfluramine	None
Budget impact analysis		
Prevalence	55 DS patients	Flexible
Incidence	2 DS patients	Flexible
Patient uptake	Proportion of relevant population that starts treatment per year: [redacted]	Proportion in year 1 is flexible.

3 Results: Cost per patient analysis

In the following, we present the result of the cost per patient analysis conducted for the two clinical questions.

3.1 Results of the base case analysis

3.1.1 Results in clinical question 1a

Results from the cost per patient analysis in clinical question 1a are presented in Table 25 and Figure 2. The cost per patient in the fenfluramine arm was DKK 5,924,403 compared to a cost per patient in the placebo arm of DKK 4,894,912. The incremental cost was DKK 1,029,491. The most influential costs in the analysis were the costs of FFA treatment, which was partial offset by reduced hospital costs and the patient and transportation costs

Table 25 **Results of the cost per patient analysis of fenfluramine compared to placebo, when added to standard of care AEDs that excludes STP, in stiripentol-experienced patients, over a time horizon of 10 years, discounted costs (DKK)**

	Fenfluramine (SoC excl. STP)	Placebo (SoC excl. STP)	Incremental costs
Fenfluramine costs	2,440,907	0	2,440,907
Other medicine costs	13,559	55,471	-41,912
Hospital costs	2,811,311	3,925,485	-1,114,174
Cross-sectional costs	0	0	0
Patient and transportation costs	658,625	913,956	-255,331
In total	5,924,403	4,894,912	1,029,491

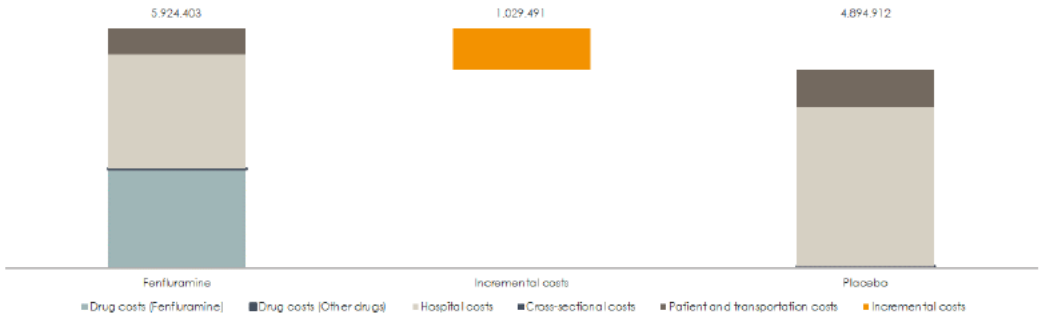


Figure 2: Total cost per patient in clinical question 1a

3.1.2 Results in clinical question 2

Results from the cost per patient analysis in clinical question 2 are presented in Table 26 and Figure 3. The cost per patient in the fenfluramine and STP arm was DKK 3,553,418 compared to a cost per patient in the placebo and STP arm of DKK 2,454,270. The incremental cost was DKK 1,099,148. The most influential costs in the analysis were the costs of FFA treatment which was partial offset by reduced hospital costs.

Table 26 **Results of the cost per patient analysis of fenfluramine (FFA+STP) compared to placebo (Placebo+STP), when added to standard of care AEDs that includes STP, over a time horizon of 10 years, discounted costs (DKK)**

	Fenfluramine (SoC incl. STP)	Placebo (SoC incl. STP)	Incremental costs
Fenfluramine cost	1,359,744	0	1,359,744
Other medicine costs	422,873	410,612	12,261
Hospital costs	1,425,960	1,646,127	-220,167
Cross-sectional costs	0	0	0
Patient and transportation costs	344,840	397,531	-52,691
In total	3,553,418	2,454,270	1,099,148

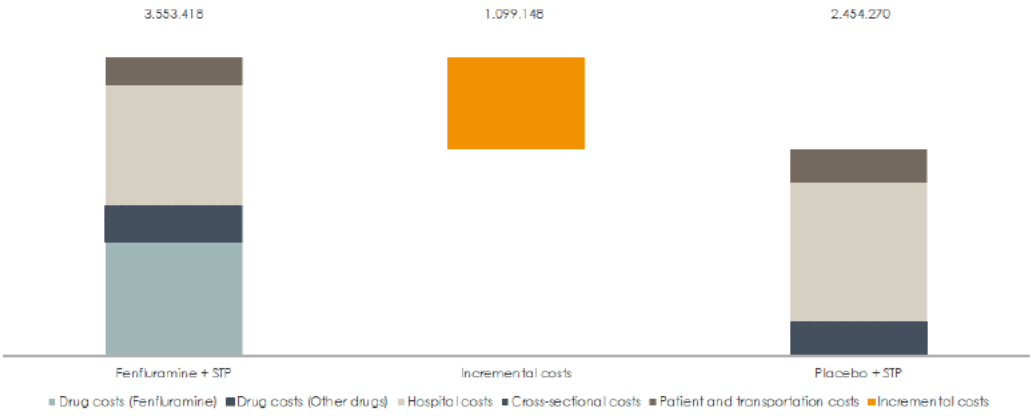


Figure 3: Cost per patient in clinical question 2

3.2 Results of the sensitivity analyses

In this section, we present the results of the sensitivity analyses. Table 27 shows that changing the time horizon from 10 years to one year or life time horizon is what impacts the result of the

base case analysis in both clinical questions the most. Moreover, changing the fenfluramine dose and the number of inpatient days also have an impact on the result of the base case.

Table 27 **Results of the sensitivity analyses on the model assumptions**

	Clinical question 1a		Clinical question 2	
	Lower	Upper	Lower	Upper
Base case incremental costs of fenfluramine, DKK	1,029,491		**1,099,148**	
Time horizon	155,117	1,847,601	182,355	1,733,508
Fenfluramine dose	541,309	1,281,518	827,199	1,371,097
Probability of death	1,012,702	1,045,734	1,094,888	1,103,174
Probability of discontinuation	1,140,425	930,289	1,221,048	990,813
Number of hospital visits	1,028,994	1,029,987	1,098,666	1,099,630
Number of inpatients days	1,307,002	751,979	1,157,221	1,041,075

4 Methods: budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending fenfluramine as the standard treatment of DS at Danish hospitals. The budget impact is estimated per year in the first five years after the recommendation of fenfluramine. The budget impact analysis compares the costs for the Danish regions in the scenario where fenfluramine is recommended as a possible standard treatment and the scenario where fenfluramine is not recommended as a possible standard treatment of DS. The total budget impact per year is the difference between the two scenarios. The costs in the budget impact analysis are based on the cost per patient analysis but exclude patient and transportation costs and apply undiscounted costs.

The general methodology of the budget impact analysis was to multiply the estimated cost per patient of fenfluramine and placebo (from clinical question 1a and clinical question 2) in each year by the number of patients in the populations, adjusted for an assumed market share and patient uptake each year in the budget impact analysis. In the following, we describe how we estimated the patient numbers applied in the budget impact analysis.

4.1 Market share

We assumed that fenfluramine would get a market share of 100% each year in the budget impact analysis if fenfluramine is recommended by the DMC. Moreover, we assumed an uptake of 0% if fenfluramine is not recommended. These assumptions were made for both clinical questions.

Table 28 **Fenfluramine market share each year in the budget impact analysis in both clinical questions**

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommended	100%	100%	100%	100%	100%
Not recommended	0%	0%	0%	0%	0%

Source: Assumption.

4.2 Patient numbers

Based on the DMC protocol on fenfluramine, we assumed a prevalence of 55 patients and a yearly incidence of 2 patients. We applied exact patient numbers in the base case analysis in the budget impact, i.e., we did not round patient numbers up or down. In the Excel-model, it is possible to perform the budget impact analyses with rounded patient numbers. In the following, we describe

how we have estimated the patient numbers in each clinical question. Due to lack of information on the likely distribution of patients in the two clinical questions, we assumed a 50/50 split between the two clinical questions.

4.2.1 Patient numbers in clinical question 1a

We assumed that the share of the prevalence and incidence for the subpopulation of stiripentol-experienced patients was 50% of the total patient population eligible for fenfluramine. It should be noted that this is a conservative estimate, as recent discussions with clinicians at Filadelfia indicate that, when considering the use of fenfluramine in current clinical practice 87% of patients are currently receiving STP and the remaining 13% have had prior experience of using STP. As the dose (and hence costs) of fenfluramine in patients not receiving concomitant STP is higher than in patients receiving concomitant STP (0.7mg/kg/day [max. 26mg/day] versus 0.4mg/kg/day [max. 17mg/day]), this assumption is likely to produce a conservative budget impact estimate. The estimation of patients each year in the budget impact analysis was based on five patient cohorts where cohort 1 consisted of 50% of the 55 prevalent patients and cohort 2-5 consisted of 50% of the incident patients (see Table 29).

Table 29 **The 5 patient cohorts in clinical question 1a**

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Number of patients	27.5	1.0	1.0	1.0	1.0

We assumed that if fenfluramine was recommended, the patient uptake would happen gradually over the years. We assumed that [redacted] of the cohorts would be distributed in the following years in the budget impact analysis, as illustrated in Table 30 and Table 31. We assumed that patients begin treatment at the beginning of the year.

Table 30 **Patient uptake per year in each cohort**

[redacted]

Source: Assumption.

Table 31 **Patient numbers per year in each cohort**

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
[redacted]					

Table 32 shows the distribution of patients and the years on treatment. Moreover, the table shows how many patients receive treatment in year 1 to year 5, how many patients for whom it is their first year in treatment (patients on 1st year of treatment), and how many patients continue treatment (patients on following years of treatment).

Table 32 **Distribution of patients and the years on treatment**

	Year on treatment							
Year in model	1	2	3	4	5	Total patients in treatment	Patients on 1st year of treatment	Patients on following years of treatment
Year 1	[redacted]							
Year 2								
Year 3								
Year 4								
Year 5								

*rounded numbers.

4.2.2 Patient numbers in clinical question 2

We assumed that the share of the prevalence and incidence for the population receiving fenfluramine and placebo with concomitant STP was 50% of the patient population eligible for fenfluramine. It should be noted that this is a conservative estimate, as recent discussions with clinicians at Filadelfia indicate that, when considering the use of fenfluramine in current clinical practice 87% of patients are currently receiving STP. As the dose (and hence costs) of fenfluramine in patients receiving concomitant STP is lower than in patients receiving concomitant STP (0.4mg/kg/day [max. 17mg/day] versus 0.7mg/kg/day [max. 26mg/day]), this

assumption is likely to produce a conservative budget impact estimate. The estimation of patients each year in the budget impact analysis were based on five patient cohorts where cohort 1 consisted of 50% of the 55 prevalent patients and cohort 2-5 consisted of 50% of the incident patients (see Table 33).

Table 33 **The 5 patient cohorts in clinical question 2**

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Population	27.5	1.0	1.0	1.0	1.0

We assumed that if fenfluramine is recommended, the patient uptake would happen gradually over the years. In clinical question 2, [redacted] of the cohorts would be distributed in the following years in the budget impact analysis, as illustrated in Table 34 and Table 35. We assumed that patients begin treatment at the beginning of the year.

Table 34 **Patient uptake per year in each cohort**

[redacted]

Source: Assumption.

Table 35 **Patient numbers per year in each cohort**

Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
[redacted]				

Table 36 shows the distribution of patients and the years on treatment. Moreover, the table shows how many patients receive treatment in year 1 to year 5, how many patients for whom it is their first year in treatment (patients on 1st year of treatment), and how many patients continue treatment (patients on following years of treatment).

Table 36 **Distribution of patients and the years on treatment**

	Year on treatment							
Year in model	1	2	3	4	5	Total in treatment	Patients on 1st year of treatment	Patients on following years of treatment
[redacted]								

*rounded numbers.

4.3 Sensitivity analyses on the budget impact analysis

In the base case analysis, we applied a prevalence of 55 DS patients being candidates to fenfluramine and an incidence of 2 new DS patients each year. We conducted sensitivity analyses on the budget impact analysis where we reduced or increased the prevalence each year by 20%. The rationale behind the sensitivity analysis was that the clinical expert informed that there is some uncertainty associated with the Danish prevalence of DS. In the sensitivity analysis with a reduction of 20%, the prevalence was changed from 27.5 to 22 patients in both clinical questions. In the sensitivity analysis with an increase of 20%, the prevalence was changed from 27.5 to 33 patients in both clinical questions. Results are presented in section 5.3.

5 Results: budget impact analysis

In the following, we present the results of the budget impact analysis in the first five years with and without a recommendation of fenfluramine for each clinical question.

5.1 Budget impact in clinical question 1a

The budget impact of recommending fenfluramine as standard treatment for stiripentol-experienced DS patients is DKK [redacted] year 5. The total budget impact in all five years is [redacted] In Table 37, the budget impact in each year is presented for clinical question 1a.

Table 37 **The budget impact each year with recommendation of fenfluramine for stiripentol-experienced patients and without recommendation, undiscounted (DKK mil)**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	9.6	14.5	16.9	18.1	18.8
Without recommendation	6.8	10.3	12.2	13.3	14.0
Budget impact	2.8	4.1	4.7	4.9	4.9

Note: Costs are rounded in millions.

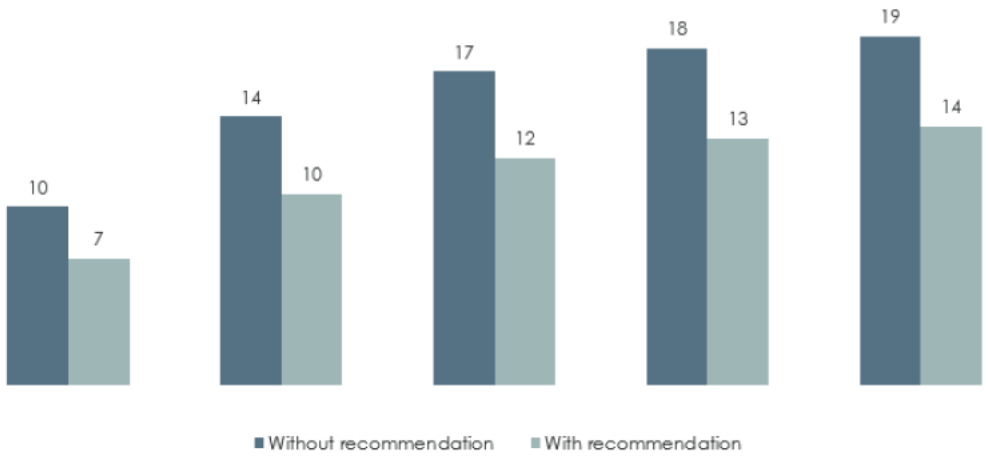


Figure 4: Budget impact analysis in year 1 to 5 in clinical question 1a

5.2 Budget impact in clinical question 2

The budget impact of recommending fenfluramine as standard treatment of DS patients is [redacted] In Table 38, the budget impact in each year is presented for clinical question 2.

Table 38 **The budget impact each year with a recommendation of fenfluramine and without recommendation, undiscounted (DKK mil)**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	6.2	9.1	10.6	11.2	11.6
Without recommendation	3.5	5.3	6.3	6.9	7.2
Budget impact	2.7	3.8	4.3	4.4	4.3

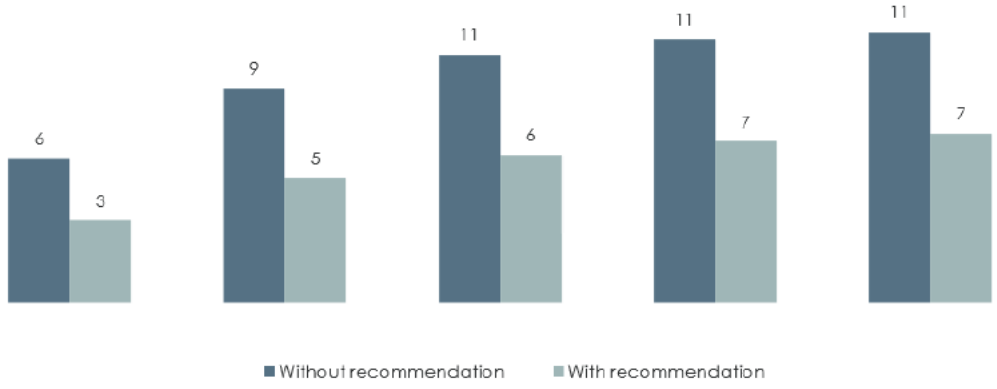


Figure 5: Budget impact analysis in year 1 to 5 in clinical question 2

5.3 Results of the sensitivity analysis of the budget impact

5.3.1 Clinical question 1a

If the number of patients who are potential candidates for treatment is reduced to 22 patients each year, the budget impact in year 5 changes from [redacted] The total budget impact in all five years is [redacted] Results of the sensitivity analysis with a reduction in the number of patients each year are presented in Table 39.

If the number of new patients who are potential candidates for treatment is increased to 33 patients each year, the budget impact changes from [redacted]

Results of the sensitivity analysis with an increase in the number of patients each year are presented in Table 40.

Table 39 **Results of the sensitivity analysis with a prevalence of 22 patients. Costs are undiscounted and rounded in millions**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	[redacted]				
Without recommendation					
Budget impact					

*rounded in millions

Table 40 **Results of the sensitivity analysis with a prevalence of 33 patients. Costs are undiscounted and rounded in millions**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	[redacted]				
Without recommendation					
Budget impact					

*rounded in millions

5.3.2 Clinical question 2

If the number of patients who are potential candidates for treatment is reduced to 22 patients each year, the budget impact does not change and [redacted] Results of the sensitivity analysis with a reduction in the number of patients each year are presented in Table 39.

If the number of new patients who are potential candidates for treatment is increased to 33 patients each year, the budget impact in year 5 changes from DKK [redacted] Results of the sensitivity analysis with an increase in the number of patients each year are presented in Table 40.

Table 41 **Results of the sensitivity analysis with a prevalence of 22 patients. Costs are undiscounted and rounded in millions**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	[redacted]				
Without recommendation					
Budget impact					

*rounded in millions

Table 42 **Results of the sensitivity analysis with a prevalence of 33 patients. Costs are undiscounted and rounded in millions**

	Year 1	Year 2	Year 3	Year 4	Year 5
With recommendation	[redacted]				
Without recommendation					
Budget impact					

*rounded in millions

6 Discussion

In the present document, we present the cost per patient analysis and a budget impact analysis conducted for fenfluramine in DS patients. The DMC protocol on fenfluramine outlined two clinical questions: 1) an assessment of fenfluramine compared to STP in patients with DS (≥2 years of age) who receive an existing combination AED therapy that does not include STP and 2) an assessment of fenfluramine compared to placebo in patients with DS (≥2 years of age) who receive an existing combination AED therapy that includes STP. In the overall patient population of patients not receiving STP, two subpopulations exist: stiripentol-naïve and stiripentol-experienced DS patients. We did not present a cost per patient analysis or budget impact analysis on the overall population in clinical question 1, nor did we present these analyses for the stiripentol-naïve subpopulation. The rationale for not presenting a cost per patient or budget impact for the overall patient population was that this was not clinically meaningful as most patients have already tried STP as a treatment option and STP naive patients that would be eligible to receive STP should continue to receive STP and then be considered for fenfluramine. As the use of fenfluramine in STP-naïve patients for whom STP is not a treatment option (e.g. due to contraindications) is anticipated to be negligible, and the cost per patient in these patients is likely to be similar to that in STP-experienced patients not currently taking concomitant STP, we have not provided a separate analysis for this minority use case. Therefore, we have focused our analyses on the anticipated use of fenfluramine in clinical practice.

In clinical question 1a, we assessed the value of fenfluramine in stiripentol-experienced patients compared to placebo. In clinical question 2, we assessed the value of fenfluramine as an add-on therapy to their existing AED SoC that includes STP compared to placebo as an add-on therapy to existing AED SoC that included STP. In clinical question 1a, we estimated an incremental cost of fenfluramine (compared to placebo) when added to SoC AEDs that exclude STP of DKK 1,043,399 and a total budget impact in all five years of DKK 21.3 mil. In clinical question 2, we estimated an incremental cost of fenfluramine (compared to placebo) when added to SoC AEDs that include STP of DKK 1,100,432 and a total budget impact in all five years of [redacted] These are likely to be overestimates as we conservatively assume equal use in these populations.

We also assessed uncertainties in the cost per patient analysis and budget impact analysis. As expected, the sensitivity analysis with the greatest impact on the result of the base case was changing the time horizon to 1 year and 50 years. Changing the dose of fenfluramine +/- 20% also had an impact on the results which is not surprising, since the drug cost of fenfluramine is a cost driver in the model. It should be noted that the modelled fenfluramine doses reflect a maximum dose that patients may receive. In practice, doses of fenfluramine may be tittered to effect. It is therefore considered that the drug costs of fenfluramine presented reflect a maximum potential dose per patient and overall budget impact. Lower dose may therefore be anticipated in clinical practice.

Given the clear relationships between convulsive seizure frequency, patient morbidity and mortality, and patient and caregiver quality of life, the significant and often profound reductions in convulsive seizure frequency demonstrated with fenfluramine as an add-on therapy are potentially life-changing for a high proportion of patients, their families and caregivers.

In the context of this devastating, rare disease, with few effective and tolerable treatment options, fenfluramine should be considered to provide a modest budgetary investment for an innovative therapy that provides a step change in the treatment of Dravet syndrome patients in Denmark.

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Medicinrådet

Medicinrådets protokol for vurdering vedrørende fenfluramin til behandling af Dravet syndrom

Version 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

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

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

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

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1. Begreber og forkortelser

AR: Bivirkning *(adverse reaction)*

CGI-I: Instrument til måling af livskvalitet *(Clinical Global Impression Improvement Scale)*

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency*)

EPAR: *European Public Assessment Report*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

GRADE: System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

HTA: Medicinsk teknologivurdering (*Health Technology Assessment)*

IQWIG: *The Institute for Quality and Efficiency in Healthcare*

ITT: *Intention to treat*

MKRF: Mindste klinisk relevante forskel

NICE: *The National Institute for Health and Care Excellence*

PedsQL: Instrument til måling af livskvalitet hos børn *(Pediatric Quality of Life Inventory Total Score)*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

PP: *Per Protocol*

RR: Relativ risiko

SAE: Alvorlig uønsket hændelse *(serious adverse event)*

SMD: *Standardized Mean Difference*

SUDEP: Pludselig uventet død *(Sudden Unexpected Death in Epilepsy)*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Zogenix, som ønsker, at Medicinrådet vurderer fenfluramin (Fintepla) til Dravet syndrom. Medicinrådet modtog den foreløbige ansøgning den 9. september 2020. Zogenix fik forhåndsgodkendelse (positive opinion) i EMA den 15. oktober 2020.

2.1 Dravet syndrom

Dravet syndrom er en sjælden, alvorlig epilepsiform, der typisk debuterer inden for det første leveår. Oftest skyldes tilstanden en genmutation i et natriumkanal-gen (*SCN1A*), men hos omkring 10 % af tilfældene er det ikke muligt at finde frem til en genetisk årsag.

Ved debut er anfaldene ofte fremprovokeret af temperaturstigninger og kan både begynde i en afgrænset del af hjernen (fokale anfald) eller i begge hjernehalvdele (generaliserede anfald) [1–3]. Dravet syndrom er karakteriseret ved hyppige, ofte daglige anfald. Anfaldstyperne kan være meget forskellige, men en stor del af anfaldene vil være konvulsive, som enten viser sig ved: *i)* trækninger og rykninger (kloniske anfald), som enten udspringer fra en afgrænset del af hjernen eller fra begge hjernehalvdele, og dels *ii)* en stivhed i kroppen (tonisk fase) og trækninger og rykninger (klonisk fase), også kaldet tonisk-kloniske anfald. Disse anfaldstyper defineres her samlet som konvulsive anfald og kan opstå i mange kombinationer. Anfaldene kan være langvarige (over fem minutter) med behov for anvendelse af anfaldsbrydende medicin. Hyppigheden af anfald er størst hos børn under 5 år og aftager med alderen. Med nuværende behandling ses der hos 0-18-årige typisk 20-50 epileptiske anfald månedligt, mens voksne patienter oftest oplever korte, natlige anfald med et spænd i hyppighed fra flere anfald dagligt til månedlige anfald. For alle aldersgrupper ses der dermed stor individuel variation i anfaldshyppigheden.

Dravet syndrom er forbundet med væsentlig overdødelighed bl.a. grundet risikoen for pludselig uventet død (*Sudden Unexpected Death in Epilepsy* (SUDEP)), ulykker ifm. anfald og status epilepticus, som er en potentielt livstruende tilstand med vedvarende anfald [1,2,4]. De fleste dødsfald sker før 10 års-alderen. I et kohortestudie af 100 patienter med Dravet syndrom blev der rapporteret en 15 % risiko for død inden for 10 år efter diagnose [5]. Patienter har oftest forskellige ledsagetilstande, bl.a. forringet finmotorik, autismelignende adfærd, indlæringsvanskeligheder, sprogforstyrrelser samt mental retardering i varierende grad. Barnet og dets familie har et væsentligt støttebehov, og kun et fåtal af voksne patienter kan klare sig uafhængigt af andre [4].

Det anslås, at der i Danmark er ca. 45.000-55.000 patienter med epilepsi på tværs af alle epilepsiformer. Patienter med Dravet syndrom udgør en lille del af denne patientpopulation. Fagudvalget vurderer, at der i Danmark er ca. 50 børn og unge samt 30-40 voksne diagnosticeret med Dravet syndrom. Disse patienter behandles overvejende på Epilepsihospitalet Filadelfia. Et dansk epidemiologisk studie fra 2015 estimerede, at den årlige forekomst af Dravet syndrom er 1 ud af 22.000 nyfødte, hvilket svarer til, at der årligt bliver født 2-3 børn med Dravet syndrom i Danmark [3].

2.2 Fenfluramin

Fenfluramin er indiceret til behandling af krampeanfald forbundet med Dravet syndrom som tillægsterapi til andre antiepileptiske lægemidler hos patienter i alderen 2 år og op.

Lægemidlet administreres peroralt to gange dagligt. Start-døgndosis er 0,2 mg/kg og kan justeres i ugentlige intervaller.

Fenfluramin er et serotoninfrigivende stof, som kan reducere krampeanfald ved at stimulere serotoninreceptorer i hjernen. Den præcise virkningsmekanisme for fenfluramin ved Dravet syndrom kendes ikke.

Fenfluramin er substrat for en række CYP450-enzymer, og koncentrationen af fenfluramin kan derfor påvirkes, hvis virkningen af disse enzymer hæmmes (inhiberes) eller øges (induceres). Lægemidlet stiripentol, som også anvendes til behandling af Dravet syndrom, hæmmer CYP450-enzymer, og samtidig behandling med stiripentol hæmmer omsætningen af fenfluramin. Særligt hvis stiripentol gives som kombinationsbehandling med valproat og clobazam, kan det medføre en stigning i koncentrationen af fenfluramin hos patienten. Behandlingen med fenfluramin skal derfor tilpasses, afhængigt af om patienten modtager samtidig behandling med stiripentol. For patienter, som *ikke* er i samtidig behandling med stiripentol, er den maximale døgndosis 0,7 mg/kg og højeste enkeltdosis 26 mg (administreret to gange dagligt). For patienter i samtidig behandling med stiripentol er den maximale døgndosis 0,4 mg/kg og højeste enkeltdosis 17 mg (administreret to gange dagligt).

Fenfluramin fik i januar 2014 *orphan drug designation* status hos EMA, hvilket bl.a. reducerer kravene til antallet af deltagere i de kliniske forsøg. Fenfluramin har tidligere været markedsført som et anoreksikum, men blev i 1997 taget af markedet grundet mistanke om, at det forårsagede øget risiko for forhøjet blodtryk i lungekredsløbet samt hjerteklapsygdom. De anvendte doser ved overvægt var 60-120 mg/dag. EMAs produktresumé for fenfluramin til behandling af Dravet syndrom angiver aorta- eller mitralklapsygdom samt pulmonal arteriel hypertension (forhøjet blodtryk i lungekredsløbet) som kontraindikationer, og det er påkrævet at overvåge hjertefunktionen ved hjælp af ekkokardiografi før og under behandlingen [6].

2.3 Nuværende behandling

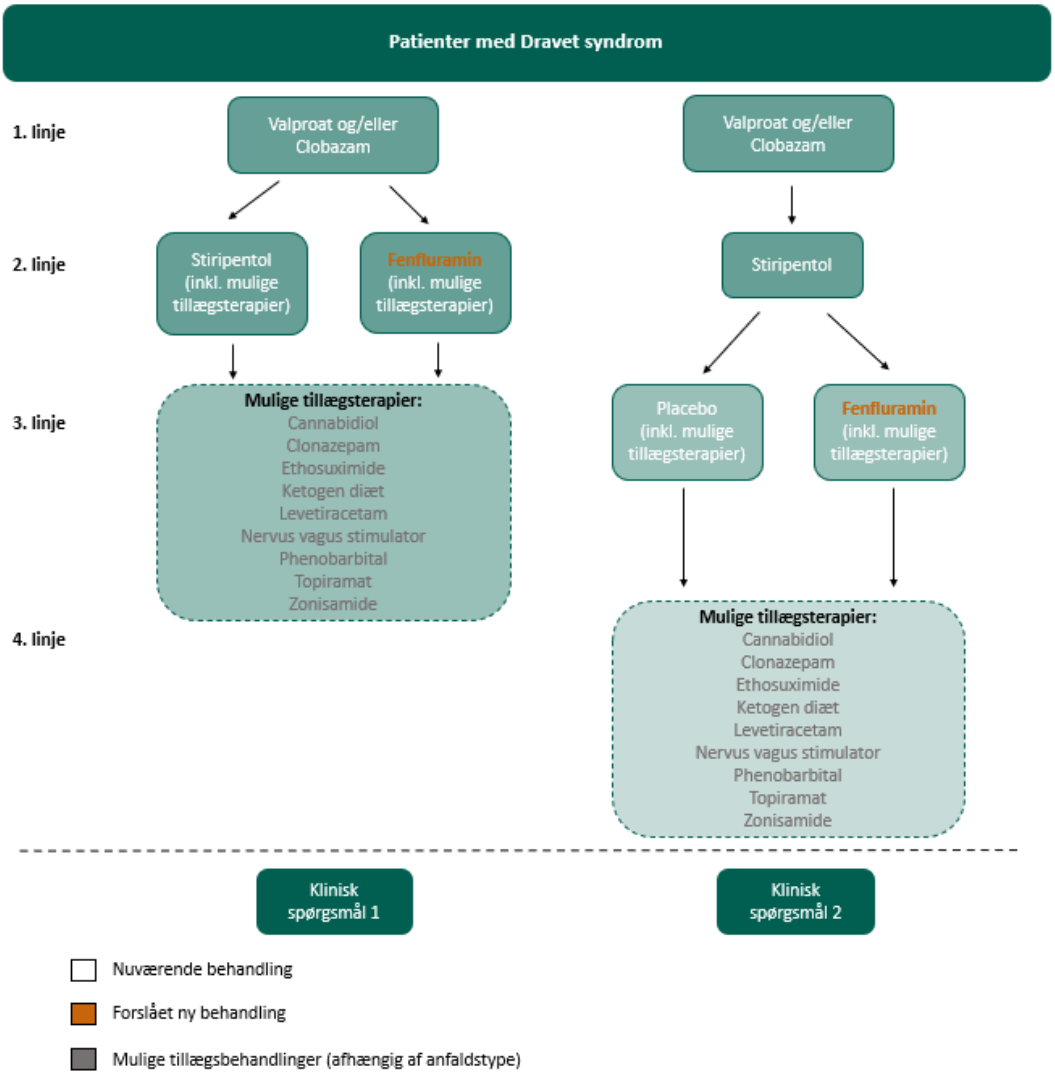
Behandlingsmålet er at reducere antallet af anfald og ideelt set at opnå anfaldsfrihed. Sidstnævnte er dog stort set aldrig muligt med nuværende behandlingsmuligheder, og tilstanden er med nuværende behandling behandlingsresistent. I tillæg til den farmakologiske antiepileptiske behandling kan ketogen diæt forsøges ved Dravet syndrom. Herudover behandles ledsagetilstande, såsom autismelignende adfærd og forringet fingermotorik, både med og uden lægemidler.

Den antiepileptiske behandling består oftest af valproat og/eller clobazam evt. med tillæg af stiripentol eller endnu en tillægsterapi såsom cannabidiol eller topiramat. Præparaterne er forbundet med bivirkninger såsom hovedpine, sedation, svimmelhed, gastrointestinale gener m.fl. samt sjældnere alvorlige bivirkninger såsom hudreaktioner

(clobazam og stiripentol) og leversvigt (valproat). Antiepileptisk behandling af Dravet syndrom er i udgangspunktet livslang men kan stoppes, hvis der ikke opnås effekt eller efter ønske fra patient og/eller pårørende.

Hvis der opstår længerevarende anfald, som kræver anfaldsbrydende medicin, såkaldt *rescue medication*, kan der behandles med benzodiazepiner.

Figur 1 illustrerer fagudvalgets vurdering af fenfluramins mulige indplaceringer i den nuværende behandlingstilgang og skitserer, hvordan de kliniske spørgsmål adresserer hver af de mulige indplaceringer.



Figur 1: Mulig indplacering af fenfluramin i behandlingsrækkefølgen for patienter med Dravet syndrom. Valproat og/eller Clobazam vil altid være 1. linjebehandling. Herefter kan enten stiripentol eller fenfluramin anvendes i 2. linje, efterfulgt af en række mulige tillægsterapier i 3. linje. Hvis stiripentol anvendes i 2. linje, kan fenfluramin anvendes i 3. linje efterfulgt af en række mulige tillægsterapier i 4. linje.

Fagudvalget vurderer, at ca. 55 ud af de ca. 85 patienter med Dravet syndrom i Danmark oplever utilstrækkeligt respons eller uacceptable bivirkninger med eksisterende behandling (clobazam, valproat og eventuelt stiripentol). Disse patienter vurderes derfor at have behov for supplerende behandling og vil således være kandidater til behandling med fenfluramin.

3. Kliniske spørgsmål

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

3.1 Klinisk spørgsmål 1

Hvilken værdi har fenfluramin sammenlignet med stiripentol for patienter med Dravet syndrom i alderen 2 år og op, som er i en behandlingskombination, der *ikke* omfatter stiripentol?

Population
Patienter i alderen 2 år og op med Dravet syndrom, uden tilfredsstillende respons på behandling med clobazam og/eller valproat, og som ikke er i behandling med stiripentol.

Intervention
Fenfluramin (maksimalt 0,7 mg/kg/dag) som tillægsterapi.

Komparator
Stiripentol (40-50 mg/kg/dag) som tillægsterapi.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.2 Klinisk spørgsmål 2

Hvilken værdi har fenfluramin sammenlignet med placebo for patienter med Dravet syndrom i alderen 2 år og op, som er i en behandlingskombination, der omfatter stiripentol?

Population
Patienter i alderen 2 år og op med Dravet syndrom, uden tilfredsstillende respons på behandling med clobazam og/eller valproat samt stiripentol.

Intervention
Fenfluramin (maksimalt 0,4 mg/kg/dag) som tillægsterapi.

Komparator
Placebo som tillægsterapi.

Effektmål
De valgte effektmål fremgår af tabel 1.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

Tabel 1. Oversigt over valgte effektmål

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Konvulsive anfald	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Gns. procentuel ændring i antallet af konvulsive anfald pr. 28 dage	20 %
	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald	20 %-point
Behov for anfaldsbrydende medicin (*rescue medication*)	*Vigtigt*	Livskvalitet, alvorlige symptomer og bivirkninger	Gns. antal dage/28 dage, hvor anfaldsbrydende medicin anvendes	1 dag
	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der opnår 50 % reduktion i antal dage/28 dage, hvor anfaldsbrydende medicin anvendes	20 %-point
Livskvalitet	*Kritisk*	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring i PedsQL	4,5 point
			Andel patienter, som scorer 1 eller 2 i CGI-I	5 %-point

Effektmål*	Vigtighed	Effektmålsgruppe**	Måleenhed	Mindste klinisk relevante forskel
Uønskede hændelser	*Vigtigt*	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter med mindst én alvorlig uønsket hændelse (SAE)	5 %-point
	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Kvalitativ gennemgang af bivirkningsdata	

*For alle effektmål ønsker Medicinrådet data med længst mulig opfølgningstid, medmindre andet er angivet.
**Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.

3.3.1 Kritiske effektmål

Konvulsive anfald
En høj forekomst af konvulsive anfald er forbundet med en høj risiko for udvikling af sygelighed og dødelighed samt forringet livskvalitet. Derfor vurderer fagudvalget, at konvulsive anfald er et kritisk effektmål. Fagudvalget ønsker effektmålet opgjort på følgende måder:

- Den gennemsnitlige procentuelle ændring i antallet af konvulsive anfald pr. 28 dage. Der foreligger ikke en valideret MKRF for dette effektmål, men fagudvalget vurderer, at en forskel på 20 % er klinisk relevant.
- Andel patienter, der opnår mindst 50 % reduktion i antallet af konvulsive anfald. Ved behandling af Dravet syndrom er det som oftest ikke muligt at opnå anfaldsfrihed, men fagudvalget vurderer, at en 50 % reduktion i antallet af konvulsive anfald vil have stor betydning for patienten. Der foreligger ikke en valideret MKRF for dette effektmål, men fagudvalget vurderer, at en forskel på 20 %-point er klinisk relevant.

Da definitionen af konvulsive anfald kan variere mellem studier, skal ansøger redegøre for definitionen i hvert af de studier, der anvendes i besvarelsen af de kliniske spørgsmål.

Livskvalitet
Livskvalitet er et afgørende helbredsrelateret mål for den enkelte patient. Hos børn med epilepsi kan livskvalitet måles med en række forskellige instrumenter, som omfatter både sygdomsspecifikke (f.eks. *Quality of Life in Childhood Epilepsy*) og generiske værktøjer (f.eks. *Pediatric Quality of Life Inventory Total Score* [PedsQL]). I dette tilfælde vil vurdering af livskvalitet blive baseret på det generiske og velvaliderede PedsQL [7], som kan anvendes til børn og unge i alderen 2-18 år. Testen kan, afhængigt af patientens alder og mentale formåen, enten besvares af patienterne selv eller deres forældre. PedsQL består af fire funktionsskalaer med i alt 23 domæner, hvorfra der kan udregnes

dels en psykosocial livskvalitetsscore og en fysisk livskvalitetsscore samt en samlet score. Data transformeres til en scoringsskala fra 0-100. Fagudvalget har fastsat MKRF til 4,5 point, jf. litteraturen [7].

Da vurdering af livskvalitet hos børn er udfordrende og kan være forbundet med ringe sensitivitet, ønsker fagudvalget ydermere at inddrage resultater fra værktøjet *Clinical Global Impression Improvement Scale* (CGI-I) som supplement. CGI-I er en 7-punkts Likert-skala, som anvendes af behandler, forælder eller omsorgsperson. Skalaen udgør en vurdering af patientens generelle helbredstilstand efter en given intervention relativt til før denne intervention. CGI-I spænder fra 1: '*very much improved',* til 7: '*very much worse'*, mens 4 svarer til ingen ændring. Fagudvalget vil vurdere resultater for andelen af patienter, som scorer 1 eller 2 på skalaen (dvs. *very much improved* eller *much improved*). Der foreligger ikke en valideret MKRF for dette effektmål, men fagudvalget vurderer, at en forskel på 5 %-point i andelen af patienter, der opnår 1 eller 2 på CGI-I skalaen, er klinisk relevant.

3.3.2 Vigtige effektmål

Behov for anfaldsbrydende medicin
Anfaldsbrydende medicin (*rescue medication*) vil kun være nødvendigt for en lille del af de anfald, som forekommer hos patienter med Dravet syndrom. Anvendelse af anfaldsbrydende medicin er typisk indiceret ved anfald, som varer længere end 3-5 minutter, eller hvor patienten oplever gentagne anfald med kortere intervaller end sædvanligt. Behov for anfaldsbrydende medicin er derfor et indirekte mål for sværhedsgraden/varigheden af de mest alvorlige anfald. Fagudvalget vurderer, at det er afgørende for patienten at opleve færrest mulige anfald, som kræver administration af anfaldsbrydende medicin og betragter derfor dette som et vigtigt effektmål. Fagudvalget vurderer, at den gennemsnitlige patient vil have behov for anfaldsbrydende medicin 2-3 dage pr. 28 dage. Der foreligger ikke en valideret MKRF for dette effektmål, men opgjort som det gennemsnitlige antal dage/pr. 28 dage, hvor anfaldsbrydende medicin administreres, vurderer fagudvalget, at en forskel på 1 dag er klinisk relevant.

Uønskede hændelser
Uønskede hændelser kan være til stor gene for patienten. Som for al behandling skal belastningen fra uønskede hændelser/bivirkninger stå i rimeligt forhold til den terapeutiske effekt. Særligt for livslang behandling kan væsentlige bivirkninger resultere i behandlingsophør eller ringe adhærens. Fagudvalget vurderer derfor, at uønskede hændelser er et vigtigt effektmål.

Fagudvalget har i fastsættelsen af de mindste klinisk relevante forskelle taget hensyn til, at sygdommen er sjælden, og at studiepopulationen dermed er lille. Derudover er Dravet syndrom og behandling med øvrige antiepileptika i sig selv hyppigt forbundet med uønskede hændelser. Af samme årsag har fagudvalget valgt at fokusere på alvorlige uønskede hændelser (SAEs) frem for bivirkninger (ARs), da det ofte vil være vanskeligt at kausalitetsbestemme én given hændelse hos børn med Dravet syndrom, der allerede modtager to eller flere antiepileptiske præparater.

Fagudvalget ønsker af disse årsager effektmålet opgjort på to forskellige måder:

- Andelen af patienter med én eller flere alvorlige uønskede hændelser (SAE). Der foreligger ikke en valideret MKRF for dette effektmål, men fagudvalget vurderer, at en forskel på 5 %-point er klinisk relevant.
- Fagudvalget ønsker en kvalitativ gennemgang af bivirkningsprofilen for fenfluramin med henblik på at vurdere bivirkningernes alvorlighed, type, hyppighed og håndterbarhed, herunder kardiovaskulære hændelser og status epilepticus. Ansøger bedes derfor bidrage med en opgørelse og narrativ beskrivelse af bivirkningsprofilen baseret på resultater fra kliniske studier, produktresuméet og EPAR'en.

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (fx NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Data skal derudover stemme overens med protokollens beskrivelser. Anvendelse af upublicerede data sker ift. Medicinrådets princippapir[1].

Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes studier, hvor fenfluramin er sammenlignet direkte med placebo:

- Lagae L, Sullivan J, Knupp K, et al.; FAiRE DS Study Group. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Dec 21;394(10216):2243-2254. doi: 10.1016/S0140-6736(19)32500-0. Epub 2019 Dec 17
- Nabbout R, Mistry A, Zuberi S, et al. FAiRE, DS Study Group. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 2019 Dec 2. doi: 10.1001/jamaneurol.2019.4113.

Det er ikke tilstrækkeligt datagrundlag til en komplet besvarelse af de kliniske spørgsmål, da der i sammenligningen mellem fenfluramin og placebo (Nabbout et al., 2019) ikke er rapporteret data for alvorlige uønskede hændelser. Derudover er fenfluramin i disse studier ikke direkte sammenlignet med stiripentol.

Ansøger skal derfor undersøge, om der findes andre studier, som indeholder/beskriver de angivne mangler. Søgestrengene fremgår af bilag 1.

Finder ansøger andre studier med fenfluramin, som indeholder de angivne mangler, skal virksomheden søge efter tilsvarende studier med placebo eller stiripentol. Ansøger skal

[1] For yderligere detaljer se Medicinrådets principper for anvendelse af upublicerede data

på baggrund af studierne foretage en indirekte sammenligning for at besvare klinisk spørgsmål 1 samt de dele af klinisk spørgsmål 2, som den direkte sammenligning ikke kan besvare.

Finder ansøger ikke andre studier med fenfluramin, som indeholder de angivne mangler, skal virksomheden ikke søge efter tilsvarende studier for komparator.

I begge tilfælde skal ansøger derudover konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator.

Virksomheden skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, fx i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstraktniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram som beskrevet i PRISMA-Statement.

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

5. Den endelige ansøgning

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

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.

- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (fx intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).

- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

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

Sundhedsøkonomiske analyser

En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.

- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, fx behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.
- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

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

7. Andre overvejelser

Fagudvalget bemærker, at den kliniske effekt og sikkerhed af fenfluramin fortrinsvist er undersøgt hos børn og unge (2-18 år). Fagudvalget finder det dog relevant også at se på data for voksne. Fagudvalget ønsker derfor at blive præsenteret for kliniske data for voksne patientpopulationer, såfremt data foreligger, samt ansøgers vurdering af, hvorvidt den kliniske effekt af fenfluramin kan ekstrapoleres til voksne.

Fagudvalget er bekendt med, at den kliniske effekt af fenfluramin er undersøgt i patienter, der ved studieinklusion enten 1) modtog samtidig behandling med stiripentol eller 2) ikke havde modtaget stiripentol inden for 21 dage. Fagudvalget finder det dog også relevant at se data for stiripentol-naive patienter. Fagudvalget ønsker derfor at blive præsenteret for kliniske data for stiripentol-naive patientpopulationer, såfremt data foreligger, samt ansøgers vurdering af den kliniske effekt af fenfluramin i denne population.

I Danmark gives stiripentol som tillægsterapi til patienter, hvor behandling med clobazam og valproat er utilstrækkelig. Såfremt data foreligger, ønsker fagudvalget derfor at se kliniske data for patienter, som er i samtidig behandling med både clobazam og valproat, samt ansøgers vurdering af den kliniske effekt af fenfluramin i denne population. Til denne vurdering skal ansøger tage udgangspunkt i klinisk spørgsmål 1.

Produktresuméet for fenfluramin til behandling af Dravet syndrom angiver, at det grundet risiko for hypertension i lungekredsløbet samt hjerteklapsygdom er påkrævet at overvåge hjertefunktionen ved hjælp af ekkokardiografi før og under behandlingen. På

denne baggrund ønsker fagudvalget, at ansøger indsender en vurdering af risikoen for ovenstående bivirkninger, særligt hos voksne patienter (dvs. patienter > 18 år).

Fagudvalget er bekendt med, at behandling med ketogen diæt og/eller topiramat eller zonisamod kan resultere i vægttab. Fagudvalget ønsker derfor, at ansøger indsender en vurdering af, hvorledes samtidig behandling af disse lægemidler og fenfluramin kan påvirke patientens vægt.

Dravet syndrom er forbundet med potentielt livstruende anfald og en væsentlig overdødelighed. Fagudvalget finder det derfor relevant at se på overlevelsesdata ved behandling med fenfluramin, såfremt data er tilgængeligt.

Fagudvalget er derudover bekendt med, at nogle patienter først oplever klinisk effekt efter længere tids behandling med fenfluramin, dvs. udover de 12 uger, som anvendes i registreringsstudier. Fagudvalget ønsker derfor at blive præsenteret for ansøgers overvejelser vedr. behandlingsvarighed og eventuel dosisjustering før potentiel seponering af lægemidlet.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

9. Referencer

1. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011;52(SUPPL. 2):3–9.

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5. Cooper MS, Mcintosh A, Crompton DE, Mcmahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. Epilepsy Res. 2016;128:43–7.

6. European Medicines Agency (EMA). Produktresumé, Fintepla. 2021.

7. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQLTM 4.0 as a pediatric population health measure: Feasibility, reliability, and validity. Ambul Pediatr. 2003;3(6):329–41.

10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende epilepsi

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Jakob Christensen *Overlæge*	Lægevidenskabelige Selskaber og Dansk Neurologisk Selskab
Medlemmer	**Udpeget af**
Hans Christian Laugaard-Jacobsen *Ledende overlæge*	Region Nordjylland
Mette Møller Handrup *Overlæge*	Region Midtjylland
Mette Rokkjær *Overlæge*	Region Syddanmark
Janne Friedrich *Overlæge*	Region Sjælland
Ioannis Tsiropoulos *Overlæge*	Region Hovedstaden
Gesche Jürgens *Overlæge, forskningslektor*	Dansk Selskab for Klinisk Farmakologi
Rikke Kudahl Jensen *Klinisk farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Kern Olofsson *Ledende overlæge*	Inviteret af formanden (fra Epilepsihospitalet Filadelphia)
Berit Andersen *Patient/patientrepræsentant*	Danske Patienter
Lotte Hillebrandt *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

Medicinrådet
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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	13. juli 2021	Godkendt af Medicinrådet.
1.1	31. august 2021	I afsnit 4 fremgår det nu korrekt, at ansøger på baggrund af studierne skal foretage en indirekte sammenligning for at besvare klinisk spørgsmål 1 samt de dele af klinisk spørgsmål 2, som den direkte sammenligning ikke kan besvare.

12. Bilag

Bilag 1: Søgestrenge

Søgestreng til PubMed:

#	Søgestreng	Kommentar
1	Dravet*[tiab] OR severe myoclonic epilepsy of infancy[tiab] OR severe myoclonic epilepsy in infancy[tiab] OR SMEI[tiab]	Population
2	Fenfluramine[tw] OR Fintepla*[tiab]	Intervention og komparatorer
3	stiripentol[tw] OR Diacomit*[tiab]	
4	placebo*[tw] OR sham[tiab] OR dummy[tiab]	
5	#2 OR #3 OR #4	
6	#1 AND #5	
7	english[la] AND hasabstract	Afgræsning til referencer på engelsk, der har abstract
8	#6 AND #7	
9	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti]	Eksklusions-kriterier
10	#8 NOT #9	Endelig søgning for begge kliniske spørgsmål

Søgestreng til CENTRAL:

#	Søgestreng	Kommentar
#1	(Dravet* or "severe myoclonic epilepsy of infancy" or "severe myoclonic epilepsy in infancy"):ti,ab,kw	Population
#2	(fenfluramine or Fintepla*):ti,ab,kw	Intervention og komparator
#3	(stiripentol or Diacomit*):ti,ab,kw	
#4	(placebo* OR sham or dummy):ti,ab,kw	
#5	#2 or #3 or #4	
#6	#1 and #5	
#7	("conference abstract" or review):ti,pt	Eksklusions-kriterier
#8	(clinicaltrials.gov or trialsearch):so	
#9	(meeting or conference or proceedings):so	
#10	nct*:au	
#11	#7 or #8 or #9 or #10	
#12	#6 not #11	
#13	#12 not pubmed:an	Endelig søgning til begge kliniske spørgsmål med eksklusion af referencer, der kommer fra Pubmed. Afgrænses til Trials.