Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende fenfluramin som tillæg til behandling af Lennox-Gastaut syndrom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. fenfluramin til Lennox-Gastaut syndrom
2. Forhandlingsnotat fra Amgros vedr. fenfluramin Lennox-Gastaut syndrom
3. Ansøgers endelige ansøgning vedr. fenfluramin Lennox-Gastaut syndrom

Dato 19. maj 2025

UCB's høringssvar på Medicinrådets vurdering af fenfluramin (Fintepla®) til patienter med Lennox-Gastaut syndrom

UCB vil gerne takke og anerkende det grundige arbejde, Medicinrådet har udført i forbindelse med vurderingen af fenfluramin til behandling af patienter med Lennox-Gastaut Syndrom i Danmark. I forlængelse af udkastet til evalueringsrapporten vil vi gerne præcisere og behandle nedenstående punkter.

Eksklusion af cannabidiolomkostninger fra nuværende standardbehandlingsarm
Der findes ingen head-to-head effektdata for fenfluramin vs cannabidiol. Dansk Real-World data (RWD) viser dog at cannabidiol anvendes som behandlingsvalg i ca. 17 % af LGS-patienter. Inklusion af disse omkostninger afspejler klinisk praksis og mindsker delvist usikkerheden i omkostningseffektivitetsanalysen. Denne tilgang blev diskuteret i dialogmødet med Medicinrådet, og da head-to-head studiedata metodisk foretrækkes til den kliniske effektvurdering, har UCB brugt de tilgængelige komparative data fra det kliniske studie, som ikke inkluderede cannabidiol i komparatorkurven. UCB mener at den mest afbalancerede tilgang er at inkludere cannabidiolomkostninger i omkostningsberegningerne samtidig med at anvende det mest valide og repræsentative kliniske studie til at estimere effekten. Ved at ekskludere cannabidiolomkostninger vurderer UCB at Medicinrådet underestimerer de reelle lægemiddelomkostninger ved nuværende standardbehandling for LGS-patienter i Danmark.

Nytteværdier og Medicinrådets base-case scenarie 2
Vi noterer os Medicinrådets beslutning om at halvere forskellen mellem nytteværdierne i scenarie 2 baseret på vurderingen af, at studieresultaterne virker "urealistiske". Samtidig anerkender vi, at der ikke findes nogen bedre livskvalitetsundersøgelser. Justeringsfaktoren på 0,5 anvendt på nytteværdierne synes ikke at være understøttet af et specifikt metodisk rationale, da den kun anvendes på 3 ud af 4 identificerede stadier. Selvom vi anerkender, at referencestudiet har begrænsninger, repræsenterer studiet empirisk evidens indsamlet ved hjælp af validerede instrumenter. Opretholdelse af de oprindelige evidensbaserede nytteværdier er i overensstemmelse med standard sundhedsøkonomiske metodologiske principper, da systematisk indsamlede data, selv med anerkendte begrænsninger, generelt giver et mere robust grundlag for beslutningstagning end justeringer uden empirisk begrundelse. Derfor mener vi, at scenarie 2 ikke bør overvejes i beslutningssammenhæng.

Markedsoptag i budgetkonsekvensanalysen
I BI-beregningen er der anvendt et fast markedsoptag på 80 % på tværs af år 1-5 i stedet for UCBs oprindelige tilgang med et gradvist optag. Vi mener, at en tilgang baseret på gradvist optag er mere repræsentativt for det forventede optag i den virkelige verden efter en positiv anbefaling for fenfluramin. Dette vil også være i overensstemmelse med Medicinrådets tilgang og metode i tidligere vurderinger. Derudover fremgår det i Medicinrådet evalueringsrapport: "I praksis vil fenfluramin blive forsøgt efter topiramat og clobazam, fordi der er mere erfaring med disse to lægemidler," hvilket understøtter, at fenfluramin ikke ville opnå 80 % markedsoptagelse i år 1. Med dette in mente mener vi, at den foreslåede progression på 7 %, 10 %, 20 %, 30 % og 50 % fra år 1-5 er mere repræsentativ for virkeligheden og bør anvendes i vurderingen.

Non-SUDEP-dødelighed
Vi sætter pris på muligheden for at præcisere, hvordan non-SUDEP-dødelighed beregnes. I vores tidligere svar leverede vi den detaljerede beregningsmetode, som vi gerne vil gentage til Medicinrådets overvejelse:
Studiet af Cooper et al. (2016) anvendes til at bestemme både baseline SUDEP-dødelighed og Status Epilepticus (SE) dødelighed. For SUDEP-dødelighed konverteres incidensraten på 9,32 pr. 1000 personår i studiet til en 3-måneders cyklussandsynlighed ved hjælp af den eksponentielle standardformel:
P = 1 - e^(-rate × tid), hvor tiden er 0,25 år, hvilket resulterer i P = 1 - e^(-(9,32/1000) × 0,25) = 0,2327%. For SE-dødelighed (non-SUDEP) beregnes raten ved hjælp af andre resultater fra samme studie. Specifikt bliver den samlede dødelighed på 15,84 pr. 1000 personår ganget med andelen af dødsfald, der kan tilskrives status epilepticus (4/17 = 23,53 %) for at udlede den SE-specifikke dødelighed på 3,7271 pr. 1000 personår. Dette konverteres derefter til en 3-måneders cyklussandsynlighed ved hjælp af den samme eksponentielle formel: P = 1 - e^(-(3,7271/1000) × 0,25) = 0,0931 %.

Denne metode følger samme tilgang anvendt i NICE-vurderingen for Dravet syndrom, med den forskel, at den nuværende model bruger en 3-måneders cykluslængde i stedet for NICE's 28-dages cyklus, hvilket forklarer forskellen mellem den aktuelle værdi (0,0931%) og værdien i Dravet-ansøgningen (0,0286%).

Stopregel
I vurderingsrapporten anerkender Medicinrådet, at behandlingsmålet er at reducere antallet af anfald: "*Hos patienter med LGS, der er refraktære over for medicinsk behandling (dvs. de kan ikke gøres anfaldsfrie med medicin), er behandlingsmålet ved start af ny medicin at reducere antallet af anfald.*" Implementering af en streng >50 % anfaldsreduktionsstopregel for disse behandlingsrefraktære patienter synes uforenelig med denne tidligere vurdering af behandlingsmålet for LGS-patienter. Desuden er brugen af en 50 % stopregel ikke forankret i dansk (eller international) klinisk praksis, hvilket bekræftes af danske eksperter fra Filadelfia (Cathrine Elisabeth Gjerulfsen, Afdeling for Epilepsigenetik og Personlig Medicin, Dansk Epilepsicenter, Filadelfia).

På baggrund af overstående, foreslår UCB at Medicinrådet genovervejer implementeringen af stopreglen for at være mere i overensstemmelse med dansk klinisk praksis og stopreglerne for Dravet og cannabidiol. UCB anerkender dog, at introduktionen af nye behandlingsmuligheder kan tilføje økonomisk pres på sundhedsvæsenet og forstår Medicinrådets argumenter for en >50 % stopregel.

QOLCE som et effektmål
Vi anerkender Medicinrådets vurdering af QOLCE-instrumentet som et effektmål: "Medicinrådet inkluderer ikke livskvalitet målt med QOLCE, fordi QOLCE ikke er egnet til at vurdere ændringer i livskvalitet hos børn med LGS". Det skal dog bemærkes, at selvom QOLCE måske ikke er den bedst egnede til at generere sundhedsrelaterede livskvalitetsestimater, betragtes den stadig af eksperter på området som et valideret instrument til måling af effekt.
"QOLCE måler forskellige domæner inden for adfærds- og følelsesliv, kognitive udfordringer og sociale vanskeligheder samt individuelle spørgsmål direkte rettet mod vanskeligheder grundet barnets epilepsi. Det er derfor muligt at se på, om barnets vanskeligheder er blevet mindre/større over tid, hvis man ser på de enkelte områder (eller den samlede score)... Så QOLCE kan bruges som effektmål (Anne Vagner Jakobsen, Enhed for Tværfaglig Sundhedsforskningsspecialist i Børneneuropsykologi, Filadelfia).
Selvom dets begrænsninger er anerkendt, giver QOLCE stadig eksperter værdifuld indsigt i LGS-patienter. *"... Jeg synes ikke altid, at et standardiseret spørgeskema som QOLCE giver meget indsigt i den enkelte families oplevelse af livskvalitet, men det er nok det bedste mål vi har, hvis man ikke skal ud i individuelle kvalitative interviews* (Cathrine Elisabeth Gjerulfsen, Afdeling for Epilepsigenetik og Personlig Medicin, Dansk Epilepsicenter, Filadelfia/Syddansk Universitet).

Brug af medianer mod middelværdier i den sundhedsøkonomiskemodel.
Vi vil med al respekt kommentere Medicinrådets udtalelse: *"Medicinrådet mener, at dette bør baseres på gennemsnitstal i stedet for medianer, som alt andet i den sundhedsøkonomiske model, men ansøgeren har ikke imødekommet dette. I ansøgerens tilgang er der en risiko for, at antallet af anfald undervurderes for både interventionen og komparatoren, da der er patienter, der har en meget høj forekomst af anfald*". LGS en meget heterogen sygdom med forskellige medvirkende ætiologier, der resulterer i en høj variation i anfaldsfrekvens mellem patienter og signifikant intravariabilitet hos individuelle patienter. Denne variation i anfald understøtter brugen af medianreduktion frem for middelværdier i den sundhedsøkonomiske analyse. Medicinrådet anerkender denne variation i vurderingen: *"der er en stor variation i antallet af anfald mellem patienter, det laveste antal over 28 dage er 2 anfald og det højeste 2943 anfald."* På trods af at Medicinrådet anerkender dette, foretrækker Medicinrådet kontraintuitivt gennemsnit. Vi fastholder, at stadieestimater (0 til 3) bør baseres på median anfaldstal ved baseline. Data fra studie 1601 bekræfter denne skæve fordeling (median = 85; middel = 195; min = 4; max = 2943), hvor brug af gennemsnitsværdier sandsynligvis vil skævvride mod ikke-realistiske høje baseline anfaldsfrekvenser.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

22.09.2025

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.10.2025
Leverandør	UCB
Lægemiddel	Fintepla (fenfluramin)
Ansøgt indikation	Behandling af epileptiske anfald forbundet med Lennox-Gastaut syndrom som tillægsterapi til andre antiepileptiske lægemidler hos patienter i alderen 2 år og derover.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Fintepla (fenfluramin) med originalleverandøren UCB:

Tabel 1: Forhandlingsresultat

Lægemiddel (leverandør)	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP (DKK) frem til 30.11.25	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK) fra 01.03.26	Forhandlet rabat ift. AIP
Fintepla (Orifarm)	2,2 mg/ml (120 ml, oral opløsning)	13.890,49	[redacted]	[redacted]		
Fintepla (Orifarm)	2,2 mg/ml (360 ml, oral opløsning)	41.689,72	[redacted]	[redacted]		

Fintepla (UCB)	2,2 mg/ml (120 ml, oral opløsning)	12.234,56			[redacted]	[redacted]
Fintepla (UCB)	2,2 mg/ml (360 ml, oral opløsning)	36.584,00			[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Informationer fra forhandlingen

[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter til patientpopulationerne jævnfør Medicinrådets vurderingsrapport.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Gennemsnitsvægt (kg)*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling per år (SAIP, DKK)
Fintepla 2-5 årige	2,2 mg/ml (120 ml)	17,63	[redacted]	[redacted]
Fintepla 6-11 årige	2,2 mg/ml (120 ml)	30,11	[redacted]	[redacted]
Fintepla 12-17 årige	2,2 mg/ml (120 ml)	48,07	[redacted]	[redacted]
Fintepla 18-36 årige	2,2 mg/ml (120 ml)	62,11	[redacted]	[redacted]

Fintepla** 37+ årige	2,2 mg/ml (120 ml)	78,00	[redacted]	[redacted]

*Dosis = 0,413 mg/kg/dag i vedligeholdelsesfasen jævnfør Medicinrådets vurderingsrapport
** Maksimal anbefalet daglig dosis er 26 mg jævnfør produktresuméet.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of fenfluramine (Fintepla®) for treatment of Lennox-Gastaut Syndrome

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Version 2.0

Contact information

Contact information	
Name	**Mari-Ann Retz / UCB Nordic A/S**
Title	Managing Director & Head Market Access
Phone number	+45 21216090
E-mail	mari-ann.retz@ucb.com
Name (External representation)	**N/A**
Title	N/A
Phone number	N/A
E-mail	N/A

Abbreviations: N/A = not applicable.

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Abbreviations

Abbreviation	Definitions
AE	Adverse event
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
ASM	Anti-seizure medication
ANCOVA	Analysis of covariance
BMI	Body mass index
BRIEF	Behavior Rating Inventory for Executive Function
CBD	Cannabidiol
CFB	Change from baseline
CGI-I	Clinical Global Impression - Improvement
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DSF	Drop seizure frequency
DMC	Danish Medicines Council
ECG	Electrocardiogram
ECHO	Echocardiogram
EOS	End of study
ESC	Epilepsy Study Consortium
FFA	Fenfluramine
GABA	Gamma-aminobutyric acid
GTC	Generalised tonic-clonic
HL	Hodges-Lehmann
LGS	Lennox-Gastaut syndrome
LOTV	Last On-Treatment Visit
M	Maintenance
mITT	Modified intent-to-treat
NMA	Network meta-analysis
ns	Not significant
N/A	Not applicable
OLE	Open-label extension
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review

SoC	Standard of care
SUDEP	Sudden unexpected death in epilepsy
TEAE	Treatment-emergent adverse event
T+M	Titration and maintenance
UK	United Kingdom
US	United States

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Fintepla®
Generic name	Fenfluramine
Therapeutic indication as defined by EMA	Fintepla is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.
Marketing authorization holder in Denmark	UCB Nordic A/S Edvard Thomsens Vej 14, 7. DK-2300 Copenhagen S
ATC code	N03AX26
Combination therapy and/or co-medication	Yes, as fenfluramine is an add-on therapy to other anti-seizure medications (ASMs)
(Expected) Date of EC approval	31 January 2023
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, 27 February 2017
Other therapeutic indications approved by EMA	Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other ASMs for patients 2 years of age and older.
Other indications that have been evaluated by the Danish Medicines Council (DMC) (yes/no)	Yes (for the indication for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other ASMs for patients 2 years of age and older).
Joint Nordic assessment (JNHB)	The current treatment practices for LGS are different across the Nordic countries. Fenfluramine is not suitable for a joint Nordic assessment due to different treatment practices across the Nordics and as it is currently under assessment in Sweden and Finland and reassessment in Norway.
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	Fintepla (fenfluramine) 2.2 mg/ml, 120 ml oral solution Fintepla (fenfluramine) 2.2 mg/ml, 360 ml oral solution

Abbreviations: ASM = anti-seizure medication; DMC = Danish Medicines Council; LGS = Lennox-Gastaut syndrome.
Sources: European Medicines Agency, 2024 (1); European Commission, 2024 (2); European Medicines Agency, 2024 (3); Medicinrådet, 2022 (4); Danish Medicines Agency, 2024 (5).

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Fintepla is indicated for the treatment of seizures associated with LGS as an add-on therapy to other ASMs for patients 2 years of age and older.
Dosage regiment and administration	Fenfluramine is administered as an oral solution twice daily. The recommended starting dose is 0.1 mg/kg twice daily. At day 7 (second week)*, the dose can be increased to 0.2 mg/kg twice daily if additional seizure control is needed. At day 14*, the dose can be increased up to 0.35 mg/kg twice daily if tolerated and further seizure control is needed. The maximal dose is 26 mg (13 mg twice daily). *For further detail refer to section 3.4.
Choice of comparator	Based on insights from clinical practice as well as inputs from the dialogue meeting with the DMC, standard of care (SoC) is the relevant clinical comparator.
Prognosis with current treatment (comparator)	The most frequent type of seizures for LGS patients are drop seizures (6-8) including generalised tonic-clonic (GTC), secondary GTC, tonic, atonic, and tonic-atonic seizures as described by the Epilepsy Study Consortium (ESC) (9, 10). These seizures are highly frequent and physically demanding as they may result in falls, serious debilitating injury, subsequent pain, hospitalisation, or even death (9, 11-13). Focal seizures and GTC seizures can be serious and result in pre-mature death either through status epilepticus or sudden unexpected death in epilepsy (SUDEP). All types of seizures can turn into status epilepticus (14, 15). LGS has a high mortality (around 5%) (16). Patients with LGS are at increased risk of SUDEP, which is highly correlated with the experience of multiple GTC seizures (17). Patients with any number of GTCs in the previous year are 27 times more likely to die suddenly compared with people with epilepsy who have not experienced any GTC seizures (17). This highlights the importance of controlling the numbers of seizures particularly GTC patients experience. High seizure burden also significantly negatively affects cognition. The effects of LGS extend beyond the patient and may cause a profound impact on caregivers and families and leading to a high social care burden (18, 19). Hospital Anxiety and Depression Scale scores in Gallop et al. (2010) suggested that some parents had substantial anxiety (20).

Summary	
	Given the heterogeneous nature of the LGS patient population, high degree of treatment resistance, seizure- and non-seizure burden, and treatment effects waning over time, there is a high unmet need for additional treatment options with novel mechanisms of action for LGS patients who previously tried and failed multiple other ASMs (21, 22).
Type of evidence for the clinical evaluation	Head-to-head as the phase 3 ZX008-1601 study comparing fenfluramine (FFA) as add-on treatment to ASMs vs SoC (i.e., placebo as add-on treatment to ASMs) provides the most relevant comparison and evidence. The ZX008-1601 study comprises Part 1 (a double-blinded randomised study of fixed dose of FFA+ASMs vs SoC) and Part 2 (an open-label, flexible-dose extension study of FFA+ASMs). The Part 2 dosing followed the international and national recommendation to use the lowest effective dose that was tolerated and demonstrated equal effect in the low dose group as in the high dose group.
Most important efficacy endpoints (Difference/gain compared to comparator)	Efficacy was evaluated in three studies based on the same cohort. In the pivotal phase 3 RCT study (ZX008-1601 Part 1), the primary endpoint was median percentage change from baseline (CFB) in drop seizure frequency (DSF) during titration and maintenance (T+M) and maintenance (M) only in FFA 0.7 mg/kg/day group vs the placebo group. **During M, the FFA 0.7 mg/kg/day group had a median CFB of -27.2%** compared with a median CFB of -7.3% in the placebo (SoC) group (p=0.0018). Reduction in GTC during the M-phase was a second endpoint and **the FFA 0.7 mg/kg/day group had a median GTC reduction of -52.6%**, compared with an increase in frequency of GTCs of +2.6% in the placebo (SoC) group (P=0.001). The ZX008-1601 Part 2 study is an 12-15 months open-label extension (OLE) with flexible doses (mean dose 0.413 mg/kg/day). **30.46% (p<0.0001) median DSF reduction during the whole study period was demonstrated with an 50.5% (p<0.0001) reduction after 13-15-months**. The seizure reduction was dose-independent and showed continuously improved effect through the study period. [redacted]
Most important serious adverse events for the intervention and comparator	In ZX008-1601 Part 1, one SUDEP and one case of somnolence occurred in the FFA 0.7 mg/kg/day group. The SUDEP reported was evaluated and judged to be unrelated to treatment. In ZX008-1601 Part 2, blood prolactin increased was identified as an AE of special interest and was reported as a serious TEAE for one subject.
Impact on health-related quality of life	Clinical documentation: Numerical improvement for the 0.7mg group (QOLCE instrument) Health economic model: Intervention better than comparator (EQ-5D instrument)
Type of economic analysis that is submitted	Type of analysis: Cost-utility analysis Type of model: Markov model

Summary	
Data sources used to model the clinical effects	Study ZX008-1601
Data sources used to model the health-related quality of life	HRQoL based on EQ-5D by Verdian et al. (23)
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Patient weight, Relative efficacy of fenfluramine, HRQoL estimates.
Number of eligible patients in Denmark	Incidence: 28 yearly patients Prevalence: 176 patients (2023 data) Eligible in Year 1 (in case of positive recommendation): 12 patients
Budget impact (in year 5)	[redacted]

Abbreviations: AE = adverse event; ASM = anti-seizure medication; CFB = change from baseline; DMC = Danish Medicines Council; DSF = drop seizure frequency; ESC = Epilepsy Study Consortium; FFA = fenfluramine; GTC = generalised tonic-clonic; LGS = Lennox-Gastaut syndrome; M = maintenance; NMA = network meta-analysis; OLE = open-label extension; SoC = standard of care; SUDEP = sudden unexpected death in epilepsy; TEAE = treatment-emergent adverse event; T+M = titration and maintenance.
Sources: European Medicines Agency, 2024 (1); Zogenix International Limited, 2021 (24); Knupp et al. 2022 (9); Zogenix International Limited, 2021 (25).

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

LGS is a rare and severe chronic developmental encephalopathy with onset in early childhood. The condition is considered an encephalopathy (brain disease), where the main symptoms are severe epileptic seizures, intellectual impairment, a specific pattern on the electroencephalogram examination, delayed development, and loss of skills (15, 26).

LGS is a syndrome with many different aetiologies, including cortical malformations, pre-, peri-, or postnatal brain injuries (hypoxic ischemia, infections, trauma), brain tumours, and genetic conditions (27). Approximately 70% of LGS cases are caused by congenital brain malformations (16). For 25-40% of the patients there will be no identified underlying cause (27). Some early-onset epilepsy syndromes, such as West syndrome, can evolve into LGS over time. No monogenetic causes have been identified for LGS as a syndrome, but mutations in genes that lead to other syndromes (e.g., Dravet syndrome) have been detected in adults with LGS (16).

3.1.2 Clinical presentation and symptoms of the condition

Seizures onset between one and seven years of age, with a peak age of onset at three to five years (15, 26). LGS is characterised by a triad of symptoms: multiple drug resistant seizure types, slow spike-and-wave electroencephalogram pattern, and varying degrees of mental deterioration in the majority of cases (10). LGS patients will have multiple daily attacks of various seizure types. The types, frequency, and severity of seizures experienced by patients are subject to intra- and interpatient variability. Most patients develop three to five seizure types, which wax and wane as their disease progresses (9).

The most frequent type of seizures for LGS patients are drop seizures (6-8). Drop seizures result in a loss of muscle tone or stiffening of muscles, where patients suddenly and unpredictably drop to the ground either falling on their face or on the back-head without being able to protect themselves (11, 13). Drop seizures include GTC, secondary GTC, tonic, atonic, and tonic-atonic seizures as described by the ESC (9, 10). These seizures are highly frequent (sometimes more than a hundred times per day), dangerous, and debilitating (9, 12). Tonic and atonic seizures, atypical absences, myoclonus, and non-convulsive status are common among LGS patients. All types of seizures can turn into status epilepticus (14, 15).

Severe cognitive deficits are nearly universal in LGS patients, with 90% of children being moderately to severely intellectually impaired (19). Behavioural disorders such as hyperactivity, aggressiveness, and autistic traits are present in approximately 50% of patients with LGS, making the condition more difficult to manage (13). Patients with LGS also suffer from sleep disturbances/deprivation, hyperactivity, and aggression (28).

3.1.3 Prognosis with current treatments

As LGS is a rare disease, limited data are available concerning the prognosis for Danish patients with LGS. Therefore, the following information is based on international literature in addition to information from the Danish Epilepsy Association (16).

Drop seizures are physically demanding as they may result in falls, serious debilitating injury, subsequent pain, hospitalisation, or even death (11, 13). Focal seizures and GTC seizures, although not the most characteristic seizure type of LGS, can be serious and result in pre-mature death either through status epilepticus or SUDEP (14, 15). Up to 90% continue to experience seizures in adulthood (16).

LGS has a high mortality (around 5%) (16). Based on data from the Swedish National Board of Health and Welfare, the median age of death among LGS patients was 46.5 years (29). Patients with LGS are at increased risk of SUDEP, which is highly correlated with the experience of multiple GTC seizures (17). Patients with any number (one or more) of GTCs in the previous year are 27 times more likely to die suddenly compared with people with epilepsy who have not experienced any GTC seizures (17). The predominant risk factor for SUDEP is GTC seizures, with risk increasing from 22% to 32% according to the number of GTC seizures (17). This highlights the importance of controlling the numbers of seizures, particularly GTC, patients experience. SUDEP is the most frequent cause of death among patients with LGS (30).

3.1.4 Patients' functioning and health-related quality of life

Drop seizures are accompanied by a high likelihood of accidental injury including concussions, jaw, limb, or tooth fractures (31, 32). Patients are often required to use protective equipment (e.g., wheelchair, helmet, faceguard) to minimise the physical effects of the seizures (13). This can further impact their ability to perform activities of daily living and their quality of life. In a long-term prognosis study, which included 68 adult patients with LGS, 25% of LGS patients were non-ambulatory, and approximately 60% were unable to complete independent daily living skills such as eating, bathing, toileting, and functional mobility (20). Long-term outcomes for patients with LGS are typically very poor. Most patients require homecare or institutionalisation (13, 33).

The effects of LGS extend beyond the patient and may cause a profound impact on caregivers and families and leading to a high social care burden (18, 19). Hospital Anxiety and Depression Scale scores in Gallop et al. (2010) suggested that some parents had substantial anxiety. Patients' families have reported that their most significant concerns are fear of dying and the unpredictability of seizures, side effects, and social isolation (20).

Prioritising the control and severity of seizures is imperative for the wellbeing of patients with LGS and their caregivers. Uncontrolled LGS can lead to a significantly impaired quality of life, a high mortality risk, and distress for patients, their caregivers, and families (20).

3.2 Patient population

The Danish population relevant for this application includes patients 2 years of age and older, who are treated with ASMs for seizures associated with LGS.

Estimates of the incidence and prevalence of LGS in 2020-2024 are provided in Table 1. According to the Danish Epilepsy Association, there are 0.2-2.8 incident LGS cases per 10,000 children per year (16). This information (using the average of 1.5 incident LGS cases per 10,000 children) and information on the mid-year population size of Danish children 3-5 years of age in 2020-2024 are used to estimate the incidence of LGS in Denmark (34). The number of children of 3-5 years of age were chosen, as the peak age for onset of seizures is 3-5 years (15, 16, 26). This results in a derived annual incidence of 27-28 patients.

Danish registry data for the number of patients with ICD-10 diagnosis code G40.4E was applied to estimate the prevalence of LGS. In 2023 the prevalence was 176 and in 2024 the prevalence was 87. However, data from 2024 was obtained from 1st of January 2024 through 31st of October 2024 (35). In addition, the 2024-prevalence might be affected by delays in reporting from the hospitals, recording practices, e.g., patients do not receive their diagnosis timely, or for other reasons. Therefore, the 2023-prevalence and the mid-year population size were used to calculate the proportion of patients with LGS in Denmark, which was applied to the mid-year population size in 2021, 2022, and 2023, respectively, to estimate the prevalence in these years (34, 35). This corresponds to a prevalence of approximately 2.96 per 100,000 people.

LGS prevalence is difficult to track, due to its heterogeneous character and diagnostic challenges. Therefore, a global prevalence per year is not provided in Table 1. Instead, prevalence values in different countries are provided. Recent epidemiology studies from the United Kingdom (UK) and Germany provide prevalence rates between 2.89-6.5 per 100,000 inhabitants, while in the United States (US) the LGS prevalence is estimated to be 8-10 per 100,000 inhabitants, based on real-world evidenced (21, 36, 37). It is estimated that LGS affects 103,000 people in the EU (38).

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	27	28	28	28	28
Prevalence in Denmark‡	172	173	175	176	87Ω
Global prevalence *	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A = not applicable.

Notes: * For small patient groups, also describe the worldwide prevalence. ‡ 40 patients are currently linked to the Danish epilepsy specialist hospital, Filadelfia, treating patients that are not well managed (39). Ω The prevalence was retrieved from the Danish registries on the 31st of October 2024 and thus does not cover a full year.
Sources: Epilepsiforeningen (16); Danmarks Statistik, 2024 (34); UCB, 2024 (35).

The patient population relevant for this application corresponds to LGS patients.

In case of a positive recommendation, the base-case budget impact analysis will consider 6.8% of patients in year 1 (12 out of 176 from the complete 2023 estimates). This share corresponds to 25% of LGS patients currently eligible for treatment with fenfluramine at the Filadelfia hospital 12 out of 40). Uptake numbers are expected to increase to up to 50% of LGS Danish patients in year 5 (Table 2). As a comparison, the current uptake of CBD in LGS patients in Denmark is 14% (35).

More details for the budget impact are available in section 13.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Expected uptake	6.8%[a]	10%	20%	30%	50%
Number of patients in Denmark who are eligible for treatment in the coming years (not adjusted for market share)	176[b]	204[c]	232[c]	260[c]	288[c]

Notes:
[a]Based on internal UCB estimates and data from the Filadelfia hospital
[b]Estimates on prevalent patients are based on data from 2023 (since 2024 data is incomplete).
[c]Assuming a fixed incidence of 28 new patients each year.

3.3 Current treatment options

With the current treatment options available in Denmark, the mortality of LGS is high (around 5%) (16). According to the Danish Epilepsy Association treatment guideline from 2022, the first choice of LGS treatment is valproate and the first add-on treatment choice is lamotrigine. Among fertile females, valproate should only be administered, if it is not possible to administer another treatment. Lamotrigine is a possible treatment alternative to valproate in fertile females. The second choice for add-on treatment is rufinamide. Hereafter, topiramate, clobazam, felbamate, and “other treatments” can be administered. However, felbamate can only be used with an individual compassionate use permit and following consultation with a specialised neuropediatric department. Furthermore, felbamate is not available in Denmark (5) and therefore, it is not included as comparator in this application (see section 3.5). Finally, in the treatment guideline it is specified that cannabidiol (CBD) can be used after consultation with a specialised neuropediatric department. The treatment guideline also describes that non-pharmacological treatments can be used including ketogenic diet, vagus nerve stimulation, resective surgery in selective cases, or callosotomy in case of drop attacks (40).

In the Danish Epilepsy Association treatment guideline, “other treatments” are not specified, except for the mention of cannabidiol. However, sundhed.dk lists treatment options for the treatment of LGS and myoclonic/atonic epilepsy, which includes levetiracetam (41).

3.4 The intervention

Table 3 Overview of fenfluramine

Overview of fenfluramine	
Indication relevant for the assessment	Fintepla is indicated for the treatment of seizures associated with LGS as an add-on therapy to other ASMs for patients 2 years of age and older.
Advanced Therapy Medicinal Products (ATMP)	Fenfluramine is not an ATMP.
Method of administration	Fenfluramine is administered as an oral solution.
Dosing	The starting dose (first week) is 0.1 mg/kg taken twice daily (0.2 mg/kg/day). Day 7 (second week)*, the dose can if additional seizure control is needed be increased to 0.2 mg/kg twice daily (0.4 mg/kg/day). At day 14 the dose can further be increased if additional seizure control is needed to a maximum dose of 0.35 mg/kg twice daily (0.7 mg/kg/day). The maximum dose is 26 mg (13 mg twice daily i.e., 6.0 ml twice daily). *The dosage should be increased if additional seizure control is required to the lowest efficacious dose providing seizure control that is tolerated. For patients requiring more rapid titration, the dose may be increased every 4 days instead of every 7th day.
Dosing in the health economic model (including relative dose intensity)	Maintenance period: 0.7mg/kg/day (month 0.5 to month 3.5) Open label extension period: 0.413mg/kg/day (month 3.5+)
Should the medicine be administered with other medicines?	Yes, fenfluramine is an add-on therapy to other ASMs.
Treatment duration / criteria for end of treatment	If seizure frequency is either increased during treatment or do not reach sufficient reduction, the dose of fenfluramine and/or concomitant ASMs should be evaluated and discontinuation of fenfluramine be done if the benefit-risk is negative. Discontinue therapy in patients with acute decreases in visual acuity. Consider discontinuation if there is ocular pain and another cause cannot be determined.

Overview of fenfluramine	
	When discontinuing treatment, the dose should be decreased gradually. Abrupt discontinuation should be avoided, when possible, to minimise the risk of increased seizure frequency and status epilepticus. A final echocardiogram (ECHO) should be conducted 3-6 months after the last dose of treatment with fenfluramine.
Necessary monitoring, both during administration and during the treatment period	Fenfluramine should be initiated and supervised by physicians with experience in the treatment of epilepsy. Monitoring with echocardiography should take place every 6 months during the first 2 years, and then once a year thereafter.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Before initiating treatment, an echocardiogram should be performed to determine the baseline value and rule out any pre-existing valvular disease or pulmonary hypertension. The patient's weight should be monitored.
Package size(s)	Fintepla (fenfluramine) 2.2 mg/ml, 120 ml oral solution Fintepla (fenfluramine) 2.2 mg/ml, 360 ml oral solution

Abbreviations: ASM = anti-seizure medication; ATMP = Advanced Therapy Medicinal Products; ECHO = echocardiogram; LGS = Lennox-Gastaut syndrome.
Sources: European Medicines Agency, 2024 (1); medicin.dk – professionel, 2024 (42); Danish Medicines Agency, 2024 (5).

3.4.1 Treatment with fenfluramine

Fenfluramine is a novel treatment with a dual mechanism of action that targets both seizure and non-seizure pathways (43). Fenfluramine is a serotonin releasing agent and thereby stimulates multiple 5-HT receptor sub-types through the released serotonin. FFA also reduces seizures by acting directly as an agonist at specific serotonin receptors in the brain, including the 5-HT1D, 5-HT2A, and 5-HT2C receptors. Furthermore, FFA also acts on the sigma-1 receptor that is associated with improved learning capabilities. The precise mode of action of FFA in Dravet syndrome and LGS is not known (1).

3.4.2 The intervention in relation to Danish clinical practice

FFA is expected to be used in line with topiramate, clobazam, and “other treatments” including CBDas described in section 0. Therefore, the current clinical practice will be altered by adding an additional treatment option.

3.5 Choice of comparator(s)

Based on insights from clinical practice as well as inputs from the dialogue meeting with the DMC, SoC is deemed the most relevant comparator. This includes valproate, lamotrigine, rufinamide, topiramate, clobazam, levetiracetam, and cannabidiol.

Table 4 Overview of valproate

Overview of valproate	
Generic name	Valproate
ATC code	N03AG01
Mechanism of action	Valproate exerts its antiepileptic effects through two primary mechanisms of action. The first involves the inhibition of gamma-aminobutyric acid (GABA) breakdown. During an epileptic seizure, certain neurons become overstimulated, leading to excessive neural activity. By inhibiting the degradation of GABA, valproate increases its concentration in the brain, thereby enhancing its inhibitory effect. This results in the suppression of hyperactive neuronal activity and a subsequent reduction in the frequency and severity of seizures. The second mechanism is the inhibition of sodium (Na^+) and calcium (Ca^{2+}) ion channels. By blocking these channels, valproate limits the excessive firing of overstimulated neurons, thereby stabilising neuronal excitability.
Method of administration	Either oral or intravenous administration. Oral forms are typically given once or twice daily. For patients unable to take oral medication, intravenous administration can be used to ensure appropriate daily dosing.
Dosing	The dosing of valproate should aim to use the lowest effective dose that achieves optimal seizure control. **Dosing guidelines** Tablets: **Adults** • Initial dose: 600 mg once daily. • Maintenance dose: Typically, 600-1200 mg/day, divided into 1-2 doses. **Children** • Maintenance dose: Typically, 20-30 mg/kg body weight/day, divided into 1-2 doses. IV: • **Adults**: Individualised dosing, typically 20 mg/kg body weight/day. • **Adolescents (14–17 years)**: Individualised dosing, typically 25 mg/kg body weight/day. • **Children**: Individualised dosing, typically 30 mg/kg body weight/day. **Maximum dose** For adults, the maximum recommended dose is 2400 mg/day. Doses exceeding this are rarely necessary. **Special considerations** For small children, precise dosing can be achieved using an oral solution. In infants under 2 months, the elimination half-life of valproate can be up to 67 hours, requiring careful consideration when increasing doses during maintenance treatment.
Dosing in the health economic model (including relative dose intensity)	Age<5: 20mg/kg/day Age>5: 25mg/kg/day
Should the medicine be administered with other medicines?	N/A

Overview of valproate	
Treatment duration/ criteria for end of treatment	Treatment with valproate is usually long-term and continues unless toxicity occurs, or effectiveness is lost. Treatment should be stopped immediately if any of the following occur: unexplained general deterioration, clinical signs of liver or pancreatic damage, coagulation disorders, significant worsening of coagulation parameters, or an increase in alanine aminotransferase (ALAT)/ aspartate aminotransferase (ASAT) levels by more than 2-3 times, even without symptoms. Moderate increases (1-1.5 times) in ALAT/ASAT with acute infection and fever, or dose-independent adverse effects, also require cessation. Additionally, severe liver toxicity or confirmed pancreatitis necessitates immediate discontinuation, as both conditions can be life-threatening.
Need for diagnostics or other tests (i.e. companion diagnostics)	Before initiating treatment with valproate, specific diagnostic tests must be performed to establish baseline health and monitor for potential adverse effects. These include assessments of haemoglobin, leukocytes, platelets, P-ASAT/ALAT (liver enzymes), alkaline phosphatase, P-bilirubin, P-coagulation factors, P-amylase, and P-creatinine. These tests are essential to evaluate liver, kidney, pancreatic, and haematological function. The tests should be repeated at regular intervals during the first six months of treatment, for example, after 1, 3, and 6 months, to monitor for early signs of toxicity or dysfunction.
Package size(s)	**Enteric-coated tablets** • 100 mg, 100 tablets • 300 mg, 100 tablets • 500 mg, 100 tablets • 600 mg, 100 tablets **Prolonged-release tablets** • 300 mg, 100 tablets • 500 mg, 100 tablets • 500 mg, 120 tablets **Hard prolonged-release capsules** • 150 mg, 100 capsules • 300 mg, 100 capsules **Prolonged-release granules** • 500 mg, 100 sachets • 1000 mg, 100 sachets **Oral solution** • 60 mg/ml, 200 ml solution • 60 mg/ml, 250 ml solution • 200 mg/ml, 100 ml solution **Injection and infusion solution:** • 100 mg/ml, 5 x 3 ml vials • 100 mg/ml, 5 x 10 ml vials

Abbreviations: ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; GABA = gamma-aminobutyric acid; N/A = not applicable; P = plasma.
Source: Danish Medicines Agency, 2022 (44); Danish Medicines Agency, 2023 (45); Danish Medicines Agency, 2024 (5, 46-49).

Table 5 Overview of lamotrigine

Overview of lamotrigine	
Generic name	Lamotrigine
ATC code	N03AX09
Mechanism of action	Lamotrigine acts as a use- and voltage-dependent blocker of voltage-sensitive sodium channels. By blocking these channels, it prevents sustained and repetitive neuronal firing, a process central to the development of epileptic seizures. Additionally, lamotrigine inhibits the release of glutamate, an excitatory neurotransmitter that plays a key role in seizure generation and propagation.
Method of administration	Oral administration.
Dosing	The dosing of lamotrigine should aim to use the lowest effective dose that achieves optimal seizure control. Doses are typically given once or twice daily. **Adults and adolescents (13 years and older) with valproate** • Week 1+2: 12.5 mg once daily (administered as 25 mg every other day) • Week 3+4: 25 mg once daily • Maintenance dose: 100-200 mg daily, administered once daily or divided into two doses **Children (2–12 years) with valproate** • Week 1+2: 0.15 mg/kg daily • Week 3+4: 0.3 mg/kg daily • Maintenance dose: 1-15 mg/kg/day, with a maximum dose of 200 mg daily Doses exceeding the maximum recommended dose are rarely necessary. **Important notes** The initial dosing and titration schedule must be strictly followed to reduce the risk of serious skin reactions. For children under 2 years, lamotrigine is not recommended due to limited data. Doses should be adjusted based on age, weight, and clinical response.
Dosing in the health economic model (including relative dose intensity)	Age<11: 3mg/kg/day Age>11: 150mg/day
Should the medicine be administered with other medicines?	Lamotrigine is administered as an adjunctive therapy with valproate for seizures associated with LGS.
Treatment duration/ criteria for end of treatment	Treatment with lamotrigine is generally long-term to maintain seizure control and should be regularly evaluated by a physician. Discontinuation may be considered in cases of toxicity, loss of clinical effectiveness, or if the patient has been seizure-free for a significant period. In such cases, gradual dose reduction under medical supervision is recommended.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A

Overview of lamotrigine	
Package size(s)	**Tablets** • 25 mg, in packages of: 50, 56, 60, 98, or 100 tablets • 50 mg, in packages of: 56 or 100 tablets • 100 mg, in packages of: 56, 60, 98, 100, or 119 tablets • 200 mg, in packages of: 56, 60, 98, or 100 tablets **Dispersible tablets** • 2 mg, 30 tablets • 5 mg, 60 tablets • 25 mg, in packages of: 50, or 60 tablets • 50 mg, in packages of: 50, 56, 60, or 100 tablets • 100 mg, in packages of: 50, 56, 60, 100, or 112 tablets • 200 mg, in packages of: 50, 56, 60, 100, or 112 tablets

Abbreviations: LGS = lennox-gastaut syndrome; N/A = not applicable.
Source: Danish Medicines Agency, 2024 (5, 50, 51).

Table 6 Overview of rufinamide

Overview of rufinamide	
Generic name	Rufinamide
ATC code	N03AF03
Mechanism of action	Rufinamide modulates the activity of sodium channels, prolonging their inactive state. Rufinamide is active in a range of animal models of epilepsy.
Method of administration	Oral use taken with water and food.

Overview of rufinamide	
Dosing	The dosing of rufinamide should aim to use the lowest effective dose that achieves optimal seizure control. Generally, the daily doses provided below must be divided into two halves, taken morning and evening about 12 hours apart. **Children from 1 year to <4 years of age with valproate** • Initial dose: 10 mg/kg/day (0.25 ml/kg/day) • Based on clinical response and tolerability, the dose may be increased by up to 10 mg/kg/day (0.25 ml/kg/day) every third day to a target dose of 30 mg/kg/day (0.75 ml/kg/day) • The maximum recommended dose is 30 mg/kg/day (0.75 ml/kg/day) • If the recommended calculated dose of rufinamide is not achievable, the dose should be rounded to the nearest 0.5 ml of rufinamide **Children ≥4 years of age and <30 kg with valproate** • Initial dose: 200 mg/day (5 ml dosing suspension) • After a minimum of 2 days, the dose may be increased by 200 mg/day increments to a maximum recommended dose of 600 mg/day (15 ml/day), depending on clinical response and tolerability **Adults, adolescents, and children ≥4 years of age and ≥30 kg with valproate** • Initial dose: 400 mg/day (10 ml dosing suspension) • Based on clinical response and tolerability, the dose may be increased by 400 mg/day increments every other day The maximum recommended dose depends on weight: • 30–50 kg: 1,200 mg/day (30 ml/day) • 50–70 kg: 1,600 mg/day (40 ml/day) • ≥70 kg: 2,200 mg/day (55 ml/day) Doses exceeding the maximum recommended dose are rarely necessary. **Special considerations** Rufinamide should be withdrawn gradually to reduce the possibility of seizures on withdrawal.
Dosing in the health economic model (including relative dose intensity)	Age<6: 37.5mg/kg/day Age>6: 400gm/day
Should the medicine be administered with other medicines?	Rufinamide is used with other medicines to treat seizures associated with LGS, such as carbamazepine, lamotrigine, phenobarbital, topiramate, phenytoin or, valproate steady state concentrations.
Treatment duration/ criteria for end of treatment	Treatment with rufinamide is usually long-term and continues unless toxicity occurs, or effectiveness is lost. The medicine should not be used in patients who have severe problems with their liver.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A

Overview of rufinamide	
Package size(s)	**Tablets** • 100 mg, 10 tablets • 200 mg, 60 tablets • 400 mg, 100 tablets **Oral suspension** • 40 mg/ml, 460 ml solution

Abreviations: LGS = lennox-gastaut syndrome.
Source: European Medicines Agency, 2023 (52).

Table 7 Overview of topiramate

Overview of topiramate	
Generic name	Topiramate
ATC code	N03AX11
Mechanism of action	Topiramate exerts its antiepileptic effects through several mechanisms that help reduce neuronal excitability and prevent seizures. The first mechanism involves the blockade of sodium (Na^+) channels, preventing sustained neuronal firing and stabilising neuronal activity, which reduces seizure occurrence. The second mechanism is the enhancement of GABA activity. Topiramate increases the activation of GABAA receptors, strengthening GABA's inhibitory effects on neurons, which suppresses overactive neuronal firing. Additionally, topiramate modulates glutamate receptors by antagonising kainite receptors, reducing excitatory neurotransmission and further stabilising neuronal activity.
Method of administration	Oral administration.
Dosing	The dosing of topiramate should aim to use the lowest effective dose that achieves optimal seizure control. **Adults - adjunctive therapy** • Initial dose: 25 mg once daily in the evening for the first week • Titration: Increase by 25-50 mg every 2 weeks, adjusting based on clinical response • Maintenance dose: 200-400 mg daily, divided into two doses. **Children (2 years and older) - adjunctive therapy** • Initial dose: 1-3 mg/kg daily, taken at night for the first week • Titration: Increase by 1-3 mg /kg every 1-2 weeks • Maintenance dose: 5-9 mg/kg/day, divided into two doses Doses exceeding the maximum dose are rarely necessary. **Important note** It is important to note that renal impairment may require dose adjustments, particularly for patients with reduced kidney function (creatinine clearance ≤ 70 ml/min). For patients with liver impairment, topiramate should be used with caution, particularly in those with moderate to severe liver dysfunction.
Dosing in the health economic model (including relative dose intensity)	Age<18: 7mg/kg/day Age>18: 300mg/day

Overview of topiramate	
Should the medicine be administered with other medicines?	Topiramate is indicated as adjunctive therapy for children (from 2 years), adolescents, and adults with partial epileptic seizures, with or without secondary generalised seizures, primary generalised tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome.
Treatment duration/ criteria for end of treatment	Treatment with topiramate is generally long-term to maintain seizure control, but it should be regularly evaluated by a healthcare provider. Discontinuation may be considered if significant side effects occur, such as severe skin reactions or other adverse effects. If topiramate no longer effectively controls seizures, a change in therapy may be required. Additionally, if the patient has been seizure-free for a significant period, a gradual dose reduction under medical supervision can be considered to assess if discontinuation is possible. Regular monitoring is essential to determine whether treatment should continue.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	**Film-coated tablets** • 25 mg, 60 tablets • 50 mg, 60 tablets • 100 mg, 60 tablets • 200 mg, 60 tablets **Hard capsules** • 15 mg, 60 tablets • 25 mg, 60 tablets

Abbreviations: GABA = gamma-aminobutyric acid; N/A = not applicable.
Source: Danish Medicines Agency, 2024 (5, 53, 54).

Table 8 Overview of clobazam

Overview of clobazam	
Generic name	Clobazam
ATC code	N05BA09
Mechanism of action	Clobazam works by enhancing the effect of GABA through binding to benzodiazepine receptors on the GABA-A complex. This reduces neuronal excitability, suppressing excessive neural activity to prevent seizures, and reduce anxiety. Its active metabolite, N-desmethylclobazam, supports its prolonged anticonvulsant effect with less sedation than other benzodiazepines.
Method of administration	Oral administration.

Overview of clobazam	
Dosing	The dosing of clobazam should aim to use the lowest effective dose that achieves optimal seizure control. **Adults and children over 15 years:** • 10-80 mg daily, divided into 1-3 doses, with typical doses ranging from 10-40 mg daily **Paediatrics over 6 years:** • Treatment should start with 5 mg daily. Maintenance doses are typically 0.3-1 mg/kg body weight per day, adjusted gradually under careful supervision For both adults and paediatric patients' doses distributed throughout the day, the largest dose should be taken in the evening. Doses exceeding the maximum dose are rarely necessary.
Dosing in the health economic model (including relative dose intensity)	Age <18: 0.65mg/kg/day Age>18: 25mg/day
Should the medicine be administered with other medicines?	Clobazam is used in combination with other antiepileptic drugs for epilepsy treatment. However, careful dose adjustments may be needed due to potential interactions. For example, co-administration with valproate can increase its plasma levels, while phenytoin may reduce clobazam levels or increase phenytoin toxicity. Stiripentol and carbamazepine can alter clobazam metabolism.
Treatment duration/ criteria for end of treatment	The treatment duration with clobazam should be as short as possible, typically not exceeding 8-12 weeks, including the tapering period. Treatment may be extended in exceptional cases but requires regular re-evaluation by a specialist to ensure its continued necessity. Patients should be reassessed after no more than 4 weeks, with periodic evaluations to determine whether ongoing treatment is required, particularly if symptoms have resolved. When ending treatment, it is essential to taper the dose gradually under medical supervision to avoid withdrawal symptoms. Abrupt discontinuation is strongly discouraged, especially following long-term use, as this can lead to significant adverse effects. Treatment should cease when symptoms are well-controlled, and the risks of continued use, such as dependence or tolerance, outweigh the benefits.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	**Tablets** • 10 mg, 40 tablets • 10 mg, 45 tablets • 10 mg, 50 tablets

Abbreviations: GABA = gamma-aminobutyric acid; N/A = not applicable.
Source: Danish Medicines Agency, 2024 (5, 55).

Table 9 Overview of cannabidiol

Overview of cannabidiol	
Generic name	Cannabidiol
ATC code	N03AX24

Overview of cannabidiol	
Mechanism of action	The precise mechanisms by which CBD exerts its anticonvulsant effects in humans are unknown. CBD reduces neuronal hyper-excitability through modulation of intracellular calcium via G protein-coupled receptor 55 and transient receptor potential vanilloid 1 channels, as well as modulation of adenosine-mediated signalling through inhibition of adenosine cellular uptake via the equilibrative nucleoside transporter 1.
Method of administration	Oral administration.
Dosing	The dosing of CBD should aim to use the lowest effective dose that achieves optimal seizure control. CBD is indicated for use as adjunctive therapy of seizures associated with LGS or Dravet syndrome, in conjunction with clobazam, for patients 2 years of age and older. **LGS and Dravet syndrome, adults and paediatric >2 years:** • Starting dose: 2.5 mg/kg twice daily (5 mg/kg/day) for the first week • Maintenance dose: 5 mg/kg twice daily (10 mg/kg/day) after the first week • Further titration: Weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), up to a maximum of 10 mg/kg twice daily (20 mg/kg/day), based on clinical response and tolerability. Doses exceeding the maximum recommended dose are rarely necessary.
Dosing in the health economic model (including relative dose intensity)	20 mg/kg/day
Should the medicine be administered with other medicines?	Within the LGS indication, CBD should be administered with clobazam.
Treatment duration/ criteria for end of treatment	The treatment duration for CBD depends on the patient's clinical response and seizure control. It is typically used as long-term therapy for epilepsy but requires regular reassessment by a healthcare professional. If treatment is discontinued, it should be tapered gradually to minimise the risk of withdrawal seizures. The decision to stop treatment may be based on sustained seizure freedom, intolerable side effects, or a change in treatment strategy.
Need for diagnostics or other tests (i.e. companion diagnostics)	CBD treatment may necessitate liver function tests (ALAT, ASAT, and bilirubin) due to its potential to cause liver-related adverse effects. Monitoring is particularly important at the initiation of therapy and when co-administered with valproate, to detect and manage any hepatic complications promptly, ensuring the safe administration of the medication.
Package size(s)	**Oral solution** • 100 mg/ml, 100 ml

Abbreviations: ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; CBD = cannabidiol; GABA = gamma aminobutyric acid; LGS = lennox-gastaut syndrome.
Source: Danish Medicines Agency, 2024 (5); European Medicines Agency, 2024 (56).

Table 10 Overview of levetiracetam

Overview of levetiracetam	
Generic name	Levetiracetam
ATC code	N03AX14

Overview of levetiracetam	
Mechanism of action	The mechanism of action of levetiracetam still remains to be fully elucidated. *In vitro* studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. Furthermore, levetiracetam has been shown in *in vitro* studies to bind to the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogues show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to levetiracetam's antiepileptic mechanism of action.
Method of administration	Administered orally as tablets or as an oral solution. The oral solution is particularly suitable for patients who cannot swallow tablets, require doses below 250 mg, or need precise dosing adjustments. Additionally, levetiracetam is available as an intravenous infusion for patients who cannot temporarily take oral medication. The infusion should be diluted and administered over a 15-minute period.
Dosing	The dosing of levetiracetam should aim to use the lowest effective dose that achieves optimal seizure control. **Oral administration (tablets or solution)** Adults and adolescents (≥12 years, ≥50 kg): • Initial dose: 500 mg twice daily • Maximum dose: Up to 1,500 mg twice daily, adjusted based on clinical response and tolerability Children (6 years and older, <50 kg): • Initial dose: 10 mg/kg twice daily • Maximum dose: Up to 30 mg/kg twice daily Infants and children (1 month to 6 years): • Initial dose: 7 mg/kg twice daily • Maximum dose: Up to 21 mg/kg twice daily Doses exceeding the maximum recommended dose are rarely necessary. **Intravenous administration** The dose is equivalent to the total daily oral dose, divided into two doses, administered as a 15-minute infusion. It serves as an alternative when oral administration is not feasible.
Dosing in the health economic model (including relative dose intensity)	Age<18: 1000mg/day Age>18: 2000mg/day
Should the medicine be administered with other medicines?	Levetiracetam can be administered as adjunctive therapy with other antiepileptic drugs. It has minimal interactions with most antiepileptic drugs, such as valproate, carbamazepine, and phenytoin, and generally does not affect their serum levels. However, caution is advised when combining levetiracetam with medications that impact renal function or when used with enzyme-inducing antiepileptic drugs, which may slightly increase its clearance.

Overview of levetiracetam	
Treatment duration/ criteria for end of treatment	Levetiracetam is typically a long-term treatment, with the duration dependent on the patient's seizure control and clinical response. Regular reassessments by a healthcare provider are necessary to evaluate the need for continued therapy. If treatment is to be discontinued, it should be tapered gradually to minimise the risk of withdrawal seizures. The decision to end treatment may be based on sustained seizure freedom, intolerable side effects, or a planned switch to an alternative therapy, always under medical supervision.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	**Tablets** • 250 mg, 50 tablets • 250 mg, 100 tablets • 500 mg, 100 tablets • 500 mg, 200 tablets • 750 mg, 100 tablets • 1000 mg, 100 tablets • 1000 mg, 200 tablets **Oral solution** • 100 mg/ml, 150 ml + 3 ml solution • 100 mg/ml, 150 ml + 1 ml solution • 100 mg/ml, 300 ml + 5 ml solution **Injection and infusion solution:** • 5 mg/ml, 10 x 100 ml vials • 10 mg/ml, 10 x 100 ml vials • 100 mg/ml, 10 x 5 ml vials

Abbreviations: GABA = gamma-aminobutyric acid; N/A = not applicable.
Source: Danish Medicines Agency, 2023 (57); Danish Medicines Agency, 2024 (5); European Medicines Agency, 2023 (58, 59).

3.6 Cost-effectiveness of the comparator(s)

None of the treatments included in ASMs basket of the 1601 studies (valproate, lamotrigine, rufinamide, topiramate, clobazam, cannabidiol, and levetiracetam) have been evaluated by the DMC. SoC, defined as the ASMs included in the trial plus a share of patients receiving CBD, can reasonably be assumed the most relevant comparator in Denmark. This decision is based on the dialogue with DMC, where it was agreed that the proposed more complete SoC basket (ASMs from Study1601 plus CBD) is used in Danish clinical practice.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In Table 11, efficacy outcome measures relevant for the application are presented. Outcome measures assessing change in drop-seizure frequency (DSF) are included, as drop seizures are extremely debilitating for LGS patients. Reduction in GTC seizures is

presented, as patients with LGS are at increased risk of SUDEP, and the highest risk-factor for SUDEP is demonstrated to be GTC seizures and reduction of GTC seizures has been shown to significantly reduce the risk of SUDEP (17). The Clinical Global Impression - Improvement (CGI-I) scale is included as it permits a global evaluation of the subject's improvement from a specific point in time. In an assessment by the DMC of FFA for Dravet syndrome, the DMC determined that the CGI-I ratings by the investigator and parent/caregiver, respectively, reflect different perceptions and, therefore, included both types of records in their evaluation (60). Therefore, improvement on the CGI-I scale assessed by Investigator and by the parent/caregiver are included in this application.

Table 11 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
CFB in DSF [Included study ZX008-1601 – Part 1 and Part 2]	During M and T+M$^{\Omega}$ During OLE treatment period	Percent CFB in the DSF per 28 days. Seizures that result in drops are GTC, secondarily GTC, tonic, atonic, and tonic/atonic confirmed for each subject as a drop seizure by the ESC.	Parent/caregiver seizure diary record will be used to assess frequency, type, and duration of seizure activity.
Reduction in GTC seizures [Included study ZX008-1601 – Part 1]	During M$^{\Omega}$	Reduction in ESC-confirmed GTC seizures.	Parent/caregiver seizure diary record will be used to assess frequency, type, and duration of seizure activity.
≥50% reduction from baseline in the DSF [Included study ZX008-1601 – Part 1 and Part 2]	During M and T+M$^{\Omega}$ During OLE treatment period	Proportion of subjects who achieved a ≥50% reduction from baseline in the DSF.	Parent/caregiver seizure diary record will be used to assess frequency, type, and duration of seizure activity.
Improvement on the CGI-I scale [Included study ZX008-1601 – Part 1 and Part 2]	End of study (EOS) (Visit 12)$^{\Omega}$ At last OLE assessment$^{\pi}$	Proportion of subjects who achieved clinically meaningful improvement or improvement on the CGI-I scale as assessed by Principal Investigator.	Improvement on the CGI-I scale was assessed by Principal Investigator.
Improvement on the CGI-I scale [Included study ZX008-1601 – Part 1 and Part 2]	EOS (Visit 12)$^{\Omega}$ At last OLE assessment$^{\pi}$	Proportion of subjects who achieved clinically meaningful improvement or improvement on the CGI-I scale as	Improvement on the CGI-I scale was assessed by the parent/caregiver.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		assessed by the parent/care-giver.	

Abbreviations: CFB = change from baseline; DSF = drop seizure frequency; EOS = end of study ESC = Epilepsy Study Consortium; CGI-I = Clinical Global Impression - Improvement; GTC = generalised tonic-clonic; M = maintenance; OLE = open-label extension; T+M = titration and maintenance.
Notes: * Time point for data collection used in analysis (follow up time for time-to-event measures). Ω Part 1 timepoint: 2-week titration period, 12-week maintenance, visit 12 was on Day 99. π The last OLE assessment was the last CGI-I rating available for each subject as of the data cutoff date (19th of October 2020)
Sources: Zogenix International Limited, 2021 (24); ClinicalTrials.gov (61); Zogenix International Limited, 2021 (25).

Efficacy results for the M phase is presented in section 6, while results for the T+M phase are presented in Appendix B. The M phase is in focus, as patients are not on a stable dose in the titration phase, while patients are treated with their randomly assigned stable dose in the M phase. Handling of missing values is described in Appendix B.

Validity of outcomes

Drop seizures including GTC seizures are most reliably identified by caregivers and therefore, DSF is assessed by parent/caregiver in the ZX008-1601 – Part 1 and Part 2 study (24, 25).

The CGI-I is a well-validated, clinician-rated scale commonly used to measure outcomes in central nervous system therapeutic development trials across multiple conditions. The structure of the scale supports reliable and valid adaptation to many different conditions (62). Improvement in CGI-I scale was assessed in ZX008-1601 as follows. The Investigator was asked to indicate the appropriate response that adequately described how the patient's symptoms had improved or worsened relative to baseline. The improvement in the patient's condition is rated on a 7-point scale as follows: 1 very much improved, 2 much improved, 3 minimally improved, 4 no change, 5 minimally worse, 6 much worse, or 7 very much worse. Subjects with a score of ≤2 were defined as showing a clinically meaningful improvement (24, 25).

4. Health economic analysis

A Markov state-transition cohort model was developed in Microsoft Excel® to represent the major characteristics and natural history of LGS.

In line with the clinical outcomes reported in the FFA trials, the model uses 3-month cycles to capture disease progression, clinical pathways, and patient outcomes over the long term. A cohort model approach was selected over an individual patient simulation (IPS) approach due to its simplicity and suitability for limited patient-level data. IPS requires a more complex model structure and extensive data, particularly for efficacy parameters, which were not available.

4.1 Model structure

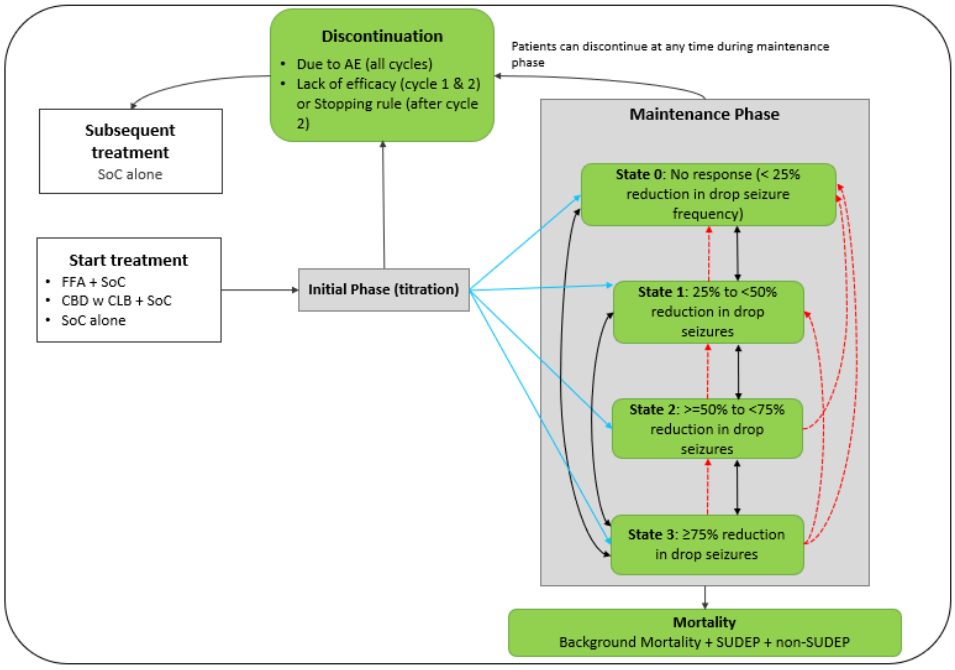
The structure of the model relied on 3-month cycles, deemed appropriate to represent the treatment and disease progression of patients with LGS. The Markov model, developed in Microsoft Excel®, uses percentage change in drop-seizure frequency as the main efficacy driver, which is the primary endpoint in Study ZX008-1601. Health states are defined as four mutually exclusive and clinically established categories of percent change in DSF from baseline. Health states 0 to 3 represent the following:

- State 0: <25% decrease
- State 1: 25% to <50% decrease
- State 2: 50% to <75% decrease
- State 3: >75% decrease.

The model includes two additional states: one for discontinued patients and an absorbing state of death. Discontinuation may occur at titration and at any subsequent cycle within the time horizon. The model includes discontinuation due to AEs, lack of efficacy and a stopping rule. Mortality is also considered, integrating the increased risk of SUDEP which is correlated with the experience of multiple GTC seizures.

The model cohort receives either **FFA** (i.e., FFA + ASMs), or **SoC**. SoC includes a combination of ASMs such as sodium valproate, lamotrigine, clobazam, rufinamide, topiramate, and, based on Danish real-world data, a proportion of patients is also assumed to be receiving CBD.

Figure 1 Model structure



Notes:

Cycle 1 (T+M, Blue arrows): Movement between states according to State occupancies based on RCT ITC efficacy data for FFA and CBD. SoC state occupancies are assumed stable throughout the time horizon.

Cycle 2 to 9 (T+M, Black arrows):

Cycle 2 – cycle 5 (OLE): State occupancies based on Study ZX008-1601 efficacy data for FFA and SoC. SoC state occupancies are assumed stable throughout the time horizon.

Cycle 5- cycle 9: maintained efficacy can be applied, with patients remaining in same state occupancies as in cycle 5. Other options include equal efficacy for FFA or applying average efficacy of cycles 2-5. SoC state occupancies are assumed stable throughout the time horizon.

Cycle 10+ (T+M, Red arrows): From cycle 10 onwards, patients are assumed to remain in the same state occupancies with only competing discontinuation and death affecting patient state.

Treatment waning can also be applied using deteriorating TPs from FFA-OLE study.

4.2 Model features

The model uses a 3-month cycle length, reflecting the reporting intervals of clinical outcomes in the FFA trials. In line with recommended good practice, a standard half-cycle correction was applied to account for the fact that events and transitions can occur at any point during the cycle, rather than strictly at the start or end of each cycle. The titration cycle had a duration of 2 weeks for both FFA and SoC as per the duration in the respective phase 3 trials (9, 63). Titration is also considered in the SoC treatment arm (2 weeks). The titration length is accounted for in cost, life year and QALY gain calculations.

Proportions between health states for FFA and SoC (cycle 1), were informed with relative risks calculated from Study ZX008-1601 data. Transitions between the states for the OLE period (cycles 2-5) were informed by transition probabilities from the FFA OLE study (66).

In the post-OLE period (cycles 6-9), the model offers two different options to estimate the treatment response for FFA, based on different assumptions:

1. The first option, used in the base-case analysis, is to have state occupancies maintained for FFA, assuming efficacy is equal to the latest observed data (cycle 5). This relies on the efficacy data in the OLE studies showing continued efficacy up to 36 months (66, 74).

2. Option two estimates for the FFA treatment arm an average efficacy (average state occupancies) observed in cycles 2-5 which is applied to the post-OLE period (cycles 6-9).

The model assumes that the SoC treatment arm maintains state occupancy distribution in cycle 1, OLE and post-OLE periods, with only mortality and discontinuation affecting the movement of patients.

From cycle 10 onwards, patients are considered to remain in the same health state unless they discontinue treatment or die. Alternatively, a proportion of patients may be assumed to undergo treatment waning, implemented through deteriorating transition probabilities (TPs) estimated from cycles 4 to 5 from FFA OLE study. Deteriorating TPs were estimated from FFA OLE TPs assuming that patients can only remain in the same state or progress to a worse health state. Treatment waning is excluded from base-case analysis due to the lack of evidence (OLE studies, clinical expert interviews conducted in Denmark, Germany, Norway and Sweden) supporting any assumption on treatment waning. Section 8 of this submission presents a detailed description on how efficacy was modelled.

Table 12 Features of the economic model

Model features	Description	Justification
Patient population	Patients with Lennox-Gastaut Syndrome	Application scope
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Up to 86 years	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	3 months	To match the reporting intervals of clinical outcomes in FFA and CBD trials
Half-cycle correction	Yes	
Discount rate	3.5 %	According to DMC guidelines
Intervention	FFA (FFA+ASMs)	

Model features	Description	Justification
Comparator(s)	SoC (CBD+ASMs)	Based on insights from clinical practice as well as inputs from the dialogue meeting with the DMC, SoC is deemed the most relevant comparator
Outcomes	Proportion of patients with 25/50/75% reduction of seizures	To match the reported clinical outcomes in FFA trials.

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5. Overview of literature

5.1 Literature used for the clinical assessment

This application is based on a head-to-head study of FFA+ASMs vs placebo+ASMs as the comparator relevant to Danish clinical practice (see section 3.5). Therefore, no clinical SLR has been conducted for this application

Table 13 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Knupp KG, Scheffer IE, Ceulemans B, et al. Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial. JAMA Neurol. 2022 Jun 1;79(6):554-564 (9) Knupp KG, Scheffer IE, Ceulemans B, et al. Fenfluramine provides clinically meaningful reduction in frequency of drop seizures in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. Epilepsia. 2023 Jan;64(1):139-151 (64) Clinical study report for Part 1 Cohort A (Study ZX008-1601), 2021, Data on file (24) Interim clinical study report for Part 2 Cohort A (Study ZX008-1601), 2021, Data on file (25)	ZX008-1601 – Part 1 and 2	NCT03355209	Start: 27/11/17 Completion: 23/05/24 Data cut-off: 19/10/20Ω Future data cut-offs: N/A	Part 1: FFA+ASMs vs placebo+ASMs for patients 2-35 years with LGS. Part 2: open-label FFA for patients 2 years of age 2-35 years with LGS.

Abbreviations: ASM = anti-seizure medication; FFA = fenfluramine; LGS = Lennox-Gastaut syndrome; N/A = not applicable; SoC = standard of care.
Notes: * If there are several publications connected to a trial, include all publications used. Ω Data cut-off applied in this application for the ZX008-1601 – Part 2 study, as analyses based on the final study have not been completed yet. The ZX008-1601 – Part 1 is finalised, i.e., no data cut-off is applied.

Sources: ClinicalTrial.gov (61).

5.2 Literature used for the assessment of health-related quality of life

Given that no health state utility values were directly derived from the trial data (see section 10), an SLR was conducted to identify HRQoL measures and (dis)utility values relevant for patients with LGS (Full details in Appendix I). After full-text screening, eight unique publications were included in the model. Ultimately, the only study using the EQ-5D instrument was considered in the base-case analysis. The sources for utility scores used to inform the model and the base-case analysis are further discussed in section 10.3.

Table 14 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Eliciting utility scores for health states associated with Lennox-Gastaut syndrome. Value in Health. Verdian et al. (23)	Health state utility values	Section 10.3
Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. Qual Life Res. Matza et al. 2019 study (65)	Disutility value for fatigue	Section 10.3

5.3 Literature used for inputs for the health economic model

Additional inputs used in the health economic model are presented in Table 15. These were based on the results of the SLR presented in Appendix J

Table 15 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: retrospective linkage cohort study. Seizure - European Journal of Epilepsy. Chin et al. (2021) (66)	To calculate HCRU for LGS patients accounting for age distribution.	Targeted literature review	Section 11.4

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Characteristics and acute outcomes of ICU patients with initial presentation of seizure. Seizure. Tobochnik et al. (2015) (67).	To calculate proportion of inpatients requiring ICU visits.	Targeted literature review	Section 11.4
Health care resource utilization in patients with active epilepsy. Epilepsia. Kurth et al. (2010) (68).	To calculate HCRU for LGS patients by type of seizure (GTC and other seizures)	Targeted literature review	Section 11.4
Eliciting utility scores for health states associated with Lennox-Gastaut syndrome. Value in Health. Verdian et al. (23)	Health state utility values	Targeted literature review	Section 10.3
Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. Qual Life Res. Matza et al. 2019 study (65)	Disutility value for fatigue	Targeted literature review	Section 10.3

Abbreviations: LGS = Lennox gastaut syndrome; HCRU = Healthcare resource use; GTC = generalised tonic-clonic

6. Efficacy

6.1 Efficacy of fenfluramine compared to ASMs for patients with LGS

6.1.1 Relevant studies

Table 16 presents studies included in the comparison of FFA and SoC (i.e., placebo + ASMs). Part 1 of ZX008 was finalised and therefore, no early data cut is used for Part 1. The mean treatment duration was 113.41 days (standard deviation [SD]: 13.03) in the ASMs arm, 109.55 days (SD: 23.07) in the FFA 0.2 mg/kg/day arm, and 107.02 days (SD: 23.37) in the FFA 0.7 mg/kg/day arm. In all treatment arms, the median treatment duration was 112 days (24). Part 2 of ZX008 is based on the 19th of October 2020 predefined data cut with a mean treatment duration of 298.9 days (SD: 122.88) and a median treatment duration of 364.0 days (25).

All patients in the Part 1 RCT-study (247), were allowed to enter the Part 2 OLE-study and 241 did receive at least 1-dose in the OLE-study. In this study, flexible dosing was allowed, and all patients regardless previous dose were placed on 0.2 mg/kg/day for 2-week and titrated up to the dose required to provide clinical meaningful seizure reduction without intolerable side-effects. The length of the study was 12-months, but due to the Covid-19 pandemic and lockdown restrictions some patients were followed for up to 15-months. The seizure baseline during Part 1 (the RCT phase) was used to determine efficacy also in this OLE-study. The average dose used in the OLE-study was 0.413 mg/kg/day, and efficacy was determined in three sub-dose groups (<0.4 mg/kg/day; 0.4-<0.6 mg/kg/day and >0.6 mg/kg/day) and for the whole cohort irrespective of dose.

Table 16 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
ZX008-1601 – Part 1 and 2, NCT03355209 (61) Knupp et al. 2022 (9) Knupp et al. 2023 (64)	Part 1: Double-blinded randomised placebo-controlled phase 3 study. Part 2: Open-label, flexible-dose extension study (phase 3).	Part 1: The study consisted of a 4-week Baseline, 2-week Titration Period, 12-week Maintenance, and 2-week Taper or Transition Period. Part 2: Date of first subject enrolled in Part 2 (18 April 2017) to DCO date (19 October 2020).	Patients 2 to 35 years of age at Part 1 baseline with LGS.	**Part 1** FFA 0.2 mg/kg/day or 0.7 mg/kg/day administered orally as add-on to ASMs. **Part 2** Starting dose of 0.2 mg/kg/day FFA administered orally. Dosing was decreased or increased based on effectiveness and tolerability, up to maximum 0.7 mg/kg/day. The maximum dose administered was 26 mg/day.	**Part 1** Matching placebo administered orally and added to ASMs dosed in the same manner as FFA. **Part 2** N/A	**Part 1** Primary endpoint: percent CFB in the DSF in T+M period (FFA 0.7 mg/kg/day vs placebo). Key secondary endpoints: CFB in DSF in T+M period (FFA 0.2 mg/kg/day vs placebo); proportion with a ≥50% reduction from Baseline in the DSF in T+M and M period (FFA 0.7 mg/kg/day and 0.2 mg/kg/day groups independently vs placebo); and proportion with improvement on the CGI-I scale as assessed by Principal Investigator (Visit 12, Day 99) (FFA 0.7 mg/kg/day and 0.2 mg/kg/day independently vs placebo). Additional secondary endpoints were FFA 0.7 mg/kg/day and 0.2 mg/kg/day groups compared independently vs placebo on the following: CFB during T+M in frequency of all seizures that typically result in drops whether ESC-confirmed as drop or not; CFB during T+M in frequency of all countable motor seizures; CFB during T+M in frequency of all countable nonmotor seizures; CFB during T+M in the frequency of all countable seizures; CFB during M in the frequency of seizures that result in drops; CFB during M in the frequency of seizures that typically result in drops; CFB during M in the frequency of all countable motor seizures; CFB during M in the frequency of all countable nonmotor seizures; CFB during M in the frequency of all countable seizures; Proportion of subjects who achieve a worsening from Baseline (i.e., ≤0% reduction), or >0%, ≥25%, ≥50%, ≥75%, or 100% reduction between baseline and T+M, and baseline and M, in seizures that result in drops, seizures that typically result in drops, all countable motor seizures, all countable nonmotor seizures, and all countable seizures; Number of seizure-free days in the Baseline, M, and T+M, defined as 1) days with no seizures that results

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						in drops, and 2) days with no countable motor seizures; The longest interval (days) between seizures that result in drops in T+M comparing the FFA 0.7 mg/kg/day and 0.2 mg/kg/day independently vs placebo; and CGI-I as assessed by the parent/caregiver during T+M. **Part 2** Endpoints evaluated in the interim analyses were: CFB in the DSF during OLE treatment period; Change in frequency of all seizures that typically result in drops between baseline and the OLE whether ESC-confirmed as drop or not; Proportion of subjects who achieved a worsening from baseline (i.e., ≤ 0% reduction), or > 0%, ≥ 25%, ≥ 50%, ≥ 75%, 100% reduction, and "near seizure freedom" (i.e., 0 or 1 seizure) from baseline in frequency of seizures that result in drops, seizures that typically result in drops during OLE; Number of seizure-free days, i.e., days with no seizures that result in drops (OLE); Longest interval between seizures that result in drops (OLE); CGI-I rating, as assessed by the Principal Investigator (OLE); and CGI-I rating, as assessed by the parent/caregiver (OLE). Safety endpoints measured at up to 12 months open-label were: AEs, serious adverse events (SAEs), and adverse events of special interest; Laboratory safety; Vital signs; Body weight and body mass index (BMI); Physical examination; Neurological examination; Behavior Rating Inventory for Executive Function (BRIEF) to measure changes in cognition of the subject; Columbia Suicidality Severity Rating Scale; 12-lead electrocardiogram (ECG); Doppler ECHOs; Chest x-ray; and Electroencephalogram.

Abbreviatons: AE = adverse event; ASM = anti-seizure medication; BMI = body mass index; BRIEF = Behavior Rating Inventory for Executive Function; CFB = change from baseline; CGI-I = Clinical Global Impression - Improvement; DSF = drop seizure frequency; ECG = electrocardiogram; ECHO = echocardiogram; ESC = Epilepsy Study Consortium; LGS = Lennox-Gastaut syndrome; M = maintenance; N/A = not applicable; OLE = Epilepsy Study Consortium; SAE = serious adverse event; T+M = titration and maintenance.
Sources: Zogenix International Limited, 2021 (24); Zogenix International Limited, 2021 (25); ClinicalTrials.gov (61).

6.1.2 Comparability of studies

The comparison of FFA and ASMs is based on the head-to-head trial ZX008-1601 – Part 1. Therefore, a comparison of the studies is not relevant here. However, as the ZX008-1601 comprise of a Part 1 and Part 2, a comparison of the two parts is briefly provided here. Part 1 is double-blinded randomised placebo-controlled study including three different treatment arms (placebo, FFA 0.2 mg/kg/day, and FFA 0.7 mg/kg/day). Part 2 is an open-label, flexible-dose extension study, and therefore Part 2 does not include the three treatment arms.

6.1.2.1 Comparability of patients across studies

In Table 17 baseline characteristics of patients included in the comparative analysis are presented. In Part 1 of ZX008-1601, baseline characteristics of the modified intent-to-treat (mITT) population are presented. The mITT population is defined as all randomised subjects who received at least one dose of study drug and for whom at least one week of eDiary data were available. Subjects were analysed according to the treatment group to which they were randomised. Analyses of the primary and all secondary endpoints were performed on data from the mITT population.

In Part 2 of ZX008-1601, baseline characteristics of the OLE safety population are presented, unless otherwise specified. The OLE safety population is defined as all subjects who receive at least one dose of FFA during the OLE. Efficacy analyses were performed on data from the OLE mITT population defined as all randomised subjects who receive at least one dose of FFA and have a valid estimate of the DSF from Part 1 and at least one month (30 days) of valid seizure data during the OLE.

Table 17 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (ZX008-1601 – Part 1 [mITT population] and ZX008-1601 – Part 2 [OLE safety population])

	ZX008-1601 – Part 1			ZX008-1601 – Part 2
	Placebo (N=87)	Fenfluramine 0.2 mg/kg/ day (N=89)	Fenfluramine 0.7 mg/kg/ day (N=87)	Fenfluramine (N=247)
Age, mean (SD)	14.4 (7.71)	13.4 (7.79)	13.4 (7.28)	14.3 (7.56)
Sex, n (%)				
Male	46 (52.9)	46 (51.7)	54 (62.1)	136 (55.1)
Female	41 (47.1)	43 (48.3)	33 (37.9)	111 (44.9)
Race, n (%)				
White	71 (81.6)	67 (75.3)	70 (80.5)	199 (80.6)
Black or African American	4 (4.6)	5 (5.6)	3 (3.4)	12 (4.9)
Asian	2 (2.3)	3 (3.4)	4 (4.6)	8 (3.2)
Native Hawaiian or Other Pacific Islander	0	1 (1.1)	0	1 (0.4)
Not Reported	6 (6.9)	11 (12.4)	7 (8.0)	20 (8.1)
Unknown	2 (2.3)	2 (2.2)	2 (2.3)	5 (2.0)
Multiple	2 (2.3)	0	1 (1.1)	2 (0.8)
Baseline weight in kg, mean (SD)	43.85 (20.673)	42.36 (20.979)	42.24 (21.399)	42.99 (20.797)
Baseline weight group, n (%)				

	ZX008-1601 – Part 1			ZX008-1601 – Part 2
	Placebo (N=87)	Fenfluramine 0.2 mg/kg/ day (N=89)	Fenfluramine 0.7 mg/kg/ day (N=87)	Fenfluramine (N=247)
<37.5 kg	42 (48.3)	42 (47.2)	40 (46.0)	111 (44.9)
≥37.5 kg	45 (51.7)	47 (52.8)	47 (54.0)	136 (55.1)
Baseline BMI (kg/m²), mean (SD)	19.74 (4.995)	19.60 (5.229)	19.71 (5.075)	19.48 (5.204)
DSF per 28 days during baseline, median (min, max)	53.0 (2.0, 1761.0)	85.0 (4.1, 2943.0)	83.0 (6.5, 1803.0)	75.00 (4.0, 2943.0)‡π
Number of prior ASMs, mean (SD)	6.68 (3.699)*	6.77 (3.558)*	7.58 (4.146)	N/A
≥1 concomitant ASM, n (%)	86 (98.9)	89 (100)	86 (98.9)	245 (99.2)
Number of concomitant ASMsΩ, n (%)				
1	12 (13.8)	11 (12.4)	4 (4.6)	15 (6.1)
2	19 (21.8)	24 (27.0)	24 (27.6)	59 (23.9)
3	34 (39.1)	30 (33.7)	32 (36.8)	84 (34.0)
4	21 (24.1)	23 (25.8)	26 (29.9)	75 (30.4)
5	0	1 (1.1)	0	10 (4.0)
6	N/A	N/A	N/A	1 (0.4)
7	N/A	N/A	N/A	1 (0.4)

Abbreviations: ASM = anti-seizure medication; BMI = body mass index; DSF = drop seizure frequency; mITT = modified intent-to-treat; N/A = not applicable; OLE = open-label extension; SD = standard deviation.
Notes: Percentages are calculated based on the number of subjects with non-missing data in Part 1. For Part 2, all data is from the Part 2 baseline unless otherwise specified. ‡ Based on the OLE mITT population (n=241) defined as all randomised subjects who receive at least one dose of fenfluramine and have a valid estimate of the DSF from Part 1 and at least 30 days of valid seizure data during the OLE. π Part 1 baseline (28 days prior to double-blind treatment in Part 1). * Multiple occurrences of the same antiepileptic treatment are counted once for each subject within a drug class and preferred drug name. Prior antiepileptic treatments are those with a stop date prior to first dose of study drug in Part 1. Ω A concomitant ASM in Part 1 is defined as antiepileptic treatment with a start or stop date after the first dose of study treatment in Part 1, or antiepileptic treatment started prior to the first dose in Part 1 that was ongoing. Medications started on or after the first dose in Part 2 are excluded. A concomitant ASM in Part 2 is defined as antiepileptic treatment with a start or stop date after the first dose of study treatment in Part 2, or antiepileptic treatment started prior to the first dose in Part 2 that was ongoing.
Source: Zogenix International Limited, 2021 Table 14.1.2.2.1, Table 12, Table 14, and Table 16 (24); Knupp et al. 2022, Table 1 (9); Zogenix International Limited, 2021, Table 14.1.2.1.3, Table 12, and Table 14 (25); Knupp et al. 2023, Table 1 (64).

Overall, the baseline characteristics were well balanced across the treatment arms in Part 1 of ZX008-1601, although slight differences were observed. Among patients in the 0.7 mg/kg/day FFA group, 62% were male compared to 52% to 53% among patients randomised to the 0.2 mg/kg/day FFA and placebo group. Further, the median DSF was higher in the 0.7 mg/kg/day and 0.2 mg/kg/day FFA groups than in the placebo group (83 and 85 vs 53 events per 28 days, respectively). Participants in Part 2 of ZX008-1601 were comparable with the participants in Part 1 of the study, although more participants in Part 2 (n=12) had at least five concomitant ASMs compared to one patient in Part 1.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

As LGS is a rare disease, only limited data for Danish patients are available. The Danish real-world data has been applied to the health economic model, i.e., the Danish age distribution has been applied to the model (Table 18).

Table 18 Characteristics in the relevant Danish population and in the health economic model

Age group	Value in Danish population (UCB, 2024 (35))	Value used in health economic model (reference if relevant)
Age, 0-11 years	7%	7%*
Age, ≥12 years	93%	93%*

Notes: Data on age is based on registry data from 2023 (number of patients with ICD-10 diagnosis code G40.4E in Denmark). *Values have been adapted to fit model structure as presented in Table 19.
Source: UCB, 2024 (35).

To align with real-world estimates, the base-case analysis considered the age distribution presented in Table 19. From Study ZX008-1601, we see that patients are equally distributed among the 2 age groups of 12-17, and 18+. Given that Danish data is only available for 2 age groups that do not align with the model we assumed that the 7% (age 0-11) would be equally split among the 2-5 and 6-11 groups. The remaining 93% was equally split between the 12-17 and 18+ groups.

Table 19 Base-case population characteristics

Age group	Study ZX008-1601	Value in Danish population (UCB, 2024 (35)) – model adapted
Age, 2-5 years	14.4%	**3.5%**
Age, 6-11 years	27.4%	**3.5%**
Age, 12-17 years	29.3%	**46.5%**
Age, 18+ years	28.9%	**46.5%**

The age distribution at the beginning of the model based on data from Study 1601, was explored in a separate scenario analysis.

6.1.4 Efficacy – results per ZX008-1601 – Part 1

6.1.4.1 Patient cohort description in ZX008-1601 – Part 1

The number and proportion of patients in the enrolled population (all subjects who gave informed consent/assent) that discontinued the study in each of the treatment arms and the reason for discontinuation are presented in Table 20.

Table 20 Discontinuation in ZX008-1601 – Part 1 (enrolled population)

	Placebo (N=87)	Fenfluramine 0.2 mg/kg/day (N=89)	Fenfluramine 0.7 mg/kg/day (N=87)
Discontinued, n (%)	4 (4.6)	7 (7.9)	10 (11.5)

Primary reason for discontinuation, n (%)			
Adverse event	1 (1.1)	4 (4.5)	5 (5.7)
Death	0	0	1 (1.1)
Physician decision	1 (1.1)	1 (1.1)	0
Protocol deviation	0	1 (1.1)	0
Withdrawal by subject	1 (1.1)	1 (1.1)	2 (2.3)
Other*	1 (1.1)	0	2 (2.3)

Notes: * Subjects for whom an early transfer to Part 2 (prior to Visit 12) was reported as the primary reason for Part 1 discontinuation. A total of 7 subjects transferred to Part 2 early, but another primary reason for discontinuation was reported for 4 of these subjects.
Source: Zogenix International Limited, 2021, Table 7 (24); European Medicines Agency, 2023, Table 49 (69).

Handling of missing values are described in Appendix B.

6.1.4.2 Efficacy during the maintenance phase in seizure frequency reduction

At the end of the 14-weeks RCT, the median 28-day seizure frequency was reduced by 27.16% (p=0.0018) in the 0.7 mg/kg/day FFA group, and by 18.63% (p=0.0764) in the 0.2 mg/kg/day FFA group and by 7.28% in the placebo group. This translates to a significantly (p=0.0018) higher seizure reduction with 0.7 mg/kg/day FFA compared to placebo with a difference of 20.25 percentage points at the end of the RCT (Table 21).

Table 21 Drop seizure frequency during M (mITT population)

	Placebo (N=87)	Fenfluramine 0.2 mg/kg/day (N=89)	Fenfluramine 0.7 mg/kg/day (N=87)
DSF at baseline, median (min, max)	53.00 (2.0, 1761.0)	87.00 (4.1, 2943.0)	82.00 (6.5, 1803.0)
DSF in M, median (min, max) [a]	47.33 (0.0, 1588.1)	59.17 (0.0, 1844.0)	55.73 (0.0, 1527.1)
Percentage CFB, median (min, max)	-7.28 (-100.0, 516.7)	-18.63 (-100.0, 964.0)	-27.16 (-100.0, 643.3)
P-value [b]	N/A	0.0764	0.0018
Hodges-Lehmann (HL) for median difference [c]**, estimate (standard error [SE]; 95% confidence interval [CI])**	Reference	-11.48 (7.543; 95% CI: -26.26, 3.31)	-20.25 (5.795; 95% CI: -31.61, -8.89)

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; DSF = drop seizure frequency; HL = Hodges-Lehmann; mITT = modified intent-to-treat; M = maintenance; N/A = not applicable; SE = standard error.
Notes: [a] Values for DSF per 28 days are presented in original scale. [b] DSF during M was assessed using a nonparametric, rank analysis of covariance (ANCOVA) model with treatment group and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank DSF per 28 days during baseline as a covariate, and rank of percentage CFB in DSF per 28 days during M as response variable. [c] Active group minus placebo group.
Source: Zogenix International Limited, 2021, Table 23 (24); Knupp et al. 2022 (9).

At the end of the 14-weeks RCT, the median 28-day seizure reduction of GTC seizures were 52.6% (p=0.001) in the FFA 0.7 mg/kg/day group, and 61.7% (p<0.001) in the FFA 0.2 mg/kg/day group, while an increase of 2.6% was seen with placebo. This translates into a -52.8 percentage points (95% CI: -80.3, -25.3 percentage points; p=0.001) in the

0.7 mg/kg/d FFA group and -61.0 percentage points (95% CI: -85.5, -36.5 percentage points; p<0.001) in the 0.2 mg/kg/d FFA group compared to placebo Table 22.

Table 22 GTCs during M (mITT population)

	Placebo (N=87)	Fenfluramine 0.2 mg/kg/day (N=89)	Fenfluramine 0.7 mg/kg/day (N=87)
Median percentage reduction of GTC seizures [a]	2.6	-61.7, p<0.001	-52.6, p=0.001
HL for median difference in frequency of GTC seizures, percentage points (95% CI), p-value	Reference	-61.0 (-85.5, -36.5), p<0.001	-52.8 (-80.3, -25.3), p=0.001)

Abbreviations: CI = confidence interval; GTC = generalised tonic-clonic; HL = Hodges-Lehmann; M = maintenance; mITT = modified intent-to-treat.
Notes: [a] P-values calculated using pairwise Wilcoxon rank sum test compared percentage changes from baseline between active treatment and placebo groups. P-values were nominal.
Sources: Knupp et al. 2022 (9).

6.1.4.3 ≥50% reduction from baseline in the DSF

At the end of the 14 weeks RCT, a significant fraction of the 0.7 mg/kg/day FFA group (31%; p=0.004) and of the 0.2 mg/kg/day FFA group (32%; p=0.004) while only 11% (p=not significant [ns]) in the placebo group reached a ≥50% reduction of drop-seizures (Table 23).

Table 23 Percentage who achieved a ≥50% reduction from baseline in DSF (mITT population)

	Placebo (N=87)	Fenfluramine 0.2 mg/kg/day (N=89)	Fenfluramine 0.7 mg/kg/day (N=87)
≥50% reduction in DSF during M, n (%)	11 (12.6)	28 (31.8)	27 (31.4)
OR (95% CI)	Reference	3.13 (1.44, 6.82)	3.12 (1.43, 6.84)
P-value	ns	0.0041	0.0044

Abbreviations: CI = confidence interval; DSF = drop seizure frequency; M = maintenance; mITT = modified intent-to-treat; N/A = not applicable; OR = odds ratio.
Notes: Based on a logistic regression model that included a categorical response variable (achieved 50 percentage point reduction, yes or no), weight group strata (<37.5 kg, ≥37.5 kg), and baseline DSB as covariate.
Source: Zogenix International Limited, 2021, Table 33 (24); Knupp et al. 2022 (9).

6.1.4.4 Investigator ratings of improvement on the CGI-I scale

Table 24 presents results for the key secondary endpoint: percentage of subjects who were rated as improved (a score of 1, 2, or 3) on the CGI-I scale as assessed by the Investigator. In addition, a pre-specified exploratory analysis designed to represent a higher standard of improvement is presented in Table 24. This analysis evaluated the percentages of subjects rated by the Investigator as showing clinically meaningful improvement from baseline (a score of 1 or 2) at the end of the RCT-study visit (visit 12).

Both the number and percentage of patients rated by the investigator to have a clinically meaningful improvement at day 99 in CGI-I was significantly higher with 0.7 mg/kg/day FFA (n=21; 26.3%; p=0.0007) and with 0.2 mg/kg/day FFA (n=17; 20.0%; 0.0100) while

placebo had no significant change (n=5; 6.3%; p=ns). Although not reaching statistical significance, a higher number of patients treated with FFA 0.7 mg/kg/day (n=39; 48.8%) and FFA 0.2 mg/kg/day (n=38; 44.7%) compared to the placebo group (n=27; 33.8%) was rated to show any improvement in CGI-I.

Table 24 Investigator ratings of improvement on the CGI-I scale at visit 12 (mITT population)

	Placebo (N=87)	Fenfluramine 0.2 mg/kg/day (N=89)	Fenfluramine 0.7 mg/kg/day (N=87)
Visit 12, day 99, summary statistic, n	80	85	80
Clinically meaningful improvement			
Subjects with score 1 or 2, n (%)	5 (6.3)	17 (20.0)	21 (26.3)
OR (95% CI) [a]	Reference	3.73 (1.31, 10.65)	5.30 (1.89, 14.87)
p-value [b]	ns	0.0100	0.0007
Improvement			
Subjects with score 1, 2, or 3, n (%)	27 (33.8)	38 (44.7)	39 (48.8)
OR (95% CI) [a]	Reference	1.58 (0.84, 2.97)	1.86 (0.98, 3.52)
p-value [b]	ns	0.1565	0.0567

Abbreviations: CGI-I=Clinical Global Impression - Improvement; CI = confidence interval; mITT = modified intent-to-treat; ns = not significant; N/A = not applicable; OR = odd ratio.
Notes: [a] Estimated Cochran-Mantel-Haenszel OR adjusting for weight strata. [b] p-value from Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata.
Source: Zogenix International Limited, 2021, Table 34 (24); Knupp et al. 2022 (9).

6.1.4.5 Parent/caregiver ratings of improvement on the CGI-I scale

Table 25 presents results for improvement on CGI-I scale as assessed by the parent/caregiver.

Both the number and percentage of patients rated by the caregivers to have a clinically meaningful improvement at day 99 in CGI-I was significantly higher with 0.7 mg/kg/day FFA (n=27; 34%; p<0.001) and with 0.2 mg/kg/day FFA (n=23; 27.0%; p<0.001) compared to placebo (n=4; 5%; p=ns). A statistical significantly higher number of patients reached any improvement with FFA 0.7 mg/kg/day (n=49; 61%; p=0.0023) and a numerical higher number was observed with FFA 0.2 mg/kg/day (n=37; 43.5%; p=0.3960) compared to the placebo group (n=30; 37%; p=ns).

Table 25 Parent/caregiver ratings of improvement on the CGI-I scale at visit 12 (mITT population)

	Placebo (N=87)	Fenfluramine 0.2 mg/kg/day (N=89)	Fenfluramine 0.7 mg/kg/day (N=87)
Visit 12, day 99, summary statistic, n	81	85	80
Clinically meaningful improvement			
Subjects with score 1 or 2, n (%)	4 (4.9)	23 (27.1)	27 (33.8)
OR (95% CI) [a]	Reference	7.26 (2.39, 22.03)	9.96 (3.29, 30.17)

p-value [b]	ns	<0.0001	<0.0001
Improvement			
Subjects with score 1, 2, or 3, n (%)	30 (37.0)	37 (43.5)	49 (61.3)
OR (95% CI) [a]	Reference	1.31 (0.70, 2.44)	2.68 (1.42, 5.07)
p-value [b]	ns	0.3960	0.0023

Abbreviations: CGI-I=Clinical Global Impression - Improvement; CI = confidence interval; mITT = modified intent-to-treat; ns = not significant; N/A = not applicable; OR = odd ratio.
Notes: [a] Estimated Cochran-Mantel-Haenszel OR adjusting for weight strata. [b] p-value from Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata.
Source: Zogenix International Limited, 2021, Table 46 (24); Knupp et al. 2022 (9).

6.1.5 Efficacy – results per ZX008-1601 – Part 2

6.1.5.1 Patient cohort description in ZX008-1601 – Part 2

The number and proportion of patients that discontinued the study in the open label safety population and in the open label mITT population and the primary reason for discontinuation are presented in Table 26.

Table 26 Discontinuation in ZX008-1601 – Part 2

	Overall (N=247)
Open label safety population	247
Discontinued Part 2, n (%) [a]	82 (33.2)
Reason for discontinuation from Part 2, n (%) [a]	
Adverse event	13 (5.3)
Death	1 (0.4)
Lack of efficacy	55 (22.3)
Withdrawal by subject	13 (5.3)
Open label mITT population, n (%) [a]	241 (97.6)
Discontinued Part 2, n (%) [b]	76 (31.5)
Reason for discontinuation from Part 2, n (%) [b]	
Adverse event	11 (4.6)
Death	1 (0.4)
Lack of efficacy	53 (22.0)
Withdrawal by subject	11 (4.6)

Abbreviations: AE = adverse event; mITT = modified intent-to-treat; OLE = open-label extension.
Notes: Two subjects are not counted toward the number of discontinuations due to delays in completion of the final disposition electronic case report forms. [a] Percentages are calculated using the number of subjects in the OLE Safety Population. [b] Percentages are calculated using the number of subjects in the OLE mITT Population.
Source: Zogenix International Limited, 2021, table 5 (25).

Handling of missing values are described in Appendix B.

6.1.5.2 Change from baseline in drop seizure frequency

A sustained median seizure reduction at 30.5% (p<0.0001) was observed from month 2 (when flexible dose was allowed) to EOS. When analysed over time a continuous improvement of the seizure reduction was observed reaching 50.5% (p<0.0001) after 15-months FFA (Table 27). This continuous improved seizure reduction was shown to be dose-independent with equally high seizure reduction at doses <0.4 mg/kg/day as for >0.6 mg/kg/day (Figure 2).

Table 27 Drop seizure frequency during OLE (OLE mITT population)

	Any fenfluramine OLE dose (N=241)
Percentage change from Part 1 baseline at Month 1, median, p-value	27.78, p<0.0001
Percentage change from Part 1 baseline at Month 2, median, p-value	32.50, p<0.0001
Percentage change from Part 1 baseline at Month 3, median, p-value	39.42, p<0.0001
Percentage change from Part 1 baseline at Month 4-6, median, p-value	37.12, p<0.0001
Percentage change from Part 1 baseline at Month 7-9, median, p-value	42.69 (p<0.0001)
Percentage change from Part 1 baseline at Month 10-12, median, p-value	51.77, p<0.0001
Percentage change from Part 1 baseline at Month 13-15, median, p-value	50.53, p<0.0001

Abbreviations: mITT = modified intent-to-treat; OLE = open-label extension.
Notes: [a] p-value is from a Wilcoxon signed-rank test that the median % CFB is significantly different from 0.
Source: Zogenix International Limited, 2021, Table 14.2.1.11.1.1.2 (25).

Figure 2 Monthly reduction in DSF per mean daily dose

Source: Based on data from Zogenix International Limited, 2021 (25).

Data from the Part 2 study shows that FFA is effective independently of age. Specifically, at month 12 (for the age groups 2-6, 6-12, 12-18, 18-35, and overall) the mean percentage CFB in DSF was of -22, -16, -18, -18, -7, and -14 respectively. All differences were statistically significant (p<0.05) (25). Figure 3 presents the reduction in monthly drop seizures between time 0 and month 14, stratified by age group.

Figure 3 Reduction in monthly drop seizures by age

Source: Based on data from Zogenix International Limited, 2021 (25).

6.1.5.3 ≥50% reduction from baseline in the DSF

Nearly one-third of subjects, 31.7%, achieved a ≥ 50% reduction from baseline DSF per 28 days during Month 2 to EOS. As with drop-seizure reduction, the ≥50% responder rate increased progressively with treatment-length and at 1-year 51.2% of the patients showed ≥50 reduction of their drop-seizure compared to baseline (to be compared to the RCT-data where 31.4% showed ≥50% reduction), supporting an improved efficacy with treatment length (Table 28).

Table 28 Percentage who achieved a ≥50% reduction in DSF per 28 days (OLE mITT population)

	Any fenfluramine OLE dose (N=241)
≥50% reduction in DSF from Month 2 in OLE to EOS, n (%) (95% CI)	76 (31.7) (25.8, 38.0)
≥50% reduction in DSF in Month 10-12 in OLE, n (%) (95% CI)	87 (51.2) (43.4, 58.9)

Abbreviations: CI = confidence interval; DSF = drop seizure frequency; EOS = end of study mITT = modified intent-to-treat; OLE = open-label extension.
Notes: 95% CIs represent Exact Clopper-Pearson CIs.
Source: Zogenix International Limited, 2021, Table 14.2.1.12.1.1.1 (25).

6.1.5.4 Investigator ratings improvement on the CGI-I scale

Table 29 presents results for subjects who were rated as showing clinically meaningful improvement (a score of 1 or 2) on the CGI-I scale and subjects rated as improved (a score of 1, 2, or 3) at the last assessment. At the last OLE assessment, i.e., the last CGI-I rating available for each subject as of the data cutoff date, 37.6% were rated by the Investigator as having clinically meaningful improvement and 56.5% of subjects were rated as improved, both values markedly higher than at the end of the RCT-phase (clinically meaningful improvement 26.3%, improvement 48.8%) again supporting that effect increases with treatment length.

Table 29 Investigator ratings of improvement on the CGI-I scale at last assessment (OLE mITT population)

	Any fenfluramine OLE dose (N=241)
Summary statistic at last assessment, n	237
Clinically meaningful improvement (score 1 or 2), n (%) (95% CI)	89 (37.6) (31.4, 44.1)
Improvement (score 1, 2, or 3), n (%) (95% CI)	134 (56.5) (50.0, 62.9)

Abbreviations: CGI-I=Clinical Global Impression - Improvement; CI = confidence interval; mITT = modified intent-to-treat; OLE = open-label extension.
Notes: 95% CIs represent Exact Clopper-Pearson CIs.
Source: Zogenix International Limited, 2021, table 24 (25); Knupp et al. 2023 (64).

6.1.5.5 Parent/caregiver ratings of improvement on the CGI-I scale

Table 29 presents results for subjects who were rated as showing clinically meaningful improvement (a score of 1 or 2) on the CGI-I scale and subjects rated as improved (a score of 1, 2, or 3) at the last assessment. At the last OLE assessment, 35.2% were rated by the parent/caregiver as having clinically meaningful improvement, and 59.1% of subjects were rated by the parent/caregiver as improved.

Table 30 Parent/caregiver ratings of improvement on the CGI-I scale at last assessment (OLE mITT population)

	Any fenfluramine OLE dose (N=241)
Summary statistic at last assessment, n	230
Clinically meaningful improvement (score 1 or 2), n (%) (95% CI)	81 (35.2) (29.1, 41.8)
Improvement (score 1, 2, or 3), n (%) (95% CI)	136 (59.1) (52.5, 65.5)

Abbreviations: CGI-I=Clinical Global Impression - Improvement; CI = confidence interval; mITT = modified intent-to-treat; OLE = open-label extension.
Notes: 95% CIs represent Exact Clopper-Pearson CIs.
Source: Zogenix International Limited, 2021, table 25 (25); Knupp et al. 2023 (64).

6.1.6 Efficacy – results per ZX008-1900/EP0215

6.1.6.1 Patient cohort description in ZX008-1900/EP0215

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.1.6.2 Long-term improvement on the CGI-I scale

[redacted]

Table 31 Investigator ratings of improvement on the CGI-I scale at last on-treatment visit (mITT population)

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

6.1.6.3 Long-term improvement in seizure reduction

[redacted]

[redacted]

Figure 4 Percent improvement in seizure burden since last visit

[redacted]

7. Comparative analyses of efficacy

Not applicable.

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

A summary of results from sections 6.1.4 and 6.1.5 is shown in Table 32, mainly presenting the relative results. For full results, please see section 6.1.4 and 6.1.5.

Table 32 Results from the comparative analysis of FFA vs ASMs for patients with LGS (mITT population in ZX008-1601 Part 1, OLE mITT population in ZX008-1601 Part 2)

Summary of efficacy results			
Outcome measure	**Placebo (N=87)**	**Fenfluramine 0.2 mg/kg/day (N=89)**	**Fenfluramine 0.7 mg/kg/day (N=87)**
DSF during M, HL for median difference	Reference	-11.48 (SE: 7.543; 95% CI: -26.26, 3.31)	-20.25 (SE: 5.795; 95% CI: -31.61, -8.89)

Summary of efficacy results			
HL for median difference in frequency of GTC seizures	Reference	-61.0 (95% CI: -85.5, -36.5), p<0.001	-52.8 (95% CI: -80.3, -25.3), p=0.001)
≥50% reduction in DSF during M	Reference	OR: 3.13 (95% CI: 1.44, 6.82), p=0.0041	OR: 3.12 (95% CI: 1.43, 6.84), p=0.0044
Clinically meaningful improvement at visit 12, investigator rated	Reference	OR: 3.73 (95% CI: 1.31, 10.65), p=0.0100	OR: 5.30 (95% CI: 1.89, 14.87), p=0.0007
Improvement at visit 12, investigator rated	Reference	OR: 1.58 (95% CI: 0.84, 2.97), p=0.1565	OR: 1.86 (95% CI: 0.98, 3.52), p=0.0567
Clinically meaningful improvement at visit 12, parent/caregiver rated	Reference	OR: 7.26 (95% CI: 2.39, 22.03), p<0.0001	OR: 9.96 (95% CI: 3.29, 30.17), p<0.0001
Improvement at visit 12, parent/caregiver rated	Reference	OR: 1.31 (95% CI: 0.70, 2.44), p=0.3960	OR: 2.68 (95% CI: 1.42, 5.07), p=0.0023

Outcome measure	Any fenfluramine OLE dose (N=241)
Percentage change from Part 1 baseline during Month 2 in OLE to EOS	Median: -30.46 (min, -100.0, max, 6,200.0), p<0.0001
≥50% reduction in DSF from Month 2 in OLE to EOS	n=76 (31.7%) (95% CI: 25.8, 38.0)
≥50% reduction in DSF in Month 10-12 in OLE, n (%) (95% CI)	n=87 (51.2%) (95% CI: 43.4, 58.9)
Clinically meaningful improvement at last assessment, investigator rated	n=89 (37.6%) (95% CI: 31.4, 44.1)
Improvement at last assessment, investigator rated	n=134 (56.5%) (95% CI: 50.0, 62.9)
Clinically meaningful improvement at last assessment, parent/caregiver rated	n=81 (35.2%) (95% CI: 29.1, 41.8)
Improvement at last assessment, parent/caregiver rated	n=136 (59.1%) (95% CI: 52.5, 65.5)

Abbreviations: CGI-I=Clinical Global Impression - Improvement; CI = confidence interval; DSF = drop seizure frequency; EOS = end of study; GTC = generalised tonic-clonic; HL = Hodges-Lehmann; LGS = Lennox-Gastaut syndrome; M = maintenance; mITT = modified intent-to-treat; OLE = open-label extension; OR = odds ratio; SE = standard error.
Notes: Notes are provided in the respective tables in section 6.1.4 and 6.1.5.
Source: Zogenix International Limited, 2021 (24); Knupp et al. 2022 (9); Zogenix International Limited, 2021 (25); Knupp et al. 2023 (64).

7.1.4 Efficacy – results per [outcome measure]

Not applicable.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The modelling of efficacy was based on the results of Study ZX008-1601, with the calculation of transition probabilities that fitted the model structure presented in section 4.1.

8.1.1 Extrapolation of efficacy data

Efficacy of FFA was evaluated at three key time points, these are presented in Table 33 below. Please note that the model starting age is set to 3 years. This choice is based on information showing that the peak age for the onset of seizures between 3 and 5 years of age (15, 16, 26). This extrapolation choice is further supported by the fact that efficacy of FFA has been shown to be independent of age (see Figure 3).

Table 33 Extrapolation of efficacy at different timepoints

Timepoint	Duration	Efficacy source
Up to Cycle 1 (T+M)	3.5 months	RR from Study ZX008-1601
Cycle 2 to Cycle 5 (OLE)	Months 4 to 15	Transition Probabilities from OLE study
Cycle 6 to Cycle 9 (post-OLE)	Months 16 to 27	Last observed data from cycle 5 applied to cycles 6-9.

Abbreviations: T+M = Titration and maintenance; RR = risk ratio; FFA = fenfluramine; OLE = Open label extension

8.1.1.1 Extrapolation of [effect measure 1]

N/A. No parametric extrapolation (i.e., OF, PFS) was conducted. Transition probabilities are presented below in Section 8.1.2.

Table 34 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A

Method/approach	Description/assumption
Assumption of proportioall hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

N/A. No parametric extrapolation (i.e., OF, PFS). Transition probabilities are presented below.

8.1.2 Calculation of transition probabilities

The model assumes the same state occupancy during titration as baseline (patients are distributed according to ASM arm of Study ZX008-1601). Cycle 1 corresponds to the M period of the phase 3 trial, which is the 3 months following the 2-week titration.

The initial distribution of patients across health states 0, 1, 2 and 3 respectively, are calculated using quartiles of drop-seizure distribution at baseline in Study ZX008-1601, as

described in section 6. Relative risks estimated from Study ZX008-1601 are used to assess the effect of the treatment on the distribution across health states in cycle 1.

The model uses a stepwise approach to calculate state occupancy at the end of T+M period (Cycle 2). First, binomial relative risks for each percentage of drop-seizure reduction category are multiplied by baseline proportions in the SoC arm (Table 35). Next, the difference within each cut-off point is calculated to convert cumulative states (≥25%, ≥50%, and ≥75%) into state occupancies fitting the health states of the model (State 0: < 25% reduction; State 1: 25% to 50% response; State 2: 50% to 75% response; and State 3: ≥75% response (Table 36)

Table 35 Baseline proportions in comparator arm

Cohorts	Fenfluramine 0.7 mg/kg/day, RR (95% CrI)	Baseline proportion of patients in each state at T+M (Study ZX008-1601)	Reference
≥25%	1.632 (1.134, 2.435)	31%	Study ZX008-1601
≥50%	2.942 (1.443, 6.823)	10%	Study ZX008-1601
≥75%	2.496 (0.685, 11.876)	5%	Study ZX008-1601

Abbreviations: T+M = Titration and maintenance; RR = risk ratio; CrI = Credible interval

Table 36 State occupancies in the model

Cohorts	State 0: < 25% reduction	State 1: 25% to <50% reduction	State 2: 50% to <75% reduction	State 3: >=75% response	Reference
SoC	69.0%	20.7%	5.7%	4.6%	Study ZX008-1601

Abbreviations: SoC = Standard of care

Cycles 2 to 5 correspond to the OLE study period, i.e., the 12 months following the phase 3 trial (T+M, 3.5 months). In the base-case analysis, the model allows for a comparison between FFA (i.e., FFA + ASMs) and SoC alone using the transition probabilities from the OLE FFA study to inform the movement of patients in the FFA arm. These transition probabilities are estimated from the original data on the number of patients transitioning in the OLE period (see Table 37).

Table 37 Number of patients transitioning in the OLE period

Fenfluramine OLE study	State 0	State 1	State 2	State 3
Number of patients transitioning from 3 to 6 months in the OLE study				
State 0	44	11	8	1
State 1	7	11	7	9
State 2	3	5	11	12

State 3	1	2	4	9
Number of patients transitioning from 6 to 9 months in the OLE study				
State 0	27	6	7	1
State 1	8	10	5	3
State 2	5	7	9	6
State 3	6	0	6	18
Number of patients transitioning from 9 to 12 months in the OLE study				
State 0	27	5	4	2
State 1	6	9	3	1
State 2	5	5	8	7
State 3	1	1	6	17
Number of patients transitioning from 12 to 15 months in the OLE study				
State 0	23	3	4	2
State 1	4	9	1	2
State 2	3	2	12	3
State 3	0	1	6	19

Abbreviations: OLE = Open label extension

Table 38 Transitions in the health economic model

Health state (from)	Health state (to)	Value	Description of method	Reference
3 to 6 months			**Direct number of patients transitioning**	**FFA OLE study**
State 0	State 0	0.688	As above	As above
	State 1	0.172	As above	As above
	State 2	0.125	As above	As above
	State 3	0.016	As above	As above
State 1	State 0	0.206	As above	As above
	State 1	0.324	As above	As above
	State 2	0.206	As above	As above
	State 3	0.265	As above	As above
State 2	State 0	0.097	As above	As above
	State 1	0.161	As above	As above
	State 2	0.355	As above	As above
	State 3	0.387	As above	As above
State 3	State 0	0.063	As above	As above
	State 1	0.125	As above	As above

	State 2	0.250	As above	As above
	State 3	0.563	As above	As above
6 to 9 months			**Direct number of patients transitioning**	**FFA OLE study**
State 0	State 0	0.659	As above	As above
	State 1	0.146	As above	As above
	State 2	0.171	As above	As above
	State 3	0.024	As above	As above
State 1	State 0	0.308	As above	As above
	State 1	0.385	As above	As above
	State 2	0.192	As above	As above
	State 3	0.115	As above	As above
State 2	State 0	0.185	As above	As above
	State 1	0.259	As above	As above
	State 2	0.333	As above	As above
	State 3	0.222	As above	As above
State 3	State 0	0.185	As above	As above
	State 1	0.259	As above	As above
	State 2	0.333	As above	As above
	State 3	0.222	As above	As above
9 to 12 months			**Direct number of patients transitioning**	**FFA OLE study**
State 0	State 0	0.711	As above	As above
	State 1	0.132	As above	As above
	State 2	0.105	As above	As above
	State 3	0.053	As above	As above
State 1	State 0	0.316	As above	As above
	State 1	0.474	As above	As above
	State 2	0.158	As above	As above
	State 3	0.053	As above	As above
State 2	State 0	0.200	As above	As above
	State 1	0.200	As above	As above
	State 2	0.320	As above	As above
	State 3	0.280	As above	As above
State 3	State 0	0.040	As above	As above
	State 1	0.040	As above	As above
	State 2	0.240	As above	As above
	State 3	0.680	As above	As above
12 to 15 months			**Direct number of patients transitioning**	**FFA OLE study**
State 0	State 0	0.719	As above	As above
	State 1	0.094	As above	As above

	State 2	0.125	As above	As above
	State 3	0.063	As above	As above
State 1	State 0	0.250	As above	As above
	State 1	0.563	As above	As above
	State 2	0.063	As above	As above
	State 3	0.125	As above	As above
State 2	State 0	0.150	As above	As above
	State 1	0.100	As above	As above
	State 2	0.600	As above	As above
	State 3	0.150	As above	As above
State 3	State 0	0.000	As above	As above
	State 1	0.038	As above	As above
	State 2	0.231	As above	As above
	State 3	0.731	As above	As above

Abbreviations: FFA = Fenfluramine; OLE = Open label extension

Discontinuation

Treatment discontinuation varies across the time horizon. Patients may discontinue due to adverse events (at all cycles), from lack of efficacy (cycles 1 and 2) or according to a stopping rule (after cycle 2). Discontinued patients are assumed to remain in a discontinuation state unless they die, and to follow the same trajectory in terms of costs, utilities, and mortality as patients in state 0 treated with SoC alone.

The stopping rule, applied after cycle 2, is determined by two criteria. First, the threshold percentage reduction in DSF: <25%, <30%, or <50%. Second, the interval at which the stopping rule is applied: every 3 months, or every 6 months. The base-case analysis described in this report includes a stopping rule applied to all patients experiencing <25% response (reduction in DSF), applied every 3 months. Discontinuation due to AEs is applied each cycle according to cycle specific proportions sourced from the Study ZX008-1601.

Mortality

All-cause mortality was incorporated using the general mortality data provided by the DMC. The background mortality rate, adjusted for the proportion of males/females, was converted to a cycle-specific probability of dying applied to all patients in the model.

In the base-case analysis, patients can also incur an additional risk of SUDEP as well as death from other non-SUDEP causes such as status epilepticus and accidents. SUDEP mortality is assumed to be dependent on health states and the frequency of seizures per 28 days. Due to lack of data for LGS, SUDEP mortality is informed from a publication on Dravet syndrome by Cooper et al. (2016) in line with the 2019 CBD NICE LGS submission (TA615) (73). SUDEP mortality in Dravet was observed by Cooper et al. (2016) in severe epilepsy patients (74) with an incidence rate for SUDEP of 9.32 per 1,000 person-years. Based on the incidence rate, a cycle probability of 0.00233 was calculated and used in

the model. Additionally, patients in the model experience health state specific SUDEP-related mortality based on the calculated seizure frequency mid-points of each health state (i.e., SUDEP-related mortality in a 50% to < 75% reduction state is the product of baseline SUDEP-related mortality multiplied by [1–0.625]). This mid-point approach is used in Neuberger et al. (2020) for LGS patients. With this approach, patients experiencing a higher number of drop seizures incur an increased risk of SUDEP (Table 39) (75), thus demonstrating the possible impact of treatments on SUDEP related mortality.

Table 39 SUDEP mortality

SUDEP mortality	Cycle probability	Reference
Baseline SUDEP, proportion (95% CI)	0.00233 (0.001; 0.004)	Cooper et al. (2016) (74)
State 0: < 25% reduction, proportion	0.00335	Calculated using baseline SUDEP from Cooper et al. (2016) using approach described in Neuberger et al. (2020) (74, 75)
State 1: 25% to <50% reduction, proportion	0.00146	
State 2: 50% to <75% reduction, proportion	0.00087	
State 3: ≥75% response, proportion	0.00037	

Abbreviations: SUDEP = Sudden unexpected death in epilepsy

Non-SUDEP mortality in the model captures both status epilepticus-mortality and accidental-mortality. In the absence of LGS-specific data, evidence is sourced from Cooper et al. 2016 on DS patients (Table 40). The model determines accidental mortality in relation to SUDEP and SE mortality. This value was calculated from Cooper et al. 2016 as a proportion of additional accidental deaths observed given SUDEP and SE mortality (74). To determine accidental deaths in the model, the calculated proportion (21.40%) is multiplied each cycle (except titration) by SUDEP and SE deaths.

Table 40 Non-SUDEP and SE mortality

Non SUDEP: SE and accidental mortality	Probability	Reference
Probability of SE mortality for DS patient	0.093%	Cooper et al. (2016) (74)
Additional proportion of accidental mortality compared to SE + SUDEP mortality	21.40%	Cooper et al. (2016) (74)

Abbreviations: SUDEP = Sudden unexpected death in epilepsy; SE = Status epilepticus; DS = Dravet syndrome

8.2 Presentation of efficacy data from [additional documentation]

N/A. No evidence except for Study ZX008-1601 was used to inform efficacy estimates.

8.3 Modelling effects of subsequent treatments

N/A. Effects of subsequent treatments were not modelled.

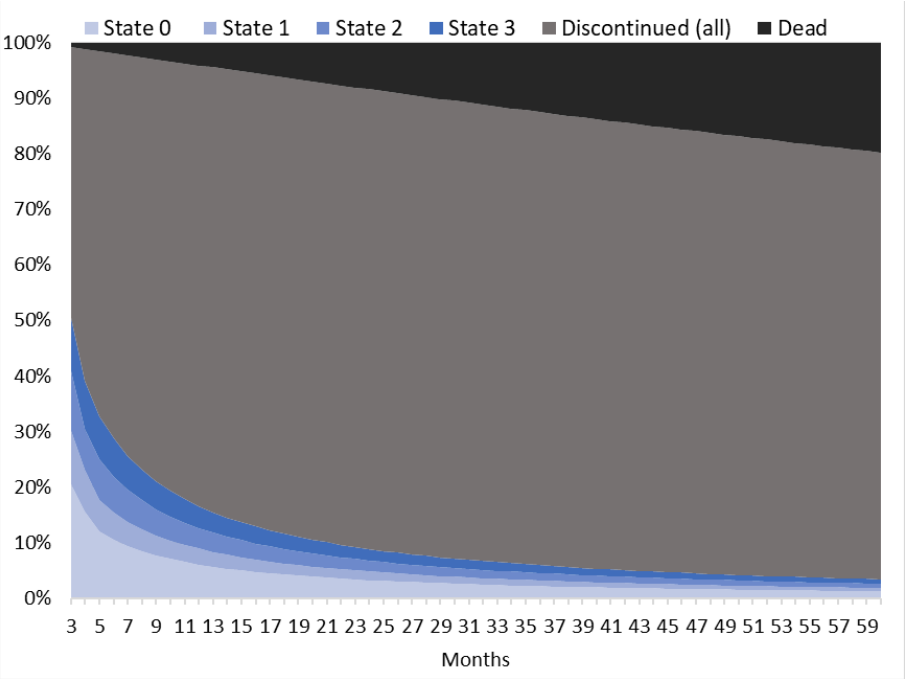
8.4 Other assumptions regarding efficacy in the model

Efficacy is based on the results of Study ZX008-1601, which compared FFA (i.e., FFA+ASMs) to a basket of ASMs. However, the base-case analysis compares FFA (i.e., FFA+ASMs) to what is considered SoC in Denmark (i.e., a basket of ASMs including CBD). The inclusion of CBD in the basket follows evidence from real world data in Denmark (2024) (35), a preliminary discussion with the DMC, and clinical expert opinions.

8.5 Overview of modelled average treatment length and time in model health state

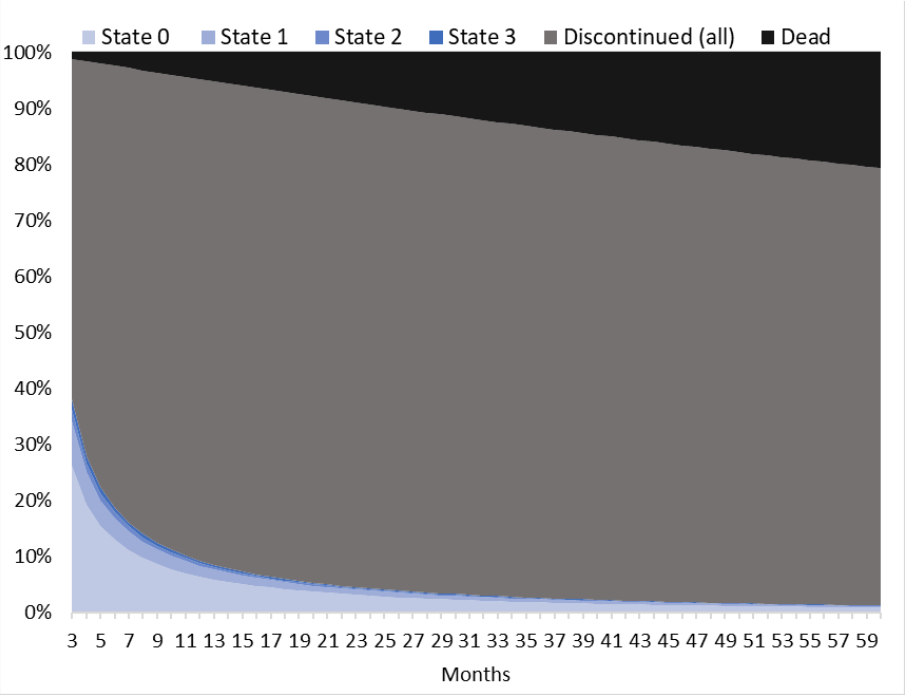
An overview of the distribution of patients among health states over time in the FFA and SoC groups is provided in Figure 5 and Figure 6 respectively.

Figure 5 Distribution of health states over time in FFA arm



Abbreviations: FFA = Fenfluramine

Figure 6 Distribution of health states over time in SoC arm



Abbreviations: SoC = Standard of care

OS and PFS are not effectiveness measures directly modelled in this analysis. Therefore Table 41 is not applicable. Estimates by modelled health state are presented in Table 42.

Table 41 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	N/A	N/A	N/A
[Name of comparator]	N/A	N/A	N/A

Table 42 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Health state 0 [months]	Health state 1 [months]	Health state 2 [months]	Health state 3 [months]	Dead [months]	Discontinued [months]
FFA+ASMs	50.2	19.0	9.2	11.3	11.3	496.5	629.7
SoC	26.2	18.0	5.5	1.9	1.3	513.3	637.0

Abbreviations: FFA = Fenfluramine; SoC = Standard of care

9. Safety

9.1 Safety data from the clinical documentation

In ZX008-1601 Part 1, safety analyses were performed on the safety population defined as all randomised subjects who received at least one dose of study drug. In Part 2, safety analyses were performed on the OLE safety population defined as all subjects who receive at least one dose of FFA during the OLE.

In Part 1 and 2, TEAEs were reported. In Part 1, an AE was classified as treatment emergent if it started on or after the date of the first dose of study treatment. An AE with partial or missing start date was classified as treatment-emergent, unless the non-missing components of the start date confirmed otherwise. In Part 2, an AE was classified as treatment emergent if it started on or after the first dose date in the OLE. Thus, AEs with onset in Part 1 that were ongoing in Part 2 were not included in the count of TEAEs in Part 2.

An overview of safety events across the treatment arms is provided in Table 43. Overall, safety events were similar across treatment arms and studies. However, a greater proportion of patients in Part 2 and in the FFA 0.7 mg/kg/day treatment arm in Part 1 experienced a serious TEAE compared to the placebo and FFA 0.2 mg/kg/day treatment arm in Part 1. In addition, a greater proportion of patients in the FFA 0.7 mg/kg/day treatment arm in Part 1 had a treatment-related TEAE compared to the other treatment arms in Part 1 and compared to Part 2. Finally, a greater proportion of patients in Part 2 discontinued treatment compared to patients in Part 1.

Table 43 Overview of safety events in ZX008-1601 Part 1 (complete Part 1 period [20 weeks]) and in ZX008-1601 Part 2 (19 October 2020)

	Placebo (N=87) (ZX008-1601 Part 1)	Fenfluramine 0.2 mg/kg/day (N=89) (ZX008-1601 Part 1)	Fenfluramine 0.7 mg/kg/day (N=87) (ZX008-1601 Part 1)	Fenfluramine (N=247) (ZX008-1601 Part 2)
Number of AEs, n	224	233	325	800
Number and proportion of patients with ≥1 AEs, n (%)	70 (80.5)	70 (78.7)	78 (89.7)	203 (82.2)
Number of serious AEs*, n	5	6	16	63
Number and proportion of patients with ≥ 1 serious AEs*, n (%)	4 (4.6)	4 (4.5)	10 (11.5)	40 (16.2)
Number of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 events Ω, n	1	1	4	39
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, Ω, n (%)	1 (1.1)	1 (1.1)	3 (3.4)	15 (6.1)
Number of adverse reactions‡, n	70	71	128	203
Number and proportion of patients with ≥ 1 adverse reaction‡, n (%)	37 (42.5)	36 (40.4)	48 (55.2)	102 (41.3)
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	4 (4.6)	7 (7.9)	10 (11.5)	83 (33.6)
Number and proportion of patients who discontinue treatment due to AEs, n (%)	0	4 (4.5)	6 (6.9)	13 (5.3)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N/A = not applicable; TEAE = treatment-emergent adverse event.
Notes: * A serious AE is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available. Ω CTCAEs were not reported in ZX008 Part 1 and Part 2, however, severe AEs were reported. A severe AE is defined as a type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. ‡ Defined as treatment-related TEAE in ZX008 Part 1 and Part 2.
Source: Zogenix International Limited, 2021, Table 7, Table 14.3.1.1.1.1, Table 14.3.1.2.1.1, Table 14.3.1.4.1.1, Table 14.3.1.6.1.1, and Table 14.3.1.5.1.1 (24); European Medicines Agency, 2023, Table 49 (69); Zogenix International Limited, 2021, Table 14.3.1.1.1.3.1, Table 14.3.1.2.1.3.1.1, Table 14.3.1.4.1.3.1, Table 14.3.1.6.1.3, Table 14.3.1.5.1.3.1, and Table 5 (25).

In Table 44, the frequency of all serious TEAEs with a frequency of ≥ 5% recorded the studies are listed. No serious TEAEs with frequency of ≥ 5% were recorded in either ZX008-1601 Part 1 or Part 2.

Table 44 Serious adverse events (ZX008-1601 Part 1 [complete Part 1 period, 20 weeks] and ZX008-1601 Part 2 [19 October 2020])

Adverse events	Placebo (N=87) (ZX008-1601 Part 1)		Fenfluramine 0.2 mg/kg/day (N=89) (ZX008-1601 Part 1)		Fenfluramine 0.7 mg/kg/day (N=87) (ZX008-1601 Part 1)		Fenfluramine (N=247) (ZX008-1601 Part 2)	
	No. of patients with AEs	No. of AEs	No. of patients with AEs	No. of AEs	No. of patients with AEs	No. of AEs	No. of patients with AEs	No. of AEs
Serious TEAEs occurring in ≥5%, n (%)	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event;
Notes: * A serious AE is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Source: Zogenix International Limited, 2021, Table 14.3.1.4.1.1 (24); Zogenix International Limited, 2021, Table 14.3.1.4.1.3.1 (25).

TEAEs of special interest, i.e., those most commonly reported in the FFA study, were included in the analysis. These AEs were assumed to occur in cycle 1. TEAEs of special interest included rash, somnolence, fatigue, diarrhoea and decreased appetite. In the model, AEs rates for FFA and ASMs were based on the safety data reported in Study ZX008-1601, over a period of 3 months, to match the cycle length.

Table 45 Adverse events used in the health economic model

Adverse events	FFA + ASMs	ASMs		
	Rate* used in economic model for intervention	Rate* used in economic model for comparator	Source	Justification
Diarrhoea	0.13	0.05	Knupp et al. 2022	Most commonly reported
Somnolence	0.17	0.10	Knupp et al. 2022	Most commonly reported
Pyrexia	0.08	0.11	Knupp et al. 2022	Most commonly reported
Decreased appetite	0.36	0.11	Knupp et al. 2022	Most commonly reported
Vomiting	0.08	0.06	Knupp et al. 2022	Most commonly reported

Notes: *Calculated over a 3-month period
Abbreviations: FFA = Fenfluramine; ASM = Anti-seizure medication

9.2 Safety data from external literature applied in the health economic model

N/A. No external data on safety was used in the model.

Table 46 Adverse events that appear in more than 5 % of patients

Adverse events	Intervention (N=87)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Constipation	8 (9.2)	N/A	Not modelled	5 (5.7)	N/A	Not modelled	3	N/A
Diarrhoea	11 (12.6)	N/A	13%	4 (4.6)	N/A	5%	7	N/A
Vomiting	7 (8.0)	N/A	8%	5 (5.7)	N/A	6%	2	N/A
Asthenia	5 (5.7)	N/A	Not modelled	3 (3.4)	N/A	Not modelled	2	N/A
Fatigue	16 (18.4)	N/A	Not modelled	9 (10.3)	N/A	Not modelled	7	N/A
Pyrexia	7 (8.0)	N/A	8%	10 (11.5)	N/A	11%	-3	N/A
Nasopharyngitis	6 (6.9)	N/A	Not modelled	8 (9.2)	N/A	Not modelled	-2	N/A
Upper respiratory tract infection	6 (6.9)	N/A	Not modelled	3 (3.4)	N/A	Not modelled	3	N/A
Weight decrease	7 (8.0)	N/A	Not modelled	2 (2.3)	N/A	Not modelled	5	N/A
Decreased appetite	31 (35.6)	N/A	36%	10 (11.5)	N/A	11%	21	N/A
Lethargy	5 (5.7)	N/A	Not modelled	2 (2.3)	N/A	Not modelled	3	N/A
Seizure	4 (4.6)	N/A	Not modelled	6 (6.9)	N/A	Not modelled	-2	N/A
Somnolence	15 (17.2)	N/A	17%	9 (10.3)	N/A	10%	6	N/A
Irritability	3 (3.4)	N/A	Not modelled	5 (5.7)	N/A	Not modelled	-2	N/A

10. Documentation of health-related quality of life (HRQoL)

HRQoL outcomes in Study ZX008-1601 were only included as additional exploratory end-points in terms of change from baseline. The included instruments were the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), the Zarit Caregiver Burden Inventory, and the Hospital Anxiety and Depression Scale (HADS). Of these, the Zarit and the HADS measured caregiver burden, which cannot be used to estimate HSUVs for LGS patients.

The remaining QOLCE instrument, only measured QoL in children, which cannot be generalized to adult patients nor mapped to EQ-5D scores due to missing algorithms and the low number of data-collection points.

Given that no health state utility values could be directly derived from the trial data, an SLR was conducted to identify HRQoL measures and (dis)utility values relevant for patients with LGS (see details in Appendix I). After full-text screening, eight unique publications were included. Ultimately, the only study using the EQ-5D instrument was included in the base-case analysis. The sources for utility scores used to inform the model and the base-case analysis are further discussed in section 10.3.

Table 47 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D	Verdian et al. (2008)	To inform model specific HSUVs

Abbreviations: HSUV = Health state utility value

10.1 Presentation of the health-related quality of life QOLCE

10.1.1 Study design and measuring instrument

The QOLCE questionnaire is a low-burden parent/caregiver assessment that evaluates how epilepsy affects day-to-day functioning of the subject in various life areas, including physical activities, well-being, cognition, social activities, behaviour, and general health. A question on overall QoL is also included. The QOLCE has been validated in children aged ≥4 years, and there are published data on the use of the QOLCE in children with epilepsy as young as 2 years of age (76) (77) . The QOLCE scores items with a possible 5-point response. To calculate subscale scores, the 5-point item scores are reverse coded as necessary so that scores of 5 represent the best possible response and 1 represents the worst possible response. Item scores are transformed to a 0-100 scale. A value of 0 represents the lowest or poorest score and 100 reflects the highest level of functioning.

10.1.2 Data collection

The QOLCE was conducted at the Randomization Visit (Visit 3) and at the EOS/ET (Visit 12) and the change from baseline was calculated. Descriptive statistics were presented for each QOLCE subscale and for the overall QoL score. The by-subject change in the overall QOLCE score was calculated by subtracting the overall score at baseline from the overall score at Visit 12 or at end-of-treatment procedures for withdrawn subjects. Each treatment group was compared pairwise with the others using pairwise Wilcoxon tests.

Table 48 Pattern of missing data and completion in SoC arm

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
SoC				
Baseline	87	2 (2.3%)	N/A	N/A
EOS	87	7 (8.0%)	N/A	N/A
Fenfluramine (0.2mg/kg/day)			N/A	N/A
Baseline	89	5 (5.6%)	N/A	N/A
EOS	89	6 (6.7%)	N/A	N/A
Fenfluramine (0.7 mg/kg/day)			N/A	N/A
Baseline	87	3 (3.4%)	N/A	N/A
EOS	87	10 (11.5%)	N/A	N/A

Abbreviations: EOS = end of study; HRQoL = Health related quality of life; SoC = Standard of care.

10.1.3 HRQoL results

The QOLCE scale scores are summarized for the ITT population in Table 49. No consistent improvements from baseline in QOLCE parameters were observed, though the 0.7mg/kg/day group did show numerical improvements on many QOLCE items compared with the SoC group. No significant differences between each of the treatment groups and SoC in change from baseline were observed on any QOLCE subscale at EOS, with the exception that subjects in the 0.2mg/kg/day group had a numerical mean decrease in the social interactions subscale that was significantly different from the SoC group

(p=0.0204). The mean (SD) overall quality of life score at baseline for the SoC, 0.2 mg/kg/day, and 0.7 mg/kg/day groups was 40.0 (13.762), 42.4 (13.574) and 37.0 (12.602), respectively. The mean (SD) change from baseline in the overall QoL total scores was similar between the treatment groups (2.5 [13.380], 0.8 [12.65], and 3.5 [12.139], respectively) (p=0.5060 for the comparison of 0.7 mg/kg/day versus SoC and p=0.6650 for the comparison of 0.2 mg/kg/day versus SoC)

Table 49 HRQoL QOLCE summary statistics

	ASMs		FFA 0.2 mg/kg/day		FFA 0.7 mg/kg/day		Intervention vs comparator
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value
Baseline	85	15.01 (14.6)	84	16.27 (15.6)	84	13.22 (14.4)	N/A
EOS	80	15.95 (13.1)	83	15.71 (15.7)	77	16.3 (17.7)	N/A

Abbreviations: SoC = Standard of care; HRQoL = Health related quality of life; ASM = Anti seizure medication; FFA = Fenfluramine; EOS = End of study

10.2 Health state utility values (HSUVs) used in the health economic model

N/A. Data from the studies forming the clinical effectiveness was not used to generate HSUVs due to the challenges highlighted at the beginning of section 10. External literature values were used, see section 10.3.

10.2.1 HSUV calculation

N/A

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

N/A

10.2.3 HSUV results

N/A

Table 50 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				
N/A	N/A	N/A	N/A	N/A

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

As described at the beginning of section 10, the publication by Verdian et al. (2008), identified through a systematic literature review, was used to inform HSUVs in the base case.

10.3.1 Study design

HRQoL data from a 2008 study by Verdian et al. (23) was identified, the reported estimates were used. Verdian et al. also referenced these data in another 2010 CEA study, Clements et al. applied it in a 2013 trial-based study, and it was also mentioned in the previous CBD NICE LGS submission (TA615) (73, 78, 79). The study provided LGS patient and caregiver utility values using EQ-5D, TTO and VAS measures for a UK community sample. Based on correspondence with Verdian in December 2024 (data on file), we were informed that EQ-5D-3L and Dolan 1997 Tariff were used. Unfortunately, the poster is not available. EQ-5D utility values can be negative, reflecting health states perceived as worse than death. This is a unique feature compared to TTO and VAS, which cannot yield negative utility values. As a result, TTO and VAS tend to show higher utility values for worse health states compared to EQ-5D. Within EQ-5D, negative utility values help reduce "floor effects" by enabling differentiation between very severe health states. This feature allows EQ-5D to provide a more nuanced assessment of severe health conditions, capturing the true burden on patients, and thus making it the most appropriate measure.

10.3.2 Data collection

Four health state (HS) descriptions of LGS outcomes and five HS descriptions of common adverse events of anti-epileptic treatments for LGS were developed following medical literature review and consultation with clinical experts. HSs were defined by tonic-atonic (drop attack) seizure frequency (SF). For LGS outcomes, the anchor state (HS-1) for uncontrolled disease was described by frequency of 21-28 seizures per week; HS-2 a reduction of < 50% in SF following adjunctive treatment; HS-3 a reduction of ≥50% and <75% in SF and HS-4 a ≥75% reduction in SF following adjunctive treatment. Time trade off interviews (TTO) were conducted with 119 members of the UK general public of whom 48% were caregivers/parents of children aged 4 to 18. A secondary analysis involved participants rating each health state on a visual analogue scale (VAS) and completing the EQ-5D questionnaire.

10.3.3 HSUV and disutility results

The mean utility score for HS-1, HS-2, H-S3 and HS-4 was 0.393, 0.461, 0.605 and 0.699 respectively using TTO method; 0.02, 0.414, 0.556 and 0.677 respectively using VAS scale; 0.02, 0.100, 0.500 and 0.596 respectively using the EQ-5D questionnaire. The study found that the differences between all LGS HSs and the anchor state were significant ($p<0.0001$) except for HS-2 when using the EQ-5D questionnaire. The preferences were reasonably consistent across age groups and gender. For adverse events the disutility score was 0.108 for concentration problems, 0.135 for weight loss, 0.174 for somnolence, 0.190 for rash and 0.193 for nausea/vomiting. Table 51 summarises the relevant HSUVs from the study used in the model.

In the absence of direct data from Study ZX008-1601, a disutility value for fatigue of -0.060 was applied to all TEAEs in the model, based on the Matza et al. 2019 study (65), which provided the only available disutility score for fatigue. Since specific disutility scores for other TEAEs of special interest were not available, the same disutility value was used for all TEAEs. TEAEs were assumed to occur only once during the initial cycle and therefore not modelled to occur in any subsequent cycles.

Table 51 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV 0: < 25% reduction	0.020	EQ-5D	UK	None
HSUV 1: 25% to <50% reduction	0.100	EQ-5D	UK	None
HSUV 2: 50% to <75% reduction	0.500	EQ-5D	UK	None
HSUV 3: >=75% response	0.596	EQ-5D	UK	None
Disutility for TEAEs of special interest	-0.060	TTO	UK	Fatigue disutility was the only TEAEs of special interest to be found in Matza et al. (2019). In the absence of other available data, fatigue disutility was applied to all TEAEs of special interest in the model.

Abbreviations: HSUV = Health state utility value; CI = Confidence Interval; UK = United Kingdom; TEAE = Treatment emergent adverse event

Table 52 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV 0				
Verdian et al. (23)	0.020	EQ-5D	UK	None
HSUV 1				
Verdian et al. (23)	0.100	EQ-5D	UK	None
HSUV 2				
Verdian et al. (23)	0.500	EQ-5D	UK	None
HSUV 3				
Verdian et al. (23)	0.596	EQ-5D	UK	None
Disutility for TEAEs of special interest				
Matza et al. (2019)	-0.060	TTO	UK	Fatigue disutility was the only TEAEs of special interest to be found in Matza et al. (2019). In the absence of other available data, fatigue disutility was applied to all TEAEs of special interest in the model.

Abbreviations: HSUV = Health state utility value; CI = Confidence Interval; UK = United Kingdom; TEAE = Treatment emergent adverse event

Given the difficulties of fully capturing the burden of disease with the available HSUVs from the literature, and the inherent characteristic of the LGS patient population. We included, in a separate scenario the results of this cost-effectiveness analysis also accounting for the impact of the disease on the HRQoL of the caregivers.

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

To inform the cost-effectiveness model, medicines AIP prices were sourced from medicinpriser.dk. Cost components of FFA and SoC are detailed in Table 55. As SoC medicines may be available in different formulations, the model allows to calculate a weighted average price per mg based on different pack sizes available. In the base-case the cheapest price reported on medicinpriser.dk was used. Standard of care includes a basket of ASMs following the baseline distribution observed in Study ZX008-1601 and CBD. Alternatively, the model allows a user to enter the proportions of each medication manually per treatment arm. In the base-case analysis, the distribution of drugs in the SoC basket is in line with the SoC arm from FFA pivotal trial, except for CBD, which is also expected to be used in Denmark. CBD uptake was based on Danish registry data which showed that 14.9 to 17.2% of LGS patients received CBD in 2024 (35). Concomitant ASM use may be reduced after the introduction of FFA, and more so than after the introduction of CBD. For simplicity and due to availability of LGS specific data, this was not incorporated into the model. This conservative approach favours SoC, as it incorporating this effect would be expected to lower the treatment costs associated with FFA.

Table 53 Distribution of medications under SoC

Treatment	Patient distribution (%)	Source
Clobazam	44%	FFA registration trial: Study ZX008-1601 ASM distribution at baseline in the SoC arm (9).
Levetiracetam	23%	
Valproate	56%	
Lamotrigine	33%	
Topiramate	14%	
Rufinamide	21%	
Cannabidiol	17.2%	Danish real-world data (35).

Abbreviations: FFA = Fenfluramine; ASM = Anti-seizure medications; SoC = Standard of care

Age and dosage

Treatment dosing of FFA, CBD and certain ASMs is calculated based on a patient's weight. The model includes two options to estimate how weight varies across a patient's life: a '*Fixed weight*' or '*Dynamic weight*' approach. In the base-case analysis, the model uses a fixed weight approach to accurately estimate drug dosing and calculate drug acquisition costs aligning with age-dependent dosing as described in the respective SmPC. The mean weight for each age group is sourced from Study ZX008-1601 (9). Drug acquisition costs are calculated according to age-dependent dosage considering mg/kg/day, mg/day and maximum daily dose (when applicable) of each add-on treatment and

basket of SoC ASMs. An average dose is calculated using the proportion of patients across age groups based on Danish real-world data Table 54. Proportion of patients in each age group only based on Study ZX008-1601, were explored in a separate scenario analysis.

Table 54 Age distribution and mean weight

Age groups	Proportion of patients used to calculate average dose (%)	Mean weight (kg)	Reference
2-5y	3.5%[a]	17.63*	Weight: Study ZX008-1601 (9, 80) Proportion of patients in age groups: Danish real-world data (35).
6-11y	3.5% [a]	30.11*	
12-17y	46.5% [a]	48.07	
≥18y	46.5% [a]	62.11	

Notes: [a] See section 6.1.3 and Table 19 for calculations

Table 55 summarises medicine costs for FFA and SoC used in the model.

Table 55 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Pack size	Price* per pack (DKK)
Fenfluramine	T+M: 0.7mg/kg/day OLE: 0.4mg/kg/day	100%	Every day	Yes, no wastage assumed	360ml	[redacted]
SoC (CBD + ASM):						
Cannabidiol	20mg/kg/day	100%	Every day	Yes, no wastage assumed	100ml	11,999
Clobazam	Age <18: 0.65mg/kg/day Age>18: 25mg/day	100%	Every day	Yes, no wastage assumed	100stk	103
Levetiracetam	Age<18: 1000mg/day Age>18: 2000mg/day	100%	Every day	Yes, no wastage assumed	50stk	20
Delepsine (Valproinsyre)	Age<5: 20mg/kg/day Age>5: 25mg/kg/day	100%	Every day	Yes, no wastage assumed	100stk	78

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Pack size	Price* per pack (DKK)
Lamoprim	Age<11: 3mg/kg/day Age>11: 150mg/day	100%	Every day	Yes, no wastage assumed	100stk	70
Topiramat	Age<18: 7mg/kg/day Age>18: 300mg/day	100%	Every day	Yes, no wastage assumed	60stk	15
Rufinamid	Age<6: 37.5mg/kg/day Age>6: 400gm/day	100%	Every day	Yes, no wastage assumed	10stk	48
Diazepam	Age<12: 7.5mg/day Age>12: 15mg/day	100%	Every day	Yes, no wastage assumed	5 x 2.5ml	80
Midazolam	Age<6: 5mg/day Age 6 to 12: 7.5mg/day Age 12+: 10mg/day	100%	Every day	Yes, no wastage assumed	10 x 5ml	1,568

Notes: *AIP prices
Abbreviations: T+M = Treatment and management; OLE = Open label extension

11.2 Medicine costs – co-administration

NA. No co-administration needed; CBD and all the other ASMs were included in SoC basket.

11.3 Administration costs

N/A. Given that all ASMs and FFA are administered orally by the parent/caregiver, this cost-effectiveness analysis assumed no treatment administration cost in both arms.

Table 56 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
[E.g. i.v. infusion, subcutaneous infusion]	N/A	N/A	N/A	N/A

11.4 Disease management costs

Patients on FFA are required to have an echocardiogram conducted every six months for the first two years and annually thereafter. A final echocardiogram is performed upon treatment discontinuation (81). The cost associated with an echocardiogram was sourced from the DRG tariff for 2025 (82). The cost of routine monitoring for serum transaminase and total bilirubin levels at months 1, 3 and 6 in patients taking CBD and the cost of intensified monitoring of serum transaminase and total bilirubin levels at 2 weeks and months 1, 2, 3 and 6 and periodically thereafter in patients taking valproate with CBD (SmPC) is not incorporated in the model, but the impact of this on the costs in the SoC group is expected to be minimal and in favour of FFA.

Two types of HCRU costs are considered in the analysis: primary care (also referenced as LGS routine care) and secondary care (also referenced as seizure related care). Health states are based on the reduction of seizures obtained at T+M, but the model estimated an equivalence in terms of frequency of seizures to account for the costs and resource use. In the absence of more up to date data, resource use for routine care cost is estimated across categories of mean number of drop seizure, i.e., (0, <45, 45-110 and >110) from CBD NICE LGS submission (TA615) which was based on clinical expert opinion (73).

Resource use for seizure-associated secondary care costs is estimated separately for GTC and other seizure types. The distribution of GTC and other seizures at T+M for each arm is estimated based on the observed GTC seizure reduction in Study ZX008-1601 (9).

LGS routine care

Health state costs in the model are linked to the number of drop seizures experienced by the patients in each health state. For each state 0, 1, 2 and 3 the mean number of drop-seizures experienced by the patients is matched to three seizure frequency ranges for the purpose of estimating the resource use consumption associated to each health state. The HCRU inputs associated with the number of seizures were sourced from the CBD NICE LGS submission (TA615) (73). The HCRU is defined for two age groups of patients those <12y and those ≥12y and included nurse visits, specialist visits, paediatrician/general practitioner visits, phone call follow-ups and number of rescue medication per intake. HCRU inputs are described in Table 57. It was assumed that the cost for paediatric services would only apply to patients below the age of 12-years old

Table 57 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Echocardiogram	Every 6 months for 2 years, then annually + 1 at treatment dis-continuation (FFA)	2,111.00	05PR04	DRG 2025
Physician visit	Table 58	156.39	Konsultation	(83)
Specialist visit	Table 58	816.35	1. konsultation	(83)
Nurse	Table 58	462	1-hour nurse visit Sygeplejersker	(83)
Phone consultation	Table 58	30.51	Telefonkonsultation	(83)

Table 58 Disease management resource frequency

Activity	Severity by drop-seizure frequency (per 28 days)	Number of annual visits <12 years	Number of annual visits >12 years
Nurse visit	Seizure-Free	2.00	2.00
	≤ 45	4.00	4.00
	>45 to ≤ 110	8.00	4.80
	> 110	12.00	12.00
Specialist visit	Seizure-Free	1.00	0.50
	≤ 45	2.00	1.00
	>45 to ≤ 110	4.00	1.20
	> 110	6.00	3.00
GP/Paediatrician Visit	Seizure-Free	2.00	0.00
	≤ 45	4.00	0.00
	>45 to ≤ 110	8.00	0.00
	> 110	12.00	0.00
Phone Call Follow-up	Seizure-Free	0.00	0.00
	≤ 45	2.00	1.00
	>45 to ≤ 110	5.00	2.50

	> 110	12.00	6.00
Rescue medication (by intake)	Seizure-Free	0.00	0.00
	≤ 45	2.00	2.00
	>45 to ≤ 110	5.00	5.00
	> 110	8.00	8.00

Seizure related care

The model uses efficacy data on proportion of reduction in GTC seizure in the treatment arms to proportionally weight the cost for each state to account for seizure-related care costs, such as hospitalisation and emergency department visits. The HCRU costs for hospitalisations are based on both general ward and intensive care unit inpatient admissions, and emergency department visits to calculate per patient per cycle cost of seizure-related care for each seizure type.

The HCRU for LGS patients is first calculated to account for patient's age distribution using Chin et al. (2021) (66). Chin et al. (2021) retrospectively investigated ASM usage and HCRU of patients with LGS. The reference analysis used data on patients with confirmed LGS diagnosis. The authors also reported data on patients with probable LGS recorded in their electronic medical records, an alternative option implemented in the model that can be used instead of confirmed LGS (base-case). The proportion of inpatients requiring ICU visits was considered independent from seizure type or age distribution and was sourced from Tobochnik et al. who analysed data from patients who initially arrived at a US emergency department with any type of seizure and required ICU management (67).

Then, the HCRU for each seizure type (GTC and other seizures) is estimated from a publication on epileptic patients by Kurth et al. (2010) (68). These data are used to derive the final HCRU for LGS patients adjusted by seizure type.

Costs of seizure related care in the base case analysis are calculated using the unit costs presented in Table 57. The costs of secondary care per patient per cycle are split between costs incurred for GTC seizure types and costs incurred for other seizure types (Table 60).

Table 59 Healthcare utilisation per year per LGS patient, adjusted for age

Healthcare resource utilisation	Age <12y Mean (SD)	Age >12y Mean (SD)	Age <12y distribution	Age >12y distribution	HCRU adjusted for age	Reference
Number of hospital inpatient admissions, PPY	1.50 (1.47)	0.96 (1.78)	41.83%	58.17%	1.19	Chin et al. (2021) - HCRU for confirmed LGS patients in the UK(66)
Hospital inpatient LOS, days[1]	2.48 (6.07)	3.24 (6.80)	41.83%	58.17%	2.92	
Number of A&E	0.85	1.15	41.83%	58.17%	1.02	

visits, PPY	(1.18)	(2.17)				
Proportion of in-patients requiring ICU visits	N/A	N/A	N/A	N/A	4.2%	Tobochnik et al. (2015) (67)

Notes: 1 This input is used to calculate the number of hospital admissions in Table 60.
Abbreviations: A&E = Accident and Emergency; LGS = Lennox-Gastaut Syndrome; HCRU = Healthcare Resource Use; ICU, Intensive Care Unit; LOS, Length of Stay; N/A, Not Applicable; PPY, Per Patient-Year; SD, Standard Deviation; UK, United Kingdom.

Table 60. Healthcare utilisation per year for epileptic patients, adjusted for seizure type

Healthcare resource utilisation	GTC seizures	Other seizures	Seizure distribution at baseline	Average HCRU (adjusted for seizure type)	Reference	
Hospital admissions[1]	2.14	0.71	47.00%	53.00%	1.38	Kurth et al. (2010) (68)
Hospital days	6.26	2.08	47.00%	53.00%	4.04	
Emergency department visits	1.52	0.78	47.00%	53.00%	1.13	Strzelczyk et al. 2024 (84)

[1] Hospital admissions = hospital days/ Hospital inpatient LOS, days.
Abbreviations: GTC = Generalised Tonic-Clonic; HCRU = Healthcare Resource Use.

Table 61 Healthcare utilisation of LGS per patient per year per seizure type

Healthcare resource utilisation	GTC seizures	Other seizures	Reference
Number of hospital inpatient admissions, PPY	1.84	0.61	Calculated: (GTC HCRU in Table 60/Average HCRU adjusted for seizure type in Table 60) * LGS HCRU adjusted for age in Table 59 (Other HCRU in Table 60/Average HCRU adjusted for seizure type in Table 60) * LGS HCRU adjusted for age in Table 59
Hospital inpatient LOS, days	4.52	1.50	
Number of emergency department visits, PPY	1.38	0.71	

Abbreviations: GTC = Generalised Tonic-Clonic; HCRU = Healthcare Resource Use; PPY = Per Patient Per Year.

11.5 Costs associated with management of adverse events

The base case analysis sourced the cost of managing adverse events from published DRG tariffs for 2025 (82) (Table 62) and the proportion of patients experiencing them from Knupp et al (2022) (Table 63). The cost was applied as a one-off cost in the first cycle when patients start treatment.

Table 62 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Diarrhoea	01MA98	2.012,00
Somnolence	01MA98	2.012,00
Pyrexia	01MA98	2.012,00
Decreased appetite	01MA98	2.012,00
Vomiting	01MA98	2.012,00

Table 63 Proportion of patients experiencing AEs

	FFA	SoC
Diarrhoea	0.13	0.05
Somnolence	0.17	0.1
Pyrexia	0.08	0.11
Decreased appetite	0.36	0.11
Vomiting	0.08	0.06

Abbreviations: AE = Adverse events

11.6 Subsequent treatment costs

The base-case analysis accounted for subsequent treatment received by patients who discontinue from the treatment arms (FFA and SoC) and move to the discontinuation state. Patients were assumed to receive ASMs (excluding CBD) with the same distribution observed in Study ZX008-1601. The model also includes the option to define the proportion of discontinued patients that receive subsequent treatment, which for the base-case was set to 100% (i.e., all discontinued patients move to subsequent treatment)

In the base-case analysis, an equal distribution of SoC treatment (as per the ASMs arm of Study ZX008-1601) in subsequent lines is given to all patients who discontinue from the treatment arms (i.e., 100% of discontinued patients move to a subsequent treatment). This is likely to be an underestimation of subsequent treatment costs, as patients likely would require higher doses or additional ASMs after stopping FFA.

Table 64 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
After FFA: ASMs	See Table 55	100%	Daily	No wastage
After SoC: ASMs	See Table 55	100%	Daily	No wastage

Abbreviations: FFA = Fenfluramine; ASM = Anti seizure medication; SoC = Standard of care

Table 65 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Clobazam	250mg	50stk	20	100%	Applied to the proportion of people in the discontinuation state
Levetiracetam	100mg	100stk	78	100%	Applied to the proportion of people in the discontinuation state
Delepsine (Valproinsyre)	100mg	100stk	70	100%	Applied to the proportion of people in the discontinuation state
Lamoprim	25mg	60stk	15	100%	Applied to the proportion of people in the discontinuation state
Rufinamide	100mg	10stk	48	100%	Applied to the proportion of people in the discontinuation state
Topiramat	100mg	10stk	48	100%	Applied to the proportion of people in the discontinuation state

11.7 Patient costs

In the base case, costs associated with transportation were accounted for. Specifically, for visits to GP, nurses, specialists, hospital, and adverse events. Based on DMC guidelines on unit costs (83) transport was valued at 3.79DKK per kilometre and the distance set to 20 km.

Table 66 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Transportation costs in case of GP, nurse, specialist visit, hospital and AE visits	20 km distance with a value of 3.79 DKK/km

Abbreviations: GP = General practitioner; km= kilometre; AE = adverse event

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A. No other costs were included.

12. Results

12.1 Base case overview

A summary of the base case is presented in Table 67. While the results are summarised in Table 68.

Table 67 Base case overview

Feature	Description
Comparator	SoC
Type of model	Markov model
Time horizon	86 years
Treatment line	Subsequent treatment line, as add-on therapy, of LGS
Measurement and valuation of health effects	HSUVs sourced from the literature (23)
Costs included	Medicine costs Disease management costs Costs of adverse events Subsequent treatment costs Transportation costs
Dosage of medicine	Based on weight
Average time on treatment	FFA: 31.8 months

Feature	Description
	SoC: 17.3 months
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	No wastage
Average time in model health state	
Health state 0: SoC 11.9 months; FFA 12 months	
Health state 1: SoC 3.7 months; FFA 6 months	
Health state 2: SoC 1.3 months; FFA 7.1 months	
Health state 3: SoC 0.9 months; FFA 6.9 months	
Discontinued: SoC 578 months; FFA 568.5 months	
Death: SoC 581.2 months; FFA 576 months	

Abbreviations: SoC= Standard of care; FFA = Fenfluramine; LGS = Lennox gastaut syndrome

12.1.1 Base case results

Table 68 presents the discounted base case results for the treatment of LGS, with FFA versus SoC. The comparison indicates a net QALY gain of [redacted] at an incremental cost of [redacted]. Results indicate that FFA is more effective but also more costly than SoC, with an overall ICER of DKK [redacted].

Table 68 Base case results, discounted estimates

	FFA	SoC	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Monitoring costs	9,363	0	9,363
Disease management costs (routine care)	80,123	80,349	-226
Disease management costs (secondary care)	704,494	766,158	-61,664
Subsequent treatment costs	84,791	86,881	-2,090
Costs associated with management of adverse events	1,041	559	482
Patient costs	10,923	10,943	-20
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (state 0)	[redacted]	[redacted]	[redacted]
Life years gained (state 1)	[redacted]	[redacted]	[redacted]

	FFA	SoC	Difference
Life years gained (state 2)	[redacted]	[redacted]	[redacted]
Life years gained (state 3)	[redacted]	[redacted]	[redacted]
Life years gained (Discontinued)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (state 0)	[redacted]	[redacted]	[redacted]
QALYs (state 1)	[redacted]	[redacted]	[redacted]
QALYs (state 2)	[redacted]	[redacted]	[redacted]
QALYs (state 3)	[redacted]	[redacted]	[redacted]
QALYs (Discontinued)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]**/LY**	
Incremental cost per QALY gained (ICER)		[redacted]**DKK/QALY**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

One-way sensitivity analysis

A one-way sensitivity analysis (OWSA) was performed to identify key model drivers based on their relative influence on results. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available or using standard errors estimated based on ±10% variation around the mean where measures of variance around the base case values were not available. Parameters were varied individually and the 10 most influential parameters on the ICER were reported. OWSA results for FFA versus SoC are presented in Figure 7 and Table 69. The OWSA showed that the parameters with the greatest influence on the ICER were patients' weight (highly correlated with dosage), the efficacy of FFA in reducing seizures, and the utility scores for the health states in the model.

Table 69 Single parameter variation results

Parameter	ICER (DKK/QALY)		
	At low value	At high value	Difference
Weight_fixed_12-17 yrs of age	[redacted]	[redacted]	[redacted]
Weight_fixed_18 -35 yrs of age	[redacted]	[redacted]	[redacted]
Relative Risk_T+M_FFA_le50%	[redacted]	[redacted]	[redacted]

Relative Risk_T+M_FFA_le25%	[redacted]	[redacted]	[redacted]
State Occupancy_cycle 1	[redacted]	[redacted]	[redacted]
Relative Risk_T+M_FFA_le75%	[redacted]	[redacted]	[redacted]
caregiver_utility_Verdian_2008_State_3_EQ5D	[redacted]	[redacted]	[redacted]
caregiver_utility_Verdian_2008_State_2_EQ5D	[redacted]	[redacted]	[redacted]
HCRU_seizure_GTC_Hospital_days	[redacted]	[redacted]	[redacted]
patient_utility_Verdian_2008_State_3_EQ5D	[redacted]	[redacted]	[redacted]

Abbreviations: FFA = fenfluramine; T+M = Titration and maintenance; HCRU = healthcare resource use; GTC = Generalised tonic-clonic

Figure 7 Tornado plot of single parameter variation

Abbreviations: FFA = fenfluramine; T+M = Titration and maintenance; HCRU = healthcare resource use; GTC = Generalised tonic-clonic

Scenario analyses

Scenario analyses were performed to test the impact of change in key inputs and assumptions on the cost-effectiveness estimates. Table 70 lists the scenarios conducted around the base case analysis presented above. The results of the scenario analyses illustrate the robustness of the analysis with ICER results varying from [redacted] to [redacted] DKK/QALY.

Table 70 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
Age distribution based on Study ZX008-1601	Changed age distribution from Danish data to Study 1601 data.	To assess the impact of age distribution	[redacted]	[redacted]	[redacted]
Results including	Included caregiver HRQoL	Due to patient population it is reasonable to	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
caregiver HRQoL	based on EQ-5D	assume a heavy impact on the caregivers HRQoL, which is also better captured by the available instruments			

For the caregiver HRQoL scenario, we assumed that 10% of patients would get institutionalised and that these would need 0.8 caregivers each (calculated based on total days with full caregiver responsibility (annual leave minimum entitlement for FTE, bank/public holidays, weekends). Non-institutionalised patients were assumed to be in contact with 2 caregivers.

12.2.2 Probabilistic sensitivity analyses

A probabilistic analysis was conducted to account for the joint uncertainty of the underlying parameter estimates. The choice of distribution (beta, gamma, log-normal, normal and Dirichlet) applied to parameters was selected based on recommendations outlined in Briggs et al. 2008(85). Standard errors were taken directly from source data if reported or calculated from published standard deviations (SD) sample size and/ or 95% confidence interval data. If none were reported SE is estimated as 10% of the default value. The probabilistic results (ICER [redacted] DKK/QALY gained) aligned well with deterministic results (ICER [redacted] DKK/QALY gained), showing that uncertainty tends to be in favour of fenfluramine. The scatterplot of all the PSA iterations is presented in Figure 8, while Figure 9 presents the cost-effectiveness acceptability curves (CEAC). The scatterplot confirms that FFA is more efficacious but also more expensive compared to SoC.

Figure 8 Cost-effectiveness plane

Figure 9 Cost-effectiveness acceptability curve

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending FFA in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted. The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where FFA is recommended as a standard treatment and the scenario where FFA is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

Number of patients (including assumptions of market share)

The company has estimated that each year, approximately 28 new patients are diagnosed with LGS, with 176 prevalent patients. Of these, in case FFA were to be

introduced, 6% will receive FFA in the first year. The share is assumed to grow up to approximately 50% in years 2 to 5.

Table 71 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
FFA	12	21	47	78	144
SoC	164	183	185	182	144
			Non-recommendation		
FFA	0	0	0	0	0
SoC	176	204	232	260	288

Budget impact

Table 72 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

Clinicians consulted during the applications are:

Cathrine Gjerulfsen, MD, Filadelfia Hospital.

Marina Nikanorova, Associate Prof, MD, Filadelfia Hospital.

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Appendix A. Main characteristics of studies included

Table 73 Main characteristic of study ZX008-1601 – Part 1

Trial name: ZX008-1601 – Part 1	NCT number: NCT03355209
Objective	To evaluate the effect of fenfluramine 0.7 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with LGS based on the change in frequency of seizures that result in drops between baseline and the combined T+M Periods.
Publications – title, author, journal, year	Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial. Knupp KG, Scheffer IE, Ceulemans B, Sullivan JE, Nickels KC, Lagae L, Guerrini R, Zuberi SM, Nabbout R, Riney K, Shore S, Agarwal A, Lock M, Farfel GM, Galer BS, Gammaitoni AR, Davis R, Gil-Nagel A. JAMA Neurol. 2022 (9)
Study type and design	Double-blinded randomised placebo-controlled phase 3 study. Subjects who qualified were randomised (1:1:1) in a double-blind manner to receive one of two doses of fenfluramine (0.2 or 0.7 mg/kg/day [or 0.5 mg for subjects taking concomitant stiripentol]) or placebo. Randomisation was stratified by weight (<37.5 kg, ≥37.5 kg). Randomisation was centralised through an interactive web response system. To ensure that the volume of study drug taken could not be associated with the dose group, thus unblinding the study, subjects were randomly assigned different concentrations of the fenfluramine oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the interactive web response system. No crossover was allowed. The study is completed. Participants, care providers, investigators, and outcomes assessors were masked.
Sample size (n)	263
Main inclusion criteria	• Male or non-pregnant, non-lactating female, age 2 to 35 years, inclusive as of the day of the Screening Visit. • Clinical diagnosis of LGS, where seizures that result in drops are not completely controlled by current antiepileptic treatments. • Onset of seizures at 11 years of age or younger. • Abnormal cognitive development. • Must be receiving at least one concomitant anti-epileptic drug and up to four concomitant anti-epileptic treatments.
Main exclusion criteria	• Degenerative neurological disease • History of hemiclonic seizures in the first year of life • Only drop seizure clusters

Trial name: ZX008-1601 – Part 1	NCT number: NCT03355209
	• Previous or current exclusionary cardiovascular or cardiopulmonary abnormality that was detected on ECHO, ECG, or physical examination • Concomitant cannabidiol use (cannabidiol was not an approved medication anywhere in the world at the time of study enrolment).
Intervention	Fenfluramine (0.2 mg/kg/day [89 subjects] or 0.7 mg/kg/day [87 subjects]) as add-on to SoC.
Comparator(s)	Matching placebo (87 subjects) added to SoC dosed in the same manner as fenfluramine.
Follow-up time	The study consisted of a 4-week Baseline, 2-week Titration Period, 12-week Maintenance, and 2-week Taper or Transition Period. The mean treatment duration was 113.41 days (SD: 13.03) in the placebo arm, 109.55 days (SD: 23.07) in the fenfluramine 0.2 mg/kg/day arm, and 107.02 days (SD: 23.37) in the fenfluramine 0.7 mg/kg/day arm. In all treatment arms, the median treatment duration was 112 days.
Is the study used in the health economic model?	Yes. Used to inform efficacy.
Primary, secondary and exploratory endpoints	***Endpoints included in this application:*** The primary endpoint was percent CFB in the frequency of seizures that result in drops (i.e., DSF) in T+M period in the fenfluramine 0.7 mg/kg/day group compared with the placebo group. Key secondary endpoints were: CFB in DSF in T+M period in the fenfluramine 0.2 mg/kg/day group compared with the placebo group; proportion of subjects who achieved a ≥50% reduction from Baseline in the DSF, comparing the fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo; and proportion of subjects who achieve improvement on the CGI-I scale as assessed by Principal Investigator, comparing the fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo. Safety endpoints are also included in this application. ***Other endpoints:*** Additional secondary endpoints included fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day groups compared independently versus placebo on the following: CFB during T+M in frequency of all seizures that typically result in drops whether ESC-confirmed as drop or not; CFB during T+M in frequency of all countable motor seizures; CFB during T+M in frequency of all countable nonmotor seizures; CFB during T+M in the frequency of all countable seizures; CFB during M in the frequency of seizures that result in drops; CFB during M in the frequency of seizures

Trial name: ZX008-1601 – Part 1	NCT number: NCT03355209
	that typically result in drops; CFB during M in the frequency of all countable motor seizures; and CFB during M in the frequency of all countable nonmotor seizures; CFB during M in the frequency of all countable seizures; Proportion of subjects who achieve a worsening from Baseline (i.e., ≤0% reduction), or >0%, ≥25%, ≥50%, ≥75%, or 100% reduction between baseline and T+M, and baseline and M, in seizures that result in drops, seizures that typically result in drops, all countable motor seizures, all countable nonmotor seizures, and all countable seizures; Number of seizure-free days in the Baseline, M, and T+M, defined as 1) days with no seizures that results in drops, and 2) days with no countable motor seizures; The longest interval (days) between seizures that result in drops comparing the fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo; and CGI-I as assessed by the parent/caregiver. None of the additional secondary endpoints are included in this application.
Method of analysis	All efficacy analyses were based on the mITT population. DSF was assessed based on a nonparametric analysis. Percentage who achieved a ≥50% reduction from baseline in DSF was analysed based on a logistic regression model. Investigator ratings of improvement on the CGI-I scale were estimated based on a Cochran-Mantel-Haenszel odds ratio.
Subgroup analyses	The following pre-specified subgroups were used for selected efficacy analyses: • Age: 2 to <6, 6 to <12, 12 to <18, and ≥18 to 35 years • Sex: male, female • Baseline weight: <37.5 versus ≥37.5 kg • Number of concomitant anti-epileptic drugs: ≤2, 3, ≥4 medications • Number of prior anti-epileptic drugs: 0 to 3, 4 to 6, 7 to 9, ≥10 medications • Baseline DSF: based on observed tertiles
Other relevant information	N/A

Abbreviations: CFB = change from baseline; CGI-I = Clinical Global Impression - Improvement; DSF = drop seizure frequency; ECG = electrocardiogram; ECHO = echocardiogram; ESC = Epilepsy Study Consortium; LGS = Lennox-Gastaut syndrome; M = maintenance; mITT = modified intent-to-treat; SD = standard deviation; SoC = standard of care; T+M = titration and maintenance.
Source: ClinicalTrials.gov, year (61); Zogenix International Limited, 2021 (24); Knupp et al. 2022 (9).

Table 74 Overview of Main characteristic of study ZX008-1601 – Part 2

Trial name: ZX008-1601 – Part 2	NCT number: NCT03355209
Objective	To assess the long-term safety and tolerability of fenfluramine in children and adults with LGS with regard to AEs, laboratory parameters, physical examination, neurological examination, Tanner Staging, cognition (BRIEF), vital signs (blood pressure, heart rate, temperature, and respiratory rate), ECG, ECHO, body weight, and BMI.
Publications – title, author, journal, year	Fenfluramine provides clinically meaningful reduction in frequency of drop seizures in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. Knupp KG, Scheffer IE, Ceulemans B, Sullivan J, Nickels KC, Lagae L, Guerrini R, Zuberi SM, Nabbout R, Riney K, Agarwal A, Lock M, Dai D, Farfel GM, Galer BS, Gammaitoni AR, Polega S, Davis R, Gil-Nagel A. Epilepsia. 2023 (64)
Study type and design	Open-label, flexible-dose extension study (phase 3). The study is completed.
Sample size (n)	247
Main inclusion criteria	• Continue to meet the eligibility criteria for the core study (ZX008-1601 Part 1) • Satisfactorily completed the core study (ZX008-1601 Part 1)
Main exclusion criteria	Experienced any of the following at the end of the core study (ZX008-1601 Part 1) • Clinically meaningful worsening of seizures • Clinically significant laboratory findings (e.g., elevated alanine transaminase levels, decreased platelet count) • Weight loss >15% during the T+M period of the core study that failed to stabilise.
Intervention	Subjects received a starting dose of 0.2 mg/kg/day fenfluramine (247 subjects). Dosing was decreased or increased based on effectiveness and tolerability, up to 0.7 mg/kg/day of fenfluramine (or 0.5 mg/kg/day if taking concomitant stiripentol). The maximum dose administered was 30 mg/day (or 20 mg/day for subjects taking concomitant stiripentol).
Comparator(s)	N/A
Follow-up time	Date of first subject enrolled in Part 2 (18 April 2017) to DCO date (19 October 2020). At the 19th of October 2020 data cut, the mean treatment duration was 298.9 days (SD: 122.88), and the median treatment duration was 364.0 days.

Trial name: ZX008-1601 – Part 2	NCT number: NCT03355209
Is the study used in the health economic model?	Yes. Used to inform efficacy.
Primary, secondary and exploratory endpoints	***Endpoints included in this application:*** Endpoints evaluated in the interim analyses were: CFB in DSF; Proportion of subjects who achieved a worsening from baseline (i.e., ≤ 0% reduction), or > 0%, ≥ 25%, ≥ 50%, ≥ 75%, 100% reduction, and "near seizure freedom" (i.e., 0 or 1 seizure) from baseline in frequency of seizures that result in drops, seizures that typically result in drops – only results for ≥ 50% included in this application; CGI-I rating, as assessed by the Principal Investigator; and safety. ***Other endpoints:*** Endpoints evaluated in the interim analyses were: Change in frequency of all seizures that typically result in drops between baseline and the OLE treatment period whether ESC-confirmed as drop or not; Number of seizure-free days, i.e., days with no seizures that result in drops; Longest interval between seizures that result in drops; and CGI-I rating, as assessed by the parent/caregiver. Exploratory endpoints evaluated in the interim analyses were: Incidence of status epilepticus; Frequency of rescue medication usage; and number of days rescue medication used.
Method of analysis	All efficacy analyses were based on the OLE mITT population. DSF was assessed using a Wilcoxon signed-rank test. 95% CIs represent Exact Clopper-Pearson CIs in the analyses of percentage who achieved a ≥50% reduction from baseline in DSF and investigator ratings of improvement on the CGI-I scale.
Subgroup analyses	Analyses of CFB during the OLE Treatment Period in DSF per 28 days and typical DSF were performed for pre-specified subgroups based on Part 1 age (2 to <6, 6 to <12, 12 to <18, and ≥18 to 35 years) and on Part 1 baseline body weight (<37.5 versus ≥37.5 kg). Also, analyses of CGI-I ratings by the Investigator and parent/caregiver were performed for the Part 1 age subgroups.
Other relevant information	N/A

Abbreviations: AE = adverse event; BMI = body mass index; BRIEF = Behavior Rating Inventory for Executive Function; CFB = change from baseline; DCO = data cut-off; DSF = drop seizure frequency; CGI-I = Clinical Global Impression - Improvement; DSF = drop seizure frequency; ECG = electrocardiogram; ECHO = echocardiogram; ESC = Epilepsy Study Consortium; LGS = Lennox-Gastaut syndrome; mITT = modified intent-to-treat; N/A = not applicable; OLE = open-label extension; SD = standard deviation; T+M = titration and maintenance.
Source: ClinicalTrials.gov, year (61); Zogenix International Limited, 2021 (25); Knupp et al. 2023 (64).

Appendix B. Efficacy results per study

Handling of missing data

Detailed methodology for ZX008-1601 – Part 1 and Part 2 is described the following, focusing on handling of missing data. There was no imputation of missing data for the efficacy endpoints. Regarding handling of missing diary information, seizures for each day were to be recorded in the eDiary. Users were required to actively confirm whether seizures did or did not occur on a given day. There was no explicit imputation of intermittent missing data for seizure diaries. Missing seizure diary data were handled as follows:

- If seizures were entered in the eDiary and the response to the question, "Is there a seizure to report that day?" was, "No, this day has been seizure free," the seizures entered in the eDiary superseded the seizure freedom affirmation.
- If no seizures were entered in the eDiary and there was no response to the question, "Is there a seizure to report that day?" that day was considered to have missing diary data.
- If no seizures were entered in the eDiary and it was indicated that there were seizures that day, that day was considered to have missing diary data.

A summary of efficacy results from ZX008-1601 – Part 1 is presented in Table 77 below.

Results during T+M

Table 75 presents results for DSF per 28 days during T+M. A median reduction from baseline of 26.49% was observed in the FFA 0.7 mg/kg/day group, compared with a median reduction from baseline of 7.59% in the placebo group. The median difference in percentage CFB in DSF between the FFA 0.7 mg/kg/day and placebo groups was statistically significant with a difference of -19.88 percentage points (95% CI: -31.02, -8.74) favouring the FFA 0.7 mg/kg/day group. The median difference between the FFA 0.2 mg/kg/day and placebo groups was -10.50 percentage points (95% CI: -24.99, 3.99) favouring the FFA 0.2 mg/kg/day group, although the difference was not statistically significant.

Table 75 Drop seizure frequency during T+M (mITT population)

	Placebo (N=87)	Fenfluramine 0.2 mg/kg/day (N=89)	Fenfluramine 0.7 mg/kg/day (N=87)
DSF at baseline, median (min, max) [a]	53.00 (2.0, 1761.0)	85.00 (4.1, 2943.0)	83.00 (6.5, 1803.0)
DSF in T+M, median (min, max) [a]	46.85 (0.0, 1683.8)	61.82 (0.0, 5110.9)	54.57 (0.3, 1562.0)

Percentage CFB, median (min, max) [a]	-7.59 (-100.0, 557.1)	-14.16 (-100.0, 3307.3)	-26.49 (-95.2, 402.1)
P-value [b]	N/A	0.0939	0.0013
HL for median difference [c], estimate (SE; 95% CI)	Reference	-10.50 (7.391; 95% CI: -24.99, 3.99)	-19.88 (5.684; 95% CI: -31.02, -8.74)

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; DSF = drop seizure frequency; HL = Hodges-Lehmann; mITT = modified intent-to-treat; N/A = not applicable; SE = standard error; T+M = titration and maintenance.
Notes: [a] Values for DSF per 28 days are presented in original scale. [b] DSF during T+M was assessed using a nonparametric, rank ANCOVA model with treatment group and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank DSF per 28 days during baseline as a covariate, and rank of percentage CFB in DSF per 28 days during T+M as response variable. [c] Active group minus placebo group.
Source: Zogenix International Limited, 2021, Table 21 (24); Knupp et al. 2022 (9).

Table 76 presents results concerning the ≥50% reduction from baseline in the DSF. Overall, the FFA groups had statistically significant higher odds of achieving a ≥50% reduction in DSF compared to the placebo group during T+M. The odds of achieving a ≥50% reduction in DSF during T+M were 2.87 (95% CI: 1.23, 6.70) times higher for subjects in the FFA 0.7 mg/kg/day group than for subjects in the placebo group. The odds of achieving a ≥50% reduction in DSF during T+M were 3.30 (95% CI: 1.43, 7.59) times higher for subjects in the FFA 0.2 mg/kg/day group than for subjects in the placebo group.

Table 76 Percentage who achieved a ≥50% reduction from baseline in DSF (mITT population)

	Placebo (N=87)	Fenfluramine 0.2 mg/kg/day (N=89)	Fenfluramine 0.7 mg/kg/day (N=87)
≥50% reduction in DSF during T+M, n (%)	9 (10.3)	25 (28.1)	22 (25.3)
Odds ratio (OR) (95% CI)	Reference	3.30 (1.43, 7.59)	2.87 (1.23, 6.70)
P-value	N/A	0.0051	0.0150

Abbreviations: CI = confidence interval; DSF = drop seizure frequency; mITT = modified intent-to-treat; N/A = not applicable; OR = odds ratio; T+M = titration and maintenance.
Notes: Based on a logistic regression model that included a categorical response variable (achieved 50 percentage point reduction, yes or no), weight group strata (<37.5 kg, ≥37.5 kg), and baseline DSB as covariate.
Source: Zogenix International Limited, 2021, Table 33 (24); Knupp et al. 2022 (9).

Results per study

Table 77 Results per ZX008-1601 – Part 1

Results of ZX008-1601 – Part 1 (NCT03355209)											
				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**		
CFB in DSF, median (during M)	Placebo	87	-7.28% (min: -100.0, max: 516.7)	N/A	N/A	N/A	Reference			Values for DSF per 28 days are presented in original scale. DSF during M was assessed using a nonparametric, rank ANCOVA model with treatment group and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank DSF per 28 days during baseline as a covariate, and rank of percentage CFB in DSF per 28 days during M as response variable. The HL for median difference was estimated as active group minus placebo group.	Zogenix International Limited, 2021 (24)
	Fenfluramine 0.2 mg/kg/day	89	-18.63% (min: -100.0, max: 964.0)				HL: -11.48	-26.26, 3.31	0.0764		
	Fenfluramine 0.7 mg/kg/day	87	-27.16% (min: -100.0, max: 643.3)				HL: -27.16	-100.0, 643.3	0.0018		
CFB in DSF, median	Placebo	87	-7.59% (min: -100.0, max: 557.1)	N/A	N/A	N/A	Reference			Values for DSF per 28 days are presented in original scale.	Zogenix International

Results of ZX008-1601 – Part 1 (NCT03355209)											
				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**		
(during T+M)	Fenfluramine 0.2 mg/kg/day	89	-14.16% (min: -100.0, max: 3307.3)				HL: -10.50	-24.99, 3.99	0.0939	DSF during T+M was assessed using a nonparametric, rank ANCOVA model with treatment group and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank DSF per 28 days during baseline as a covariate, and rank of percentage CFB in DSF per 28 days during T+M as response variable. The HL for median difference was estimated as active group minus placebo group.	Limited, 2021 (24)
	Fenfluramine 0.7 mg/kg/day	87	-26.49% (min: -95.2, max: 402.1)				HL: -19.88	-31.02, -8.74	0.0013		
Reduction in GTC seizure, median	Placebo	87	2.6%	N/A	N/A	N/A	Reference			P-values calculated using pairwise Wilcoxon rank sum test compared percentage changes from baseline between active treatment and placebo groups. P-values were nominal.	Knupp et al. 2022 (9)
	Fenfluramine 0.2 mg/kg/day	89	-61.7% p<0.001				HL: -61.0	-85.5, -36.5	<0.001		
	Fenfluramine 0.7 mg/kg/day	87	-52.6% p=0.001				HL: -52.8	-80.3, -25.3	0.001		

Results of ZX008-1601 – Part 1 (NCT03355209)											
				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**		
≥50% reduction in DSF (during M)	Placebo	87	n=11 (12.6%)	N/A	N/A	N/A	Reference			Based on a logistic regression model that included a categorical response variable (achieved 50 percentage point reduction, yes or no), weight group strata (<37.5 kg, ≥37.5 kg), and baseline DSB as covariate.	Zogenix International Limited, 2021 (24)
	Fenfluramine 0.2 mg/kg/day	89	n=28 (31.8%)				OR: 3.13	1.44, 6.82	0.0041		
	Fenfluramine 0.7 mg/kg/day	87	n=27 (31.4%)				OR: 3.12	1.43, 6.84	0.0044		
≥50% reduction in DSF (during T+M)	Placebo	87	n=9 (10.3%)	N/A	N/A	N/A	Reference			Based on a logistic regression model that included a categorical response variable (achieved 50 percentage point reduction, yes or no), weight group strata (<37.5 kg, ≥37.5 kg), and baseline DSB as covariate.	Zogenix International Limited, 2021 (24)
	Fenfluramine 0.2 mg/kg/day	89	n=25 (28.1%)				OR: 3.30	1.43, 7.59	0.0051		
	Fenfluramine 0.7 mg/kg/day	87	n=22 (25.3%)				OR: 2.87	1.23, 6.70	0.0150		
	Placebo	80	n=5 (6.3%)	N/A	N/A	N/A	Reference			Investigator rated.	

Results of ZX008-1601 – Part 1 (NCT03355209)											
				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**		
Clinically meaningful improvement on the CGI-I scale (visit 12)	Fenfluramine 0.2 mg/kg/day	85	n=17 (20.0%)				OR: 3.73	1.31, 10.65	0.0100	The OR was estimated based on Cochran-Mantel-Haenszel adjusting for weight strata. The p-value is from a Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata.	Zogenix International Limited, 2021 (24)
	Fenfluramine 0.7 mg/kg/day	80	n=21 (26.3%)				OR: 5.30	1.89, 14.87	0.0007		
Improvement on the CGI-I scale (visit 12)	Placebo	80	n=27 (33.8%)	N/A	N/A	N/A	Reference			Investigator rated. The OR was estimated based on Cochran-Mantel-Haenszel adjusting for weight strata. The p-value is from a Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata.	Zogenix International Limited, 2021 (24)
	Fenfluramine 0.2 mg/kg/day	85	n=38 (44.7%)				OR: 1.58	0.84, 2.97	0.1565		
	Fenfluramine 0.7 mg/kg/day	80	n=39 (48.8%)				OR: 1.86	0.98, 3.52	0.0567		
	Placebo	81	n=4 (4.9%)	N/A	N/A	N/A	Reference:			Parent/caregiver rated.	

Results of ZX008-1601 – Part 1 (NCT03355209)											
				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**		
Clinically meaningful imrovement on the CGI-I scale (visit 12)	Fenfluramine 0.2 mg/kg/day	85	n=23 (27.1%)				OR: 7.26	2.39, 22.03	<0.0001	The OR was estimated based on Cochran-Mantel-Haenszel adjusting for weight strata. The p-value is from a Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata.	Zogenix International Limited, 2021 (24)
	Fenfluramine 0.7 mg/kg/day	80	n=27 (33.8%)				OR: 9.96	3.29, 30.17	<0.0001		
Improvement on the CGI-I scale (visit 12)	Placebo	81	n=30 (37.0%)	N/A	N/A	N/A	Reference			Parent/caregiver rated.	Zogenix International Limited, 2021 (24)
	Fenfluramine 0.2 mg/kg/day	85	n=37 (43.5%)				OR: 1.31	0.70, 2.44	0.3960	The OR was estimated based on Cochran-Mantel-Haenszel adjusting for weight strata. The p-value is from a Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata.	
	Fenfluramine 0.7 mg/kg/day	80	n=49 (61.3%)				OR: 2.68	1.42, 5.07	0.0023		

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; DSF = drop seizure frequency; GTC = generalised tonic-clonic; HL = Hodges-Lehmann; M = maintenance; N/A = not applicable; OR = odds ratio; T+M = titration and maintenance.
Source: Zogenix International Limited, 2021 (24); Knupp et al. 2022 (9).

A summary of efficacy results from ZX008-1601 – Part 2 is presented in Table 78 below.

Table 78 Results per ZX008-1601 – Part 2

Results of ZX008-1601 – Part 2 (NCT03355209)											
				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		
Percentage change from Part 1 baseline in DSF during Month 2 in OLE to EOS	Fenfluramine	241	-30.46% (min: -100.0, max: 6,200.0), p<0.0001	N/A	N/A	N/A	N/A	N/A	N/A	P-value is from a Wilcoxon signed-rank test that the median % CFB is significantly different from 0.	Zogenix International Limited, 2021 (25)
≥50% reduction in DSF from Month 2 in OLE to EOS	Fenfluramine	241	n=76 (31.7%) (95% CI: 25.8, 38.0)	N/A	N/A	N/A	N/A	N/A	N/A	95% CIs represent Exact Clopper-Pearson CIs.	Zogenix International Limited, 2021 (25)
≥50% reduction in DSF in Month 10-12 in OLE	Fenfluramine	241	n=87 (51.2%) (95% CI: 43.4, 58.9)	N/A	N/A	N/A	N/A	N/A	N/A	95% CIs represent Exact Clopper-Pearson CIs.	Zogenix International Limited, 2021 (25)

Results of ZX008-1601 – Part 2 (NCT03355209)											
				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**		
Clinically meaningful improvement on the CGI-I scale (last assessment)	Fenfluramine	237	n=89 (37.6%) (95% CI: 31.4, 44.1)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator rated. 95% CIs represent Exact Clopper-Pearson CIs.	Zogenix International Limited, 2021 (25)
Improvement on the CGI-I scale (last assessment)	Fenfluramine	237	n=134 (56.5%) (95% CI: 50.0, 62.9)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator rated. 95% CIs represent Exact Clopper-Pearson CIs.	Zogenix International Limited, 2021 (25)
Clinically meaningful improvement on the CGI-I scale (last assessment)	Fenfluramine	230	n=81 (35.2%) (95% CI: 29.1, 41.8)	N/A	N/A	N/A	N/A	N/A	N/A	Parent/caregiver rated. 95% CIs represent Exact Clopper-Pearson CIs.	Zogenix International Limited, 2021 (25)

Results of ZX008-1601 – Part 2 (NCT03355209)											
				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**		
Improvement on the CGI-I scale (last assessment)	Fenfluramine	230	n=136 (59.1%) (95% CI: 52.5, 65.5)	N/A	N/A	N/A	N/A	N/A	N/A	Parent/caregiver rated. 95% CIs represent Exact Clopper-Pearson CIs.	Zogenix International Limited, 2021 (25)

Abbreviations: CFB = change from baseline; CGI-I=Clinical Global Impression – Improvement; CI = confidence interval; DSF = drop seizure frequency; N/A = not applicable; OLE = open-label extension.
Source: Zogenix International Limited, 2021 (25); Knupp et al. 2023 (64).

Appendix C. Comparative analysis of efficacy

Not applicable.

Appendix D. Extrapolation

N/A. All relevant information has been presented in Section 8

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

[If the extrapolation model relies on proportional hazards, provide a plot with Schoenfeld residuals and a log-cumulative hazard plot.]

D.1.4 Evaluation of statistical fit (AIC and BIC)

[Provide a table with the AIC and BIC and discuss the statistical fit.]

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

Serious TEAEs occurring in ZX008-1601 Part 1 are summarised for the safety population in Table 79.

Table 79 Serious TEAEs in ZX008-1601 Part 1 (safety population, complete Part 1 period [20 weeks])

MedDRA System Organ Class Preferred Term	Placebo (N=87) n (%)	Fenflu-ramine 0.2 mg/kg/day (N=89) n (%)	Fenfluramine 0.7 mg/kg/day (N=87) n (%)
Subject with any serious TEAE	4 (4.6)	4 (4.5)	10 (11.5)
Endocrine disorders	1 (1.1)	0	0
Thyroid mass	1 (1.1)	0	0
Eye disorders	1 (1.1)	0	0
Eye movement disorder	1 (1.1)	0	0
Gastrointestinal disorders	0	2 (2.2)	2 (2.3)
Constipation	0	1 (1.1)	0
Diarrhoea	0	0	1 (1.1)
Gastritis	0	0	1 (1.1)
Vomiting	0	1 (1.1)	0
General disorders and administration site conditions	0	0	1 (1.1)
Sudden unexplained death in epilepsy	0	0	1 (1.1)
Infections and infestations	0	1 (1.1)	4 (4.6)
Infection	0	0	1 (1.1)
Pneumonia	0	1 (1.1)	2 (2.3)
Subcutaneous abscess	0	0	1 (1.1)
Injury, poisoning and procedural complications	0	0	1 (1.1)
Humerus fracture	0	0	1 (1.1)
Metabolism and nutrition disorders	0	0	1 (1.1)
Dehydration	0	0	1 (1.1)
Nervous system disorders	2 (2.3)	2 (2.2)	4 (4.6)
Change in seizure presentation	0	2 (2.2)	0
Seizure	2 (2.3)	0	0
Somnolence	0	0	1 (1.1)

Status epilepticus	1 (1.1)	0	3 (3.4)
Psychiatric disorders	0	1 (1.1)	1 (1.1)
Irritability	0	1 (1.1)	0
Stereotypy	0	0	1 (1.1)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (1.1)
Lung disorder	0	0	1 (1.1)
Skin and subcutaneous tissue disorders	0	0	1 (1.1)
Rash	0	0	1 (1.1)

Abbreviations: TEAE = treatment-emergent adverse event.
Source: Zogenix International Limited, 2021, Table 14.3.1.4.1.1 (24).

Serious TEAEs occurring in ZX008-1601 Part 2 are summarised for the OLE safety population in Table 80.

Table 80 Serious TEAEs in ZX008-1601 Part 2 (OLE safety population, 19 October 2020)

MedDRA System Organ Class Preferred Term	Overall (N = 247) n (%)
Subjects with any serious TEAE	40 (16.2)
Blood and lymphatic system disorders	1 (0.4)
Haemolytic uraemic syndrome	1 (0.4)
Eye disorders	1 (0.4)
Keratoconus	1 (0.4)
Gastrointestinal disorders	3 (1.2)
Tooth loss	1 (0.4)
Vomiting	2 (0.8)
General disorders and administration site conditions	3 (1.2)
Asthenia	1 (0.4)
Complication of device insertion	1 (0.4)
Pyrexia	1 (0.4)
Infections and infestations	10 (4.0)
Dengue fever	1 (0.4)
Gastroenteritis	1 (0.4)
Gastroenteritis viral	1 (0.4)
Influenza	2 (0.8)
Pneumonia	5 (2.0)
Respiratory syncytial virus bronchiolitis	1 (0.4)
Urinary tract infection	1 (0.4)
Injury, poisoning and procedural complications	2 (0.8)

Foreign body in respiratory tract	1 (0.4)
Humerus fracture	1 (0.4)
Investigations	2 (0.8)
Blood prolactin increased	1 (0.4)
Weight decreased	1 (0.4)
Metabolism and nutrition disorders	5 (2.0)
Decreased appetite	2 (0.8)
Dehydration	2 (0.8)
Failure to thrive	1 (0.4)
Hypoalbuminemia	1 (0.4)
Nervous system disorders	21 (8.5)
Change in seizure presentation	9 (3.6)
Generalised tonic-clonic seizure	2 (0.8)
Seizure	2 (0.8)
Somnolence	3 (1.2)
Status epilepticus	8 (3.2)
Tonic convulsion	1 (0.4)
Psychiatric disorders	2 (0.8)
Agitation	1 (0.4)
Hallucination	1 (0.4)
Respiratory, thoracic and mediastinal disorders	4 (1.6)
Pleurisy	1 (0.4)
Pneumonia aspiration	3 (1.2)
Pneumonitis	1 (0.4)
Vascular disorders	1 (0.4)
Distributive shock	1 (0.4)

Abbreviations: OLE = open-label extension; TEAE = treatment-emergent adverse event.
Source: Zogenix International Limited, 2021, Table 14.3.1.4.1.3.1 (25).

Appendix F. Health-related quality of life

N/A. All relevant HRQoL data has been presented in Section 10 of this application.

Appendix G. Probabilistic sensitivity analyses

Table 81. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Proportion of patients with ASM at baseline_drg1_SoC	0.560	0.504	0.616	BETA
Proportion of patients with ASM at baseline_drg2_SoC	0.440	0.396	0.484	BETA
Proportion of patients with ASM at baseline_drg3_SoC	0.330	0.297	0.363	BETA
Proportion of patients with ASM at baseline_drg4_SoC	0.230	0.207	0.253	BETA
Proportion of patients with ASM at baseline_drg5_SoC	0.210	0.189	0.231	BETA
Proportion of patients with ASM at baseline_drg6_SoC	0.138	0.1242	0.1518	BETA
Proportion of patients with ASM at baseline_drg1_CBD	0.560	0.504	0.616	BETA
Proportion of patients with ASM at baseline_drg2_CBD	0.440	1	1	BETA
Proportion of patients with ASM at baseline_drg3_CBD	0.330	0.297	0.363	BETA
Proportion of patients with ASM at baseline_drg4_CBD	0.230	0.207	0.253	BETA
Proportion of patients with ASM at baseline_drg5_CBD	0.210	0.189	0.231	BETA
Proportion of patients with ASM at baseline_drg6_CBD	0.138	0.1242	0.1518	BETA
Proportion of patients with ASM at baseline_drg1	0.560	0.504	0.616	BETA
Proportion of patients with ASM at baseline_drg2	0.440	0.396	0.484	BETA
Proportion of patients with ASM at baseline_drg3	0.330	0.297	0.363	BETA
Proportion of patients with ASM at baseline_drg4	0.230	0.207	0.253	BETA
Proportion of patients with ASM at baseline_drg5	0.210	0.189	0.231	BETA
Proportion of patients with ASM at baseline_drg6	0.138	0.1242	0.1518	BETA
Mean Age at Baseline	3.000	2.7	3.3	GAMMA
Proportion Male	0.555	0.4995	0.6105	BETA
Median number of drop seizures	70.500	30	110	GAMMA
Proportion of GTC	0.470	0.423	0.517	BETA

Seizure-free days	See NMA_PSA inputs	See NMA_PSA inputs		DIRICHLET
Proportion of age group 1 (2-5 years)	0.035	0.0315	0.0385	BETA
Proportion of age group 2 (6-11 years)	0.035	0.0315	0.0385	BETA
Proportion of age group 3 (12-17 years)	0.465	0.4185	0.5115	BETA
Proportion of age group 4 (18-35 years)	0.465	0.4185	0.5115	BETA
Proportion of rescue medications Diazepam	0.667	0.6	0.733333	BETA
Weight plateau (kg)	78.000	70.2	85.8	GAMMA
Weight increase per yr of age (kg)	2.870	2.582609	3.156522	GAMMA
Weight at age 2 (kg)	12.000	10.8	13.2	GAMMA
Weight_fixed_2-5 yrs of age	17.630	10.41733	24.84267	NORMAL
Weight_fixed_6-11 yrs of age	30.110	11.01995	49.20005	NORMAL
Weight_fixed_12-17 yrs of age	48.070	20.5913	75.5487	NORMAL
Weight_fixed_18 -35 yrs of age	62.110	25.14508	99.07492	NORMAL
Weight_fixed_>35 yrs of age	78.000	41.03508	114.9649	NORMAL
Relative Risk_T+M_discontinuation_FFA	6.651	5.9859	7.3161	LOGNORMAL
Relative Risk_T+M_discontinuation_CBD	7.705	6.93468	8.47572	LOGNORMAL
Discontinuation SoC	0.011	0.0099	0.0121	BETA
Disc_FFA_titration	0.023	0.02069	0.025287	BETA
Disc_FFA_cycle2	0.037	0.032927	0.040244	BETA
Disc_FFA_cycle3	0.041	0.036986	0.045205	BETA
Disc_FFA_cycle4	0.016	0.014063	0.017188	BETA
Disc_FFA_cycle5	-	0	0	BETA
Disc_FFA_cycle6	-	0	0	BETA
Disc_FFA_cycle7	-	0	0	BETA
Disc_CBD_titration	0.023	0.02069	0.025287	BETA

Disc_CBD_cycle2	0.068	0.061475	0.075137	BETA
Disc_CBD_cycle3	0.059	0.052786	0.064516	BETA
Disc_CBD_cycle4	0.047	0.042056	0.051402	BETA
Disc_CBD_cycle5	0.013	0.011765	0.014379	BETA
Disc_CBD_cycle6	0.010	0.00894	0.010927	BETA
Disc_CBD_cycle7	-	0	0	BETA
trt_waning_proportion_FFA_init_cycle	-	0	0	BETA
trt_waning_proportion_FFA_cycle2	0.073	0.0657	0.0803	BETA
trt_waning_proportion_CBD_init_cycle	-	0	0	BETA
trt_waning_proportion_CBD_cycle2	0.073	0.0657	0.0803	BETA
State Occupancy_cycle 1	See NMA_PSA inputs	See NMA_PSA inputs		DIRICHLET
Transition Porbabilities (Follow-up)	See TP-data inputs	See TP-data inputs		DIRICHLET
Relative Risk_T+M_FFA_le25%	1.667	1.1475	2.4208	LOGNORMAL
Relative Risk_T+M_FFA_le50%	2.444	1.454	6.772	LOGNORMAL
Relative Risk_T+M_FFA_le75%	1.750	1.1942	5.0036	LOGNORMAL
Relative Risk_T+M_CBD_le25%	1.461	0.5313	1.928	LOGNORMAL
Relative Risk_T+M_CBD_le50%	2.085	1.268	5.764	LOGNORMAL
Relative Risk_T+M_CBD_le75%	2.365	0.723	5.136	LOGNORMAL
Relative Risk_OLE3months_FFA_25%	2.010	1.48	2.87	LOGNORMAL
Relative Risk_OLE3months_FFA_50%	4.530	2.48	9.94	LOGNORMAL
Relative Risk_OLE3months_FFA_75%	6.120	2.22	29.12	LOGNORMAL
Relative Risk_OLE3months_CBD_25%	1.590	1.33	1.95	LOGNORMAL
Relative Risk_OLE3months_CBD_50%	2.560	1.87	3.67	LOGNORMAL
Relative Risk_OLE3months_CBD_75%	5.400	2.96	11.38	LOGNORMAL

Relative Risk_OLE6months_FFA_25%	1.930	1.42	2.74	LOGNORMAL
Relative Risk_OLE6months_FFA_50%	4.350	2.33	9.5	LOGNORMAL
Relative Risk_OLE6months_FFA_75%	4.870	1.75	21.06	LOGNORMAL
Relative Risk_OLE6months_CBD_25%	1.690	1.41	2.06	LOGNORMAL
Relative Risk_OLE6months_CBD_50%	2.930	2.15	4.18	LOGNORMAL
Relative Risk_OLE6months_CBD_75%	6.100	3.36	12.92	LOGNORMAL
Relative Risk_OLE9months_FFA_25%	2.120	1.56	3.05	LOGNORMAL
Relative Risk_OLE9months_FFA_50%	4.760	2.57	10.38	LOGNORMAL
Relative Risk_OLE9months_FFA_75%	5.900	2.14	25.13	LOGNORMAL
Relative Risk_OLE9months_CBD_25%	1.680	1.41	2.06	LOGNORMAL
Relative Risk_OLE9months_CBD_50%	2.990	2.18	4.26	LOGNORMAL
Relative Risk_OLE9months_CBD_75%	6.650	3.67	14.01	LOGNORMAL
Relative Risk_OLE12months_FFA_25%	2.300	1.7	3.3	LOGNORMAL
Relative Risk_OLE12months_FFA_50%	5.770	3.12	12.9	LOGNORMAL
Relative Risk_OLE12months_FFA_75%	8.250	2.97	36.89	LOGNORMAL
Relative Risk_OLE12months_CBD_25%	1.710	1.42	2.1	LOGNORMAL
Relative Risk_OLE12months_CBD_50%	2.970	2.17	4.26	LOGNORMAL
Relative Risk_OLE12months_CBD_75%	6.640	3.6	14.15	LOGNORMAL
Proportion of GTC reduction-SoC	-	0	0	BETA
Proportion of GTC reduction-FFA	(0.504)	-0.768	-0.238	BETA
Proportion of GTC reduction-CBD	(0.366)	-0.613	-0.173	BETA
HCRU_seizure_number_hospital_admissions_confirmed_L12	1.500	1.35	1.65	GAMMA
HCRU_seizure_hospital_LOS_confirmed_L12	2.480	2.232	2.728	GAMMA
HCRU_seizure_number_AE_visits_confirmed_L12	0.850	0.765	0.935	GAMMA
HCRU_seizure_number_hospital_admissions_confirmed_M12	0.960	0.864	1.056	GAMMA
HCRU_seizure_hospital_LOS_confirmed_M12	3.240	2.916	3.564	GAMMA

HCRU_seizure_number_AE_visits_confirmed_M12	1.150	1.035	1.265	GAMMA
HCRU_seizure_number_hospital_admissions_probable_L12	3.040	2.736	3.344	GAMMA
HCRU_seizure_hospital_LOS_probable_L12	3.690	3.321	4.059	GAMMA
HCRU_seizure_number_AE_visits_probable_L12	0.960	0.864	1.056	GAMMA
HCRU_seizure_number_hospital_admissions_probable_M12	0.890	0.801	0.979	GAMMA
HCRU_seizure_hospital_LOS_probable_M12	5.700	5.13	6.27	GAMMA
HCRU_seizure_number_AE_visits_probable_M12	1.040	0.936	1.144	GAMMA
HCRU_seizure_GTC_Hospital_days	6.260	0	17.1574	GAMMA
HCRU_seizure_GTC_Emergency_visits	1.520	0.383221	2.656779	GAMMA
HCRU_seizure_Others_Hospital days	2.080	0	4.451556	GAMMA
HCRU_seizure_Others_Emergency room visits	0.780	0.172411	1.387589	GAMMA
Proportion_inpatients_ICU	0.042	0.037876	0.046293	BETA
Proportion_institutionalized_patients	0.100	0.09	0.11	BETA
Institutionalization_cost	20,000.000	18000	22000	BETA
Mortality_cost	-	0	0	BETA
patient_utility_Verdian_2008_State_0_EQ5D	0.020	0.018	0.022	BETA
patient_utility_Verdian_2008_State_1_EQ5D	0.100	0.09	0.11	BETA
patient_utility_Verdian_2008_State_2_EQ5D	0.500	0.45	0.55	BETA
patient_utility_Verdian_2008_State_3_EQ5D	0.596	0.5364	0.6556	BETA
caregiver_utility_Verdian_2008_State_0_EQ5D	0.020	0.018	0.022	BETA
caregiver_utility_Verdian_2008_State_1_EQ5D	0.100	0.09	0.11	BETA
caregiver_utility_Verdian_2008_State_2_EQ5D	0.500	0.45	0.55	BETA
caregiver_utility_Verdian_2008_State_3_EQ5D	0.596	0.5364	0.6556	BETA
AE_proportion_Diarrhoea_SoC	0.050	0.045	0.055	BETA
AE_proportion_Somnolence_SoC	0.100	0.09	0.11	BETA
AE_proportion_Pyrexia_SoC	0.110	0.099	0.121	BETA

AE_proportion_Decreased appetite_SoC	0.110	0.099	0.121	BETA
AE_proportion_Vomiting_SoC	0.060	0.054	0.066	BETA
AE_proportion_Diarrhoea_FFA	0.130	0.117	0.143	BETA
AE_proportion_Somnolence_FFA	0.170	0.153	0.187	BETA
AE_proportion_Pyrexia_FFA	0.080	0.072	0.088	BETA
AE_proportion_Decreased appetite_FFA	0.360	0.324	0.396	BETA
AE_proportion_Vomiting_FFA	0.080	0.072	0.088	BETA
AE_proportion_Diarrhoea_CBD	0.130	0.117	0.143	BETA
AE_proportion_Somnolence_CBD	0.140	0.126	0.154	BETA
AE_proportion_Pyrexia_CBD	0.010	0.009	0.011	BETA
AE_proportion_Decreased appetite_CBD	0.090	0.081	0.099	BETA
AE_proportion_Vomiting_CBD	0.070	0.063	0.077	BETA
AE_cost_Diarrhoea	2,012.000	1810.8	2213.2	GAMMA
AE_cost_Somnolence	2,012.000	1810.8	2213.2	GAMMA
AE_cost_Pyrexia	2,012.000	1810.8	2213.2	GAMMA
AE_cost_Decreased appetite	2,012.000	1810.8	2213.2	GAMMA
AE_cost_Vomiting	2,012.000	1810.8	2213.2	GAMMA
AE_disutility_Diarrhoea	(0.060)	-0.054	-0.066	BETA
AE_disutility_Somnolence	(0.060)	-0.054	-0.066	BETA
AE_disutility_Pyrexia	(0.060)	-0.054	-0.066	BETA
AE_disutility_Decreased appetite	(0.060)	-0.054	-0.066	BETA
AE_disutility_Vomiting	(0.060)	-0.054	-0.066	BETA
Mortality_Baseline_SUDEP	0.002	0.0015	0.00486	BETA
proportion_mortality_SE	0.001	0.000839	0.001025	BETA

proportion_mortality_accidental	0.214	0.1926	0.2354	BETA
proportion_on_CBD	0.170	0.153	0.187	BETA

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

Not applicable.

Table 82 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations: N/A = not applicable.

Table 83 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
e.g. EMA web-site	N/A	N/A	N/A

Abbreviations: N/A = not applicable.

Table 84 Conference material included in the literature search

Conference	Source of ab-stracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

Abbreviations: N/A = not applicable.

H.1.1 Search strategies

Not applicable.

Table 85 of search strategy table for [name of database]

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

Abbreviations: N/A = not applicable.

H.1.2 Systematic selection of studies

Not applicable.

Table 86 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Abbreviations: N/A = not applicable.

Not applicable.

Table 87 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A	N/A	N/A	N/A	N/A	N/A
Study 2	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A = not applicable.

H.1.3 Excluded fulltext references

Not applicable.

H.1.4 Quality assessment

Not applicable.

H.1.5 Unpublished data

Not applicable.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

To support this submission for fenfluramine, a series of HRQoL, HCRU and costs as well as economic evaluation systematic literature reviews (SLR) was undertaken. The SLRs were undertaken concurrently. This section presents the methodology and results relating to the HRQoL searches.

I.1.1.1 Objective

The objective of the HRQoL SLRs was to examine the HRQoL, utility and disabilities values associated with LGS.

I.1.1.2 Methods

The SLRs followed methodology that was designed to meet the standards of most HTA bodies, including those set out by the National Institute for Health and Care Excellence

(NICE) and the Canadian Agency for Drugs and Technologies in Health, and followed the methodological guidance of the Centre for Reviews and Dissemination and reporting requirements of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).(86-90)

I.1.1.3 Information sources

I.1.1.3.1 Bibliographic databases

Relevant studies reporting on the topics of interest for each SLR were identified by searching the data sources listed in Table 88 for literature published until 05 October 2022. Updated literature searches were conducted on 07 June 2023 and 18 December 2023, respectively, following the same processes as the original literature search.

Table 88 Bibliographic databases included in the literature search

Database	Platform/ source	Relevant period for the search	Date of search completion
Embase	Ovid	From database inception to October 5th, 2022	05.10.2022
		From July 1st, 2022, to June 7th, 2023	07.06.2023
		From March 1st, 2023, to December 18th, 2023	18.12.2024
MEDLINE and MEDLINE In-process	Ovid	From database inception to October 5th, 2022	05.10.2022
		From July 1st, 2022, to June 7th, 2023	07.06.2023
		From March 1st, 2023, to December 18th, 2023	18.12.2024
EBM reviews: CENTRAL	Ovid	From database inception to October 5th, 2022	05.10.2022
		From 2022 to June 7th, 2023	07.06.2023
		From 2023 to December 18th, 2023	18.12.2024
EBM reviews: HTA	Ovid	From database inception to October 5th, 2022	05.10.2022
		N/A*	07.06.2023
		N/A*	18.12.2024
EBM reviews: CDSR	Ovid	From database inception to October 5th, 2022	05.10.2022
		From 2022 to June 7th, 2023	07.06.2023
		From 2023 to December 18th, 2023	18.12.2024
EconLit	Ovid	From database inception to October 5th, 2022	05.10.2022
		From 2022 to 2023	07.06.2023
		From 2023 to December 18th, 2023	18.12.2024
NHS EED	Ovid	From database inception to October 5th, 2022	05.10.2022
		N/A*	07.06.2023
		N/A*	18.12.2024

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; EBM = Evidence-based Medicine; HTA = Health Technology Assessment; N/A = not applicable; NHS EED = National Health Service Economic Evaluation Database.
Notes: * EBM HTA and NHS EED were discontinued in 2015 and therefore a search update in June 2023 and December 2023 was not required.

I.1.1.3.2 HTA websites

The websites of the following HTA agencies were reviewed for recent appraisals in LGS (and similar indications, e.g., Dravet syndrome) to cross-check literature and information against the proposed SLRs:

- UK: National Institute for Health and Care Excellence
- Scotland: Scottish Medicines Consortium
- Canada: Canadian Agency for Drugs and Technologies in Health
- Australia: Pharmaceutical Benefits Advisory Committee
- Germany: Institute for Quality and Efficiency in Health Care & Federal Joint Committee
- US: Institute for Clinical and Economic Review
- France: Haute Autorité de santé
- Wales: All Wales Therapeutics and Toxicology Centre

I.1.1.3.3 Other sources

Additionally, the sources presented in Table 89 were searched.

Table 89 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
International HTA Database*	database.inahta.org	Hand search	05.10.2022
National Institute of Health Research HTA	https://www.nihr.ac.uk/	Hand search	05.10.2022
			07.06.2023
			18.12.2024
CEA registry	https://research.tufts-nemc.org/cear/Deult.aspx	Hand search	05.10.2022
			07.06.2023
			18.12.2024

Abbreviations: CEA = cost-effectiveness analysis; HTA = health technology assessment.
Notes: * International HTA Database was discontinued in 2015 and therefore a search update in June 2023 and December 2023 was not required.

I.1.1.3.4 Conference proceedings

The proceedings of relevant conferences from 2020 to December 2023 were hand-searched for any editions not yet indexed in Embase (Table 90).

Table 90 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Epilepsy Society	N/R	Hand search	N/R	N/R
The Professional Society for Health Economics and Outcomes Research	N/R	Hand search	N/R	N/R
International League Against Epilepsy	N/R	Hand search	N/R	N/R
American Academy of neurology	N/R	Hand search	N/R	N/R
European Epilepsy Congress	N/R	Hand search	N/R	N/R
European Paediatric Neurology Society	N/R	Hand search	N/R	N/R

Abbreviations: N/R = not reported.

I.1.2 Search strategies

Original searches were conducted on 05 October 2022 via the Ovid platform, with updated searches conducted on 07 June 2023, and 18 December 2023, respectively. The search strategy tables are presented below.

Table 91 Search strategy for Embase

No.	Query	Results		
		Original	June 23 update	December 23 update
1	Lennox Gastaut syndrome/	4309	4545	4641
2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	4619	4886	4958
3	1 or 2	6623	6987	7117
4	exp Health Status/ or exp Health Surveys/ or exp health survey/	526476	558888	576633
5	(euroqol* or euro qol* or euro-qol* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eqoL-5d* or eqoL5D* or eqoL 5d*).tw.	27690	30547	31443
6	(utilit* or disutilit*).tw.	349830	377072	383249
7	(hye* or health* year* equivalent* or hui*).tw.	8636	9202	9492
8	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	6479	7024	7218
9	willingness to pay.tw.	11664	12886	13217
10	(SG or TTO or WTP or DCE).tw.	35291	38295	39525
11	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).tw.	827419	887348	898451

12	(VAS or visual analog* scale* or visual-analog* scale*).tw.	138921	149464	152509
13	exp "Quality of Life"/ or exp "Surveys and Questionnaires"/ or exp questionnaire/ or exp "quality of life assessment"/	1375950	1481661	1525988
14	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).tw.	128386	139058	142118
15	(quality adj4 life).tw.	560675	608109	623554
16	(quality adj2 well?being).tw.	695	802	843
17	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).tw.	90611	96631	98191
18	("Quality of Life in Epilepsy" or QOLIE-31 or QOLIE 31 or QOLIE-89 or QOLIE 89).tw.	1235	1296	1324
19	or/4-18	2995717	3214981	3291741
20	3 and 19	656	718	744
21	case report/	2787438	2910046	2947159
22	(book or chapter or conference paper or conference review or editorial or erratum or letter or note or short or short survey or survey or tombstone).pt.	4350831	4522150	4576956
23	(animal* not human*).sh,hw.	4696980	4850936	4895881
24	conference abstract.pt.	4553688	4776805	4985486
25	limit 24 to yr="1974 - 2019"	3824800	3841763	3854576
26	21 or 22 or 23 or 25	14732395	15178399	15316968
27	20 not 26	419	466	490

June 2023 update				
28	limit 27 to dd=20220701-20230607 [Date delivered, 1 Jul 2022-7 Jun 2023]	N/A	13	N/A
29	limit 27 to rd=20220701-20230607 [Revised date, 1 Jul 2022-7 Jun 2023]	N/A	47	N/A
30	28 or 29	N/A	60	N/A
31	limit 30 to yr="2022 -Current"	N/A	54	N/A
December 2023 update				
28	limit 27 to dd=20230301-20231218 [Date delivered, 1 Mar 2023-18 Dec 2023]	N/A	N/A	14
29	limit 27 to rd=20230301-20231218 [Revised date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	36
30	28 or 29	N/A	N/A	50
31	limit 30 to yr="2023 -Current"	N/A	N/A	44

Table 92 Search strategy for MEDLINE

No.	Query	Results		
		Original	June 23 update	December 23 update
1	Lennox Gastaut syndrome/	456	486	508
2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	3062	3175	3267
3	1 or 2	3167	3280	3372
4	exp Health Status/ or exp Health Surveys/ or exp health survey/	975996	1001011	1018952
5	(euroqol* or euro qol* or euro-qol* or euroqual* or euro qual* or euro-qual* or eq5d* or eq 5d* or eq-5d* or eqoL-5d* or eqoL5D* or eqoL 5d*).tw.	15216	16473	17498
6	(utilit* or disutilit*).tw.	251680	264812	275896

7	(hye* or health* year* equivalent* or hui*).tw.	6861	7223	7524
8	(standard gamble* or time-trade-off or time trade-off or time trade off or time tradeoff or discrete choice experiment* or rosser).tw.	4535	4817	5038
9	willingness to pay.tw.	7716	8334	8886
10	(SG or TTO or WTP or DCE).tw.	23290	24796	26021
11	((valu* or measur* or preference*) adj4 (health or outcome* or effect* or change* or state*)).tw.	644255	674359	698413
12	(VAS or visual analog* scale* or visual-analog* scale*).tw.	91726	96929	101033
13	exp "Quality of Life"/ or exp "Surveys and Questionnaires"/ or exp questionnaire/	1343603	1380627	1405847
14	(QOL* or HQL* or HQOL* or H QOL* or HRQL* or HRQOL* or HR QOL*).tw.	71832	76418	80073
15	(quality adj4 life).tw.	356734	379416	398615
16	(quality adj2 well?being).tw.	427	486	533
17	(sf-36* or sf36* or sf 36* or sf thirtysix or sfthirtysix or sf-thirtysix or sf thirty six or sf-20* or sf20* or sf 20* or sf twenty or sftwenty or sf-twenty or sf-12* or sf12* or sf 12* or sf twelve or sftwelve or sf-twelve or sf-6* or sf6* or sf 6* or sf six* or sfsix* or sf-six* or short form* or shortform*).tw.	60126	63068	65400
18	("Quality of Life in Epilepsy" or QOLIE-31 or QOLIE 31 or QOLIE-89 or QOLIE 89).tw.	659	691	720
19	or/4-18	2453638	2545279	2617080
20	3 and 19	266	284	293
21	case reports/	2294994	2339187	2373944
22	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference	4906782	5045883	5158274

	nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.			
23	(animal* not human*).sh,hw.	5008408	5083357	5132595
24	or/21-23	9779296	9990965	10150824
25	20 not 24	236	252	261
June 2023 update				
26	limit 25 to dt=20220701-20230607 [Create date, 1 Jul 2022-7 Jun 2023]	N/A	24	N/A
27	limit 25 to rd=20220701-20230607 [Revised date, 1 Jul 2022-7 Jun 2023]	N/A	34	N/A
28	26 or 27	N/A	34	N/A
29	limit 28 to yr="2022 -Current"	N/A	27	N/A
December 2023 update				
26	limit 25 to dt=20230301-20231218 [Create date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	19
27	limit 25 to rd=20230301-20231218 [Revised date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	27
28	26 or 27	N/A	N/A	27
29	limit 28 to yr="2023 -Current"	N/A	N/A	20

Table 93 Search strategy for EBM Reviews - Cochrane Central Register of Controlled Trials

No.	Query	Results		
		Original	June 23 update	December 23 update

1	Lennox Gastaut syndrome/	40	82	82
2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	350	360	367
3	1 or 2	352	366	373
4	(animal* not human*).sh,hw.	2,282	2750	2777
5	erratum.kw.	3,220	3781	4195
6	(ovarian or glucose).ti.	24,387	24755	25503
7	or/4-6	29,800	31189	32374
8	3 not 7	333	346	353
June 2023 update				
9	limit 8 to yr="2022 -Current"	N/A	40	N/A
December 2023 update				
9	limit 8 to yr="2023 -Current"	N/A	N/A	15

Table 94 Search strategy for Econlit

No.	Query	Results		
		Original	June 23 update	December 23 update
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	32	36	38
June 2023 update				
2	limit 1 to yr="2022 - 2023"	N/A	6	N/A
December 2023 update				

2	limit 1 to yr="2023 -Current"	N/A	N/A	3

Table 95 Search strategy for EBM Reviews - HTA

No.	Query	Results
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	2

Table 96 Search strategy for EBM Reviews - Cochrane Database of Systematic Reviews

No.	Query	Results		
		Original	June 23 update	December 23 update
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab,kw.	3	3	3
June 2023 update				
2	(2022* or 2023*).dp.	N/A	884	N/A
3	1 and 2	N/A	1	N/A
December 2023 update				
2	(2023* or 2024*).dp.	N/A	N/A	560
3	1 and 2	N/A	N/A	0

Table 97 Search strategy in EBM Reviews - NHS Economic Evaluation Database

No.	Query	Results
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	3

I.1.2.1 Eligibility criteria

Studies were screened against the population, intervention, comparison, outcomes, and study design (PICOS) eligibility criteria (as outlined in Table 98) in the DistillerSR platform by two independent reviewers with discrepancies resolved by a third reviewer. The full texts of all included citations were retrieved and screened by two independent reviewers (in a double-blinded manner), and resolved by a third reviewer, where needed.

Table 98 Eligibility criteria – HRQoL

Domain	Inclusion criteria (HRQoL)
Population	Children and/or adults with LGS
Interventions/Comparators	Any (or no) interventions/comparators
Outcomes	Utility values QoL measures using an established questionnaire that can be mapped to utility values, such as: EQ-5D SF-12/SF-36 QOLIE-31/QOLIE-89 QOLCE
Study design	RCTs, SATs, observational studies
Language	English

Abbreviations: HRQoL, health-related quality of life; LGS, Lennox-Gastaut syndrome; QOLCE, Quality of Life of Childhood Epilepsy; QOLIE-31/QOLIE-89, Quality of Life in Epilepsy Inventory-31/89; RCT, randomised controlled trial; SAT, single-arm trial; SF-12/SF-36, 12-/36-Item Short Form health survey.

I.1.2.2 Study selection process

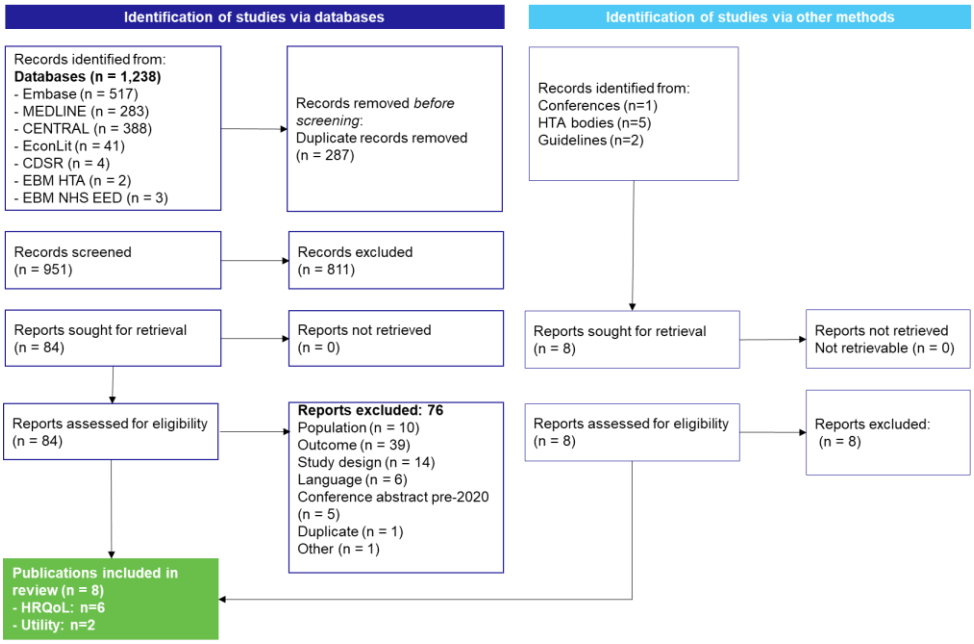
The database searches for HRQoL and utility/disutility values in LGS were conducted on 05 October 2022 and returned 1,028 records. After removing 207 duplicates, 821 records were screened at the title and abstract level, of which 71 were included for full-text screening. After full-text screening, eight unique publications were included. No records were identified from other sources.

The first set of updated literature searches were conducted on 07 June 2023 and returned 128 records. After removing 58 duplicates, 70 records were screened at the title and abstract level, of which 61 were excluded and 9 were included for full-text screening. After full-text screening, no new publications were added to the original SLR.

The second set of updated literature searches were conducted on 18 December 2023 and returned 82 records. After removing 22 duplicates, 60 records were screened at the title and abstract level, of which 56 were excluded and 4 were included for full-text screening. After full-text screening, no new publications were added to the original SLR.

Figure 10 shows the literature selection procedure across all three HRQoL SLR iterations, with the number of records excluded at each stage.

Figure 10 PRISMA flow diagram – HRQoL



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; EBM, Evidence-Based Medicine; HTA, health technology assessment; NHS EED, National Health Service Economic Evaluations Database

I.1.2.3 Results

The literature search results included in the model/analysis (n = 8) are presented in Table 99.

Table 99 Literature search results – HRQoL

Author and year	Reference
Gallop, 2010	Gallop K, Wild D, Verdian L, et al. Lennox-Gastaut Syndrome (LGS): Development of conceptual models of health-related quality of life (HRQL) for caregivers and children. Seizure. 2010;19(1):23-30. doi:https://dx.doi.org/10.1016/j.seizure.2009.10.007
Devinsky, 2018	Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. A Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P; CBD) as Adjunctive Treatment for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults. 2018;378(20):1888. doi:https://doi.org/10.1056/NEJMoa1714631
Ding, 2016	Ding P, Liang S, Zhang S, Zhang J, Hu X, Yu X. Resective surgery combined with corpus callosotomy for children with non-focal lesional Lennox-Gastaut syndrome. Acta Neurochirurgica. 2016;158(11):2177-2184. doi:https://dx.doi.org/10.1007/s00701-016-2947-5
Knupp, 2022	Knupp KG, Scheffer IE, Ceulemans B, et al. Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial. JAMA neurology. 2022;79(6):554-564. doi:https://dx.doi.org/10.1001/jamaneurol.2022.0829

Liang, 2014	Liang S, Zhang S, Hu X, et al. Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: A prospective study. European Journal of Paediatric Neurology. 2014;18(6):670-676. doi:https://dx.doi.org/10.1016/j.ejpn.2014.05.004
Weinstock, 2019(91)	Weinstock A, Agarwal N, Farooq O, Cheema Z, Hamilton D, Parrish J. Evaluation of the Effects of Clobazam on Seizure Control and Quality of Life in Children With Lennox-Gastaut Syndrome: A Pilot Study. Journal of Child Neurology. 2019;34(8):432-439. doi:https://dx.doi.org/10.1177/0883073819836534
Auvin, 2021	Auvin S, Damera V, Martin M, Holland R, Simontacchi K, Saich A. The impact of seizure frequency on quality of life in patients with Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy and Behavior. 2021;123:108239. doi:https://dx.doi.org/10.1016/j.yebeh.2021.108239
Lo, 2021	Lo SH, Lloyd A, Marshall J, Vyas K. Patient and caregiver health state utilities in lennox-gastaut syndrome and dravet syndrome. Clinical Therapeutics. 2021;43(11):1861-1876. e16.

Abbreviations: HRQoL = health-related quality of life.

I.1.3 Quality assessment and generalizability of estimates

Quality of HRQoL studies was not formally assessed as these studies are generally only reviewed with the intention to provide economic modelling inputs.

I.1.4 Unpublished data

N/A.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

To support this submission for fenfluramine, a series of HRQoL, HCRU, costs and economic evaluation systematic literature reviews (SLR) was undertaken. The SLRs were undertaken concurrently. This section presents the methodology and results relating to the HCRU, costs and economic evaluation searches.

J.1.1.1 Objective

The objective of the HCRU, costs and economic evaluation SLRs was to answer the following research questions:

- What is the HCRU associated with treatment and disease management of LGS?
- What are the direct and indirect costs associated with LGS and its treatments?
- What evidence is available from economic evaluations on cost-effectiveness modelling approaches, key modelling parameters and cost-effectiveness results available from key comparators in LGS?

J.1.1.2 Methods

Refer to appendix I.1.1.2.

J.1.1.3 Information sources

Refer to appendix I.1.1.3.

J.1.2 Search strategies

Original searches were conducted on 05 October 2022 via the Ovid platform, with updated searches conducted on 07 June 2023, and 18 December 2023, respectively. The search strategy tables are presented below.

J.1.2.1.1 HCRU and costs

Table 100 Search strategy for Embase

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	Lennox Gastaut syndrome/	4309	4545	4641
2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	4619	4886	4958
3	1 or 2	6623	6987	7117
4	Costs and Cost Analysis/ or cost/	61321	62530	63649
5	cost of illness/	20750	21188	21439
6	health care costs/ or "health care cost"/ or health expenditures/	214225	223625	230163
7	cost*.ti,ab.	976723	1044590	1066836
8	Drug Utilization/ or "drug use"/	150028	155440	160277
9	Health Resources/ or health care utilization/	181894	191026	196397
10	((resource* or health care or healthcare or health service* or drug* or medication*) adj4 (use* or usage* or utilit* or utili#ation*)).ti,ab.	594301	635403	646989
11	or/4-10	1827444	1942624	1984458

12	3 and 11	497	523	531
13	case report/	2787438	2910046	2947159
14	(book or chapter or conference paper or conference review or editorial or erratum or letter or note or short or short survey or survey or tombstone).pt.	4350831	4522150	4576956
15	(animal* not human*).sh,hw.	4696980	4850936	4895881
16	conference abstract.pt.	4553688	4776805	4985486
17	limit 16 to yr="1974 - 2019"	3824800	3841763	3854576
18	13 or 14 or 15 or 17	14732395	15178399	15316968
19	12 not 18	335	357	365
June 2023 update				
20	limit 19 to dd=20220701-20230607 [Date delivered, 1 Jul 2022-7 Jun 2023]	N/A	7	N/A
21	limit 19 to rd=20220701-20230607 [Revised date, 1 Jul 2022-7 Jun 2023]	N/A	22	N/A
22	20 or 21	N/A	29	N/A
23	limit 22 to yr="2022 -Current"	N/A	26	N/A
December 2023 update				
20	limit 19 to dd=20230301-20231218 [Date delivered, 1 Mar 2023-18 Dec 2023]	N/A	N/A	2
21	limit 19 to rd=20230301-20231218 [Revised date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	13
22	20 or 21	N/A	N/A	15
23	limit 22 to yr="2023 -Current"	N/A	N/A	12

Table 101 Search strategy for MEDLINE

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	Lennox Gastaut syndrome/	456	486	508
2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	3062	3175	3267
3	1 or 2	3167	3280	3372
4	Costs and Cost Analysis/ or cost/	50877	51352	51688
5	cost of illness/	30984	31496	31874
6	health care costs/ or "health care cost"/ or health expenditures/	64283	65436	66290
7	cost*.ti,ab.	732027	772119	804371
8	Drug Utilization/ or "drug use"/	21475	21520	21547
9	Health Resources/ or health care utilization/	68078	69001	69671
10	((resource* or health care or healthcare or health service* or drug* or medication*) adj4 (use* or usage* or utilit* or utili#ation*)).ti,ab.	410576	430126	445752
11	or/4-10	1219823	1278444	1325131
12	3 and 11	193	199	200
13	case reports/	2294994	2339187	2373944
14	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or	4906782	5045883	5158274

	personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.			
15	(animal* not human*).sh,hw.	5008408	5083357	5132595
16	or/13-15	9779296	9990965	10150824
17	12 not 16	169	171	172
June 2023 update				
18	limit 17 to dt=20220701-20230607 [Create date, 1 Jul 2022-7 Jun 2023]	N/A	9	N/A
19	limit 17 to rd=20220701-20230607 [Revised date, 1 Jul 2022-7 Jun 2023]	N/A	17	N/A
20	18 or 19	N/A	17	N/A
21	limit 20 to yr="2022 -Current"	N/A	11	N/A
December 2023 update				
18	limit 17 to dt=20230301-20231218 [Create date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	2
19	limit 17 to rd=20230301-20231218 [Revised date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	11
20	18 or 19	N/A	N/A	11
21	limit 20 to yr="2023 -Current"	N/A	N/A	2

Table 102 Search strategy for EBM Reviews - Cochrane Central Register of Controlled Trials

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	Lennox Gastaut syndrome/	40	82	82

2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	350	360	367
3	1 or 2	352	366	373
4	(animal* not human*).sh,hw.	2,282	2750	2777
5	erratum.kw.	3,220	3781	4195
6	(ovarian or glucose).ti.	24,387	24755	25503
7	or/4-6	29,800	31189	32374
8	3 not 7	333	346	353
June 2023 update				
9	limit 8 to yr="2022 -Current"	N/A	40	N/A
December 2023 update				
9	limit 8 to yr="2023 -Current"	N/A	N/A	15

Table 103 Search strategy for Econlit

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	32	36	38
June 2023 update				
2	limit 1 to yr="2022 - 2023"	N/A	6	N/A
December 2023 update				
2	limit 1 to yr="2023 -Current"	N/A	N/A	3

Table 104 Search strategy for EBM Reviews - HTA

No.	Reference	Search hits
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	2

Table 105 Search strategy for EBM Reviews - Cochrane Database of Systematic Reviews

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab,kw.	3	3	3
June 2023 update				
2	(2022* or 2023*).dp.	N/A	884	N/A
3	1 and 2	N/A	1	N/A
December 2023 update				
2	(2023* or 2024*).dp.	N/A	N/A	560
3	1 and 2	N/A	N/A	0

Table 106 Search strategy for EBM Reviews - NHS Economic Evaluation Database

No.	Reference	Search hits
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	3

J.1.2.1.2 Economic evaluations

Table 107 Search strategy for Embase

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	Lennox Gastaut syndrome/	4309	4545	4641
2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	4619	4886	4958
3	1 or 2	6623	6987	7117
4	exp "economic evaluation"/	339643	353694	359999
5	economics/ or economic aspect/	357360	361692	363825
6	Economics, Pharmaceutical/ or health economics/ or pharmacoeconomics/	43425	44600	45864
7	cost-benefit analysis/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost benefit analysis"/ or "cost utility analysis"/	258755	270378	275664
8	((economic or human*) adj3 consequence*).ti,ab.	10068	10808	10946
9	(economic* or pharmaco?economic* or pharmaco economic*).ti,ab.	421897	455182	466578
10	(cost* adj2 (effective* or utilit* or benefit* or minimi* or consequence*)).ti,ab.	261037	278908	284985
11	(CEA or CMA or CBA or CUA or CCA).ti,ab.	75681	80115	81401
12	Quality-Adjusted Life Years/ or quality adjusted life year/	32542	35306	35921
13	(quality adjusted life$ or quality-adjusted life$ or quality-adjusted-life$ or disability adjusted life$ or disability-adjusted life$ or disability-adjusted-life$).tw.	29930	32918	33526
14	(QALY or qal$ or qwb$ or qald$ or qale$ or qtime$ or daly$).tw.	31004	33898	34670
15	or/4-14	1167911	1228452	1251837

16	3 and 15	212	216	220
17	case report/	2787438	2910046	2947159
18	(book or chapter or conference paper or conference review or editorial or erratum or letter or note or short or short survey or survey or tombstone).pt.	4350831	4522150	4576956
19	(animal* not human*).sh,hw.	4696980	4850936	4895881
20	conference abstract.pt.	4553688	4776805	4985486
21	limit 20 to yr="1974 - 2019"	3824800	3841763	3854576
22	17 or 18 or 19 or 21	14732395	15178399	15316968
23	16 not 22	143	147	151
June 2023 update				
24	limit 23 to dd=20220701-20230607 [Date delivered, 1 Jul 2022-7 Jun 2023]	N/A	0	N/A
25	limit 23 to rd=20220701-20230607 [Revised date, 1 Jul 2022-7 Jun 2023]	N/A	8	N/A
26	24 or 25	N/A	8	N/A
27	limit 26 to yr="2022 -Current"	N/A	6	N/A
December 2023 update				
24	limit 23 to dd=20230301-20231218 [Date delivered, 1 Mar 2023-18 Dec 2023]	N/A	N/A	1
25	limit 23 to rd=20230301-20231218 [Revised date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	5
26	24 or 25	N/A	N/A	6
27	limit 26 to yr="2023 -Current"	N/A	N/A	6

Table 108 Search strategy for MEDLINE

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	Lennox Gastaut syndrome/	456	486	508
2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	3062	3175	3267
3	1 or 2	3167	3280	3372
4	exp "economic evaluation"/	90808	92479	93600
5	economics/ or economic aspect/	27465	27502	27518
6	Economics, Pharmaceutical/ or health economics/ or pharmacoeconomics/	3080	3105	3120
7	cost-benefit analysis/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost benefit analysis"/ or "cost utility analysis"/	139518	141762	143323
8	((economic or human*) adj3 consequence*).ti,ab.	8150	8614	8931
9	(economic* or pharmaco?economic* or pharmaco economic*).ti,ab.	339809	362880	380142
10	(cost* adj2 (effective* or utilit* or benefit* or minimi* or consequence*)).ti,ab.	192706	202876	211949
11	(CEA or CMA or CBA or CUA or CCA).ti,ab.	52563	54604	56217
12	Quality-Adjusted Life Years/ or quality adjusted life year/	15118	15652	15977
13	(quality adjusted life$ or quality-adjusted life$ or quality-adjusted-life$ or disability adjusted life$ or disability-adjusted life$ or disability-adjusted-life$).tw.	20587	22056	23291
14	(QALY or qal$ or qwb$ or qald$ or qale$ or qtime$ or daly$).tw.	18104	19425	20579
15	or/4-14	649826	684577	712021

16	3 and 15	125	129	134
17	case reports/	2294994	2339187	2373944
18	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	4906782	5045883	5158274
19	(animal* not human*).sh,hw.	5008408	5083357	5132595
20	or/17-19	9779296	9990965	10150824
21	16 not 20	86	89	93
June 2023 update				
22	limit 21 to dt=20220701-20230607 [Create date, 1 Jul 2022-7 Jun 2023]	N/A	6	N/A
23	limit 21 to rd=20220701-20230607 [Revised date, 1 Jul 2022-7 Jun 2023]	N/A	9	N/A
24	22 or 23	N/A	9	N/A
25	limit 24 to yr="2022 -Current"	N/A	7	N/A
December 2023 update				
22	limit 21 to dt=20230301-20231218 [Create date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	6
23	limit 21 to rd=20230301-20231218 [Revised date, 1 Mar 2023-18 Dec 2023]	N/A	N/A	13
24	22 or 23	N/A	N/A	13

25	limit 24 to yr="2023 -Current"	NA	N/A	6

Table 109 Search strategy for EBM Reviews - Cochrane Central Register of Controlled Trials

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	Lennox Gastaut syndrome/	40	82	82
2	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab.	350	360	367
3	1 or 2	352	366	373
4	(animal* not human*).sh,hw.	2,282	2750	2777
5	erratum.kw.	3,220	3781	4195
6	(ovarian or glucose).ti.	24,387	24755	25503
7	or/4-6	29,800	31189	32374
8	3 not 7	333	346	353
June 2023 update				
9	limit 8 to yr="2022 -Current"	N/A	40	N/A
December 2023 update				
9	limit 8 to yr="2023 -Current"	N/A	N/A	15

Table 110 Search strategy for Econlit

No.	Reference	Search hits		
		Original	June 23 update	December 23 update

1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	32	36	38
June 2023 update				
2	limit 1 to yr="2022 - 2023"	N/A	6	N/A
December 2023 update				
2	limit 1 to yr="2023 -Current"	N/A	N/A	3

Table 111 Search strategy for EBM Reviews - HTA

No.	Reference	Search hits
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	2

Table 112 Search strategy for EBM Reviews - Cochrane Database of Systematic Reviews

No.	Reference	Search hits		
		Original	June 23 update	December 23 update
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab,kw.	3	3	3
June 2023 update				
2	(2022* or 2023*).dp.	N/A	884	N/A
3	1 and 2	N/A	1	N/A
December 2023 update				
2	(2023* or 2024*).dp.	N/A	N/A	560
3	1 and 2	N/A	N/A	0

Table 113 Search strategy for EBM Reviews - NHS Economic Evaluation Database

No.	Reference	Search hits
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).mp.	3

J.1.2.2 Eligibility criteria

Studies were screened against the population, intervention, comparison, outcomes, and study design (PICOS) eligibility criteria (as outlined in Table 114) in the DistillerSR platform by two independent reviewers with discrepancies resolved by a third reviewer. The full texts of all included citations were retrieved and screened by two independent reviewers (in a double-blinded manner), and resolved by a third reviewer, where needed.

Table 114 Eligibility criteria – HCRU, costs and economic evaluations

Domain	Inclusion criteria (HCRU and costs)	Inclusion criteria (economic evaluations)
Population	Children and/or adults with LGS	

Interventions/ Comparators	Any (or no) interventions/comparators	- Pharmacological interventions including, but not limited to:
		  ○ Fenfluramine (FINTEPLA®)
		  ○ Cannabidiol
		  ○ Sodium valproate
		  ○ Lamotrigine
		  ○ Rufinamide
		  ○ Topiramate
		  ○ Felbamate
		  ○ Clobazam
		  ○ Levetiracetam
		- Ketogenic diet
		- Vagus nerve stimulation
		- Current clinical management
		- Placebo

Outcomes	Costs: - Direct costs - Indirect costs - Unit cost - Treatment costs - Administration and monitoring costs - Disease management costs - Cost of AEs Resource use, including but not limited to: - Hospitalisations - Doctor visits - Treatments - Laboratory tests	- LYG - QALYs gained - ICER/ICUR
Study design	Cost-benefit, cost-effectiveness, cost-utility, cost-minimisation, cost-consequence, budget impact and other economic evaluations; SLRs of economic evaluations, costing studies, burden-of-illness studies.	

Language	English

Abbreviations: AE, adverse event; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LGS, Lennox-Gastaut syndrome; LYG, life year gained; QALY, quality-adjusted life year; SLR, systematic literature review.

J.1.2.3 Study selection process

J.1.2.3.1 HCRU and costs

The database searches were conducted on 05 October 2022 and returned 877 records. After removing 172 duplicates, 705 records were screened at the title and abstract level, of which 27 were included for full-text screening. After full-text screening, seven unique publications in LGS were included. No records were identified from other sources.

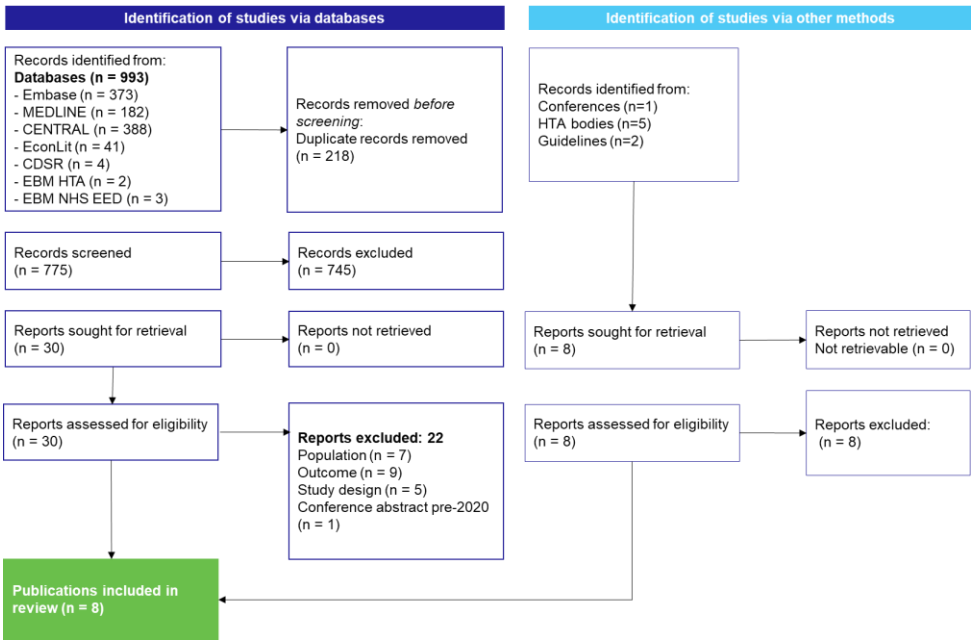
The first set of updated literature searches were conducted on 07 June 2023 and returned 84 records. After removing 36 duplicates, 48 records were screened at the title and abstract level, of which 45 were excluded and 3 were included for full-text screening. After full-text screening, one publication was included.

The second set of updated literature searches were conducted on 18 December 2023 and returned 32 records. After removing 10 duplicates, 22 records were screened at the title and abstract level, of which 21 were excluded and 1 was included for full-text screening. After full-text screening, no new publications were added to the original SLR.

In total, eight unique publications were included.

Figure 11 shows the literature selection procedure across all three HCRU and costs SLR iterations, with the number of records excluded at each stage.

Figure 11 PRISMA flow diagram – HCRU and costs



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; EBM, Evidence-Based Medicine; HTA, health technology assessment; NHS EED, National Health Service Economic Evaluations Database

J.1.2.3.2 Economic evaluations

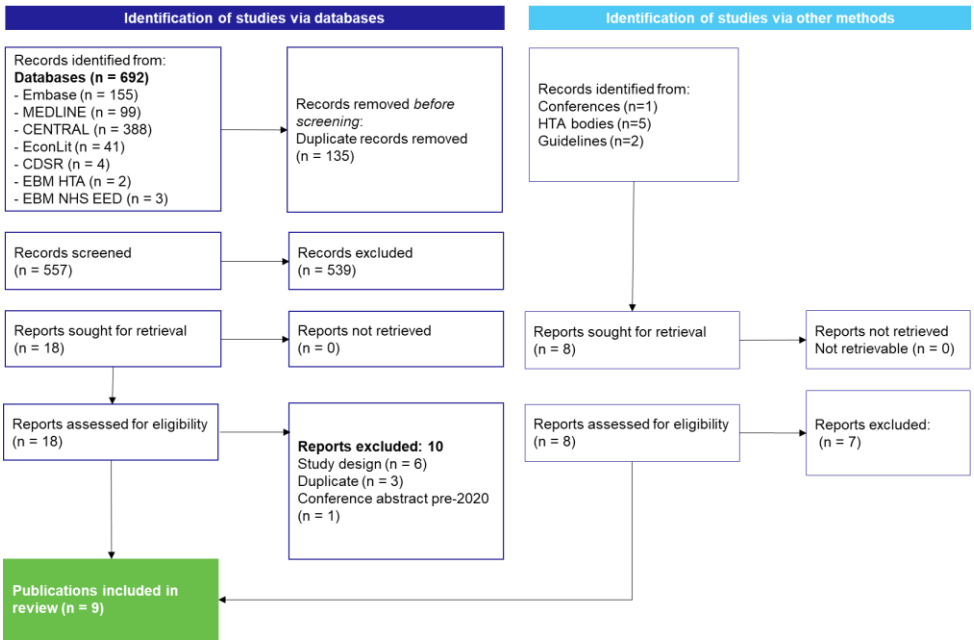
The database searches were conducted on 05 October 2022 and returned 602 records. After removing 100 duplicates, 502 records were screened at the title and abstract level, of which 502 were included for full-text screening. After full-text screening, eight publications reporting on seven unique economic evaluations in LGS were included. Additionally, one NICE HTA was identified from other sources. In total, nine publications reporting on eight unique economic evaluations were included for data extraction.

The first set of updated literature searches were conducted on 07 June 2023 and returned 60 records. After removing 26 duplicates, 34 records were screened at the title and abstract level, of which 34 were excluded and no records were included for full-text screening.

The second set of updated literature searches were conducted on 18 December 2023 and returned 30 records. After removing 9 duplicates, 21 records were screened at the title and abstract level, of which 21 were excluded and no records were included for full-text screening.

Figure 12 shows the literature selection procedure across all three economic evaluations SLR iterations, with the number of records excluded at each stage.

Figure 12 PRISMA flow diagram – economic evaluations



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; EBM, Evidence-Based Medicine; HTA, health technology assessment; NHS EED, National Health Service Economic Evaluations Database

J.1.2.4 Results

The literature search results (HCRU and costs) included in the model/analysis (n = 8) are presented in Table 115. The literature search results (economic evaluations) included in the model/analysis (n = 9) are presented in Table 116.

Table 115 Literature search results – HCRU and costs

Author and year	Reference
Reaven, 2018	Reaven NL, Funk SE, Montouris GD, Saurer TB, Story TJ. Burden of illness in patients with possible Lennox-Gastaut syndrome: A retrospective claims-based study. Epilepsy and Behavior. 2018;88:66-73. doi:https://dx.doi.org/10.1016/j.yebeh.2018.08.032
Reaven, 2019	Reaven NL, Funk SE, Lyons PD, Story TJ. The direct cost of seizure events in severe childhood-onset epilepsies: A retrospective claims-based analysis. Epilepsy & behavior : E&B. 2019;93:65-72. doi:https://dx.doi.org/10.1016/j.yebeh.2019.01.045
Pina-Garza, 2017	Pina-Garza JE, Montouris GD, Vekeman F, et al. Assessment of treatment patterns and healthcare costs associated with probable Lennox-Gastaut syndrome. Epilepsy and Behavior. 2017;73:46-50. doi:https://dx.doi.org/10.1016/j.yebeh.2017.05.021
Francois, 2017	Francois C, Stern JM, Ogbonnaya A, et al. Use and cost comparison of clobazam to other antiepileptic drugs for treatment of Lennox-Gastaut syndrome. Journal of market access & health policy. 2017;5(1):1318691. doi:https://dx.doi.org/10.1080/20016689.2017.1318691
Le, 2022	Le NMD, Dixon-Salazar T, Berg A, Danese SR, Perry MS, Meskis MA. Seizure-related outcomes with real-world use of cannabidiol in Lennox-Gastaut syndrome and Dravet syndrome: BECOME, a caregiver survey. Epilepsia. 2022;63(Supplement 2):118-119. 14th European Epilepsy Congress. Online. doi:https://dx.doi.org/10.1111/epi.17388
Chin, 2021	Chin RFM, Pickrell WO, Guelfucci F, Martin M, Holland R. Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: retrospective linkage cohort study. Seizure. 2021;91:159-166. doi:https://dx.doi.org/10.1016/j.seizure.2021.05.025
Majoie, 2001	Majoie HJM, Berfelo MW, Aldenkamp AP, Evers SMAA, Kessels AGH, Renier WO. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome: Clinical results, neuropsychological effects, and cost-effectiveness. Journal of Clinical Neurophysiology. 2001;18(5):419-428. doi:http://dx.doi.org/10.1097/00004691-200109000-00006
Strzelczyk, 2021	Strzelczyk A, Schubert-Bast S, Simon A, Wyatt G, Holland R, Rosenow F. Epidemiology, healthcare resource use, and mortality in patients with probable Lennox-Gastaut syndrome: A population-based study on German health insurance data. Epilepsy and Behavior. 2021;115:107647. doi:https://dx.doi.org/10.1016/j.yebeh.2020.107647

Table 116 Literature search results - Economic evaluations

Author and year	Reference
Benedict, 2010	Benedict A, Verdian L, MacLaine G. The cost effectiveness of rufinamide in the treatment of lennox-gastaut syndrome in the UK. PharmacoEconomics. 2010;28(3):185-199. doi:https://dx.doi.org/10.2165/11313640-000000000-00000

Clements, 2013	Clements KM, Skornicki M, O'Sullivan AK. Cost-effectiveness analysis of antiepileptic drugs in the treatment of Lennox-Gastaut syndrome. Epilepsy and Behavior. 2013;29(1):184-189. doi:https://dx.doi.org/10.1016/j.yebeh.2013.07.011
Faulkner, 2015	Faulkner MA. Comprehensive overview: efficacy, tolerability, and cost-effectiveness of clobazam in lennox-gastaut syndrome. Therapeutics and clinical risk management. 2015;11:905. doi:https://doi.org/10.2147/TCRM.S55930
Neuberger, 2020	Neuberger EE, Carlson JJ, Veenstra DL. Cost-Effectiveness of Cannabidiol Adjunct Therapy versus Usual Care for the Treatment of Seizures in Lennox-Gastaut Syndrome. PharmacoEconomics. 2020;38(11):1237-1245. Comment in: Pharmacoeconomics. 2021 Apr;39(4):477-478 PMID: 33674997 [https://www.ncbi.nlm.nih.gov/pubmed/33674997] Comment in: Pharmacoeconomics. 2021 Apr;39(4):473-475 PMID: 33674999 [https://www.ncbi.nlm.nih.gov/pubmed/33674999]. doi:https://dx.doi.org/10.1007/s40273-020-00945-z
Verdian, 2010	Verdian L, Yi Y. Cost-utility analysis of rufinamide versus topiramate and lamotrigine for the treatment of children with Lennox-Gastaut Syndrome in the United Kingdom. Seizure. 2010;19(1):1-11. doi:https://dx.doi.org/10.1016/j.seizure.2009.10.003
Abel, 2021	Abel TJ, Remick M, Welch WC, Smith KJ. One-year cost-effectiveness of callosotomy vs vagus nerve stimulation for drug-resistant seizures in Lennox-Gastaut Syndrome: A decision analytic model. Epilepsia Open. 2022;7(1):124-130. doi:https://dx.doi.org/10.1002/epi4.12570
Skornicki, 2014	Skornicki M, Clements KM, O'Sullivan AK. Budget impact analysis of antiepileptic drugs for Lennox-Gastaut syndrome. Journal of managed care & specialty pharmacy. 2014;20(4):400-6.
Majoie, 2001	Majoie HJM, Berfelo MW, Aldenkamp AP, Evers SMAA, Kessels AGH, Renier WO. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome: Clinical results, neuropsychological effects, and cost-effectiveness. Journal of Clinical Neurophysiology. 2001;18(5):419-428. doi:http://dx.doi.org/10.1097/00004691-200109000-00006
NICE, 2019	NICE. Cannabidiol for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome [ID1308]. Accessed Dec, 2022. https://www.nice.org.uk/guidance/ta615/evidence/appraisal-consultation-committee-papers-pdf-7017627422

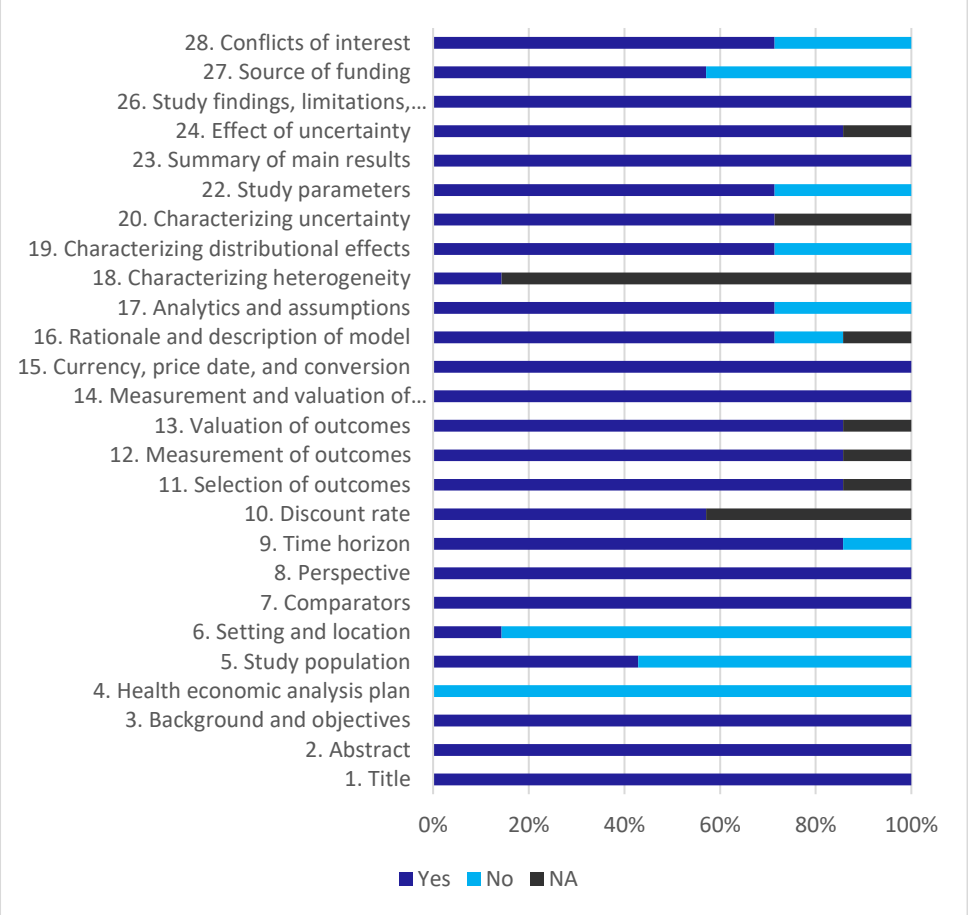
J.1.3 Quality assessment and generalizability of estimates

A quality assessment of the extracted economic evaluation studies was conducted using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.(92) Quality assessment was conducted for each unique model reported in a full-text article. Conference abstracts were not quality assessed given the limited information provided.

The methodological quality of the economic evaluations for each included study is shown in Figure 13, except for the NICE HTA submission. As a significant amount of data had been redacted from the NICE report, a quality assessment was not conducted. Furthermore, company submissions undergo an intensive quality check by the Evidence Review Groups and therefore the final model is expected to have already addressed most limitations flagged by the Evidence Review Groups.

The majority of the 28 items were fulfilled in almost all of the studies. The least frequently fulfilled items were study population, setting and location, heterogenity, and source of funding. Item 4 (health economic analysis plan) was the only item not reported in any of the studies. Item 21 and item 25 were not applicable in any of the reviewed studies since there was no patient or stakeholder engagement invloved in any of the study designs. Four studies (57.1%) met at least 80% of the CHEERS criteria(75, 93-95) (21 or more items) with three studies falling short of this threshold (20 items, 16 items, and 14 items, respectively).(96-98) The two lowest scoring studies did not provide information on several items (e.g., uncertainty, valuation of outcomes, sensitivity analysis) that were commonly reported in the higher scoring studies.(97, 98) Further, while discussion related to key findings, limitations and generalizability was provided, neither study comprehensively assess these criteria.

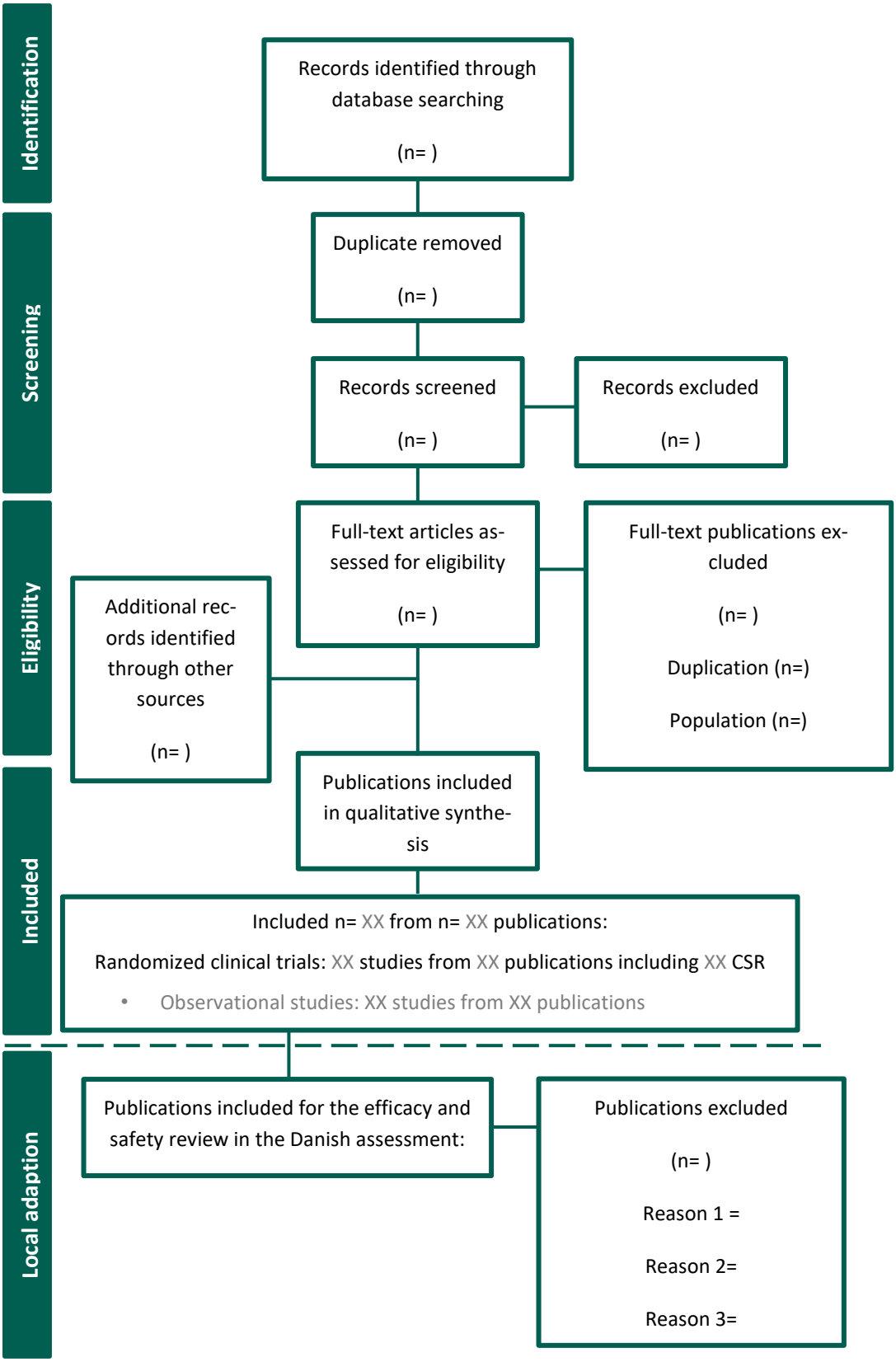
Figure 13 Quality assessment according to CHEERS checklist



Abbreviation: N/A, not applicable

Quality of HCRU and costs studies was not formally assessed as these studies are generally only reviewed with the intention to provide economic modelling inputs.

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk