Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over (ID1651)

For public – redacted

Technology appraisal committee D [11 January 2024]

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Company: UCB

Background on Lennox-Gastaut syndrome

Symptoms and prognosis

- Severely debilitating, lifelong and treatment resistant form of epilepsy
    - Experience frequent drop seizures, which may result in falls, serious injury, pain, hospitalisation and death
- Significant risk of sudden unexpected death in epilepsy (SUDEP), which is correlated with occurrence of uncontrolled and frequent generalised tonic-clonic seizures
- All-cause mortality ~14 times that of the general population (Autry et al. 2010)

Epidemiology

- Rare: LGS accounts for 3-5% of childhood epilepsies, with global incidence of ~2 per 100,000 children per year

Diagnosis

- Typically defined by triad of symptoms: frequent, heterogenous and treatment-resistant seizures; specific characteristic electroencephalogram pattern; development delay or cognitive development
- Diagnosis typically occurs between 3 and 5 years. Not all children display characteristic triad of symptoms at onset or at any one time → diagnosis can be challenging

LGS, Lennox-Gastaut syndrome; SUDEP, Sudden unexpected death in epilepsy

Patient perspectives

Submissions from Tuberous Sclerosis Association (TSA) and caregiver (patient expert)

- Limitations of currently available treatments:
  - Anti-epileptic medicines can work for a short duration but then lose effectiveness
  - Patients try ‘myriad’ of medications without success
  - Substantial side effects, such as weight loss and mouth ulcers
- LGS is hugely debilitating for patients and their families/carers – issues include learning disabilities, behavioural problems, seizures at any moment, risk of injury from seizures
- LGS can have deeper impact on families’ QoL and on ability to cope and support child's ability to reach acceptable level of well-being
  - Families and carers reported the experience of losing control and feelings of despair and helplessness
- Fenfluramine could be a lifeline to people with LGS with inadequate seizure control

“[Current treatments] don’t provide a complete cure for our seizures. We’ve tried 8 and he still has seizures despite being on 5 now. The side effects also make him feel sick.”

“I gave up my job... to look after my son. He had 21 seizures a day at birth. He needs one-to-one care. My family can’t go to social events as we normally would”

LGS, Lennox-Gastaut syndrome; TSA, Tuberous Sclerosis Association; QoL, Quality of life

Clinical perspectives

Submissions from 3 clinical experts

Current treatment

- Aims of treatment are to have seizures under optimal control and to minimise injury and side effects. Substantial unmet need for new treatments
- Clinically significant treatment response is reduction in seizures by >30%, particularly drop attacks, with no deterioration in behaviour. Also important to consider seizure severity, seizure free days and reduction in emergency admissions

Fenfluramine

- Demonstrated benefit in children resistant to existing treatments for LGS
- Fenfluramine is rapidly titrated and clinical effect can be evident rapidly – improves safety
- Benefit in LGS does not appear to be as dramatic as in Dravet syndrome
- Most common side effects (decreased appetite or somnolence) respond to dose adjustments. Behavioural side effects not common and less sedating than some other anti-seizure medications. Needs cardiac monitoring
- One expert suggested fenfluramine could be used 3rd line; other expert suggested 4th line

"Lennox Gastaut syndrome is a complex developmental and epileptic encephalopathy with a poor prognosis for seizure control and neurodevelopmental outcome"

"For patients who fail on all current treatment, fenfluramine could provide another final treatment option to help control symptoms and improve quality of life"

Equality considerations

Potential equality issues raised by Tuberous Sclerosis Association (TSA; charity focussed on tuberous sclerosis complex [TSC]):

- Uncontrolled seizures may lead to learning disabilities
    - 1 in every 2 people living with TSC have learning disabilities - 30% have profound learning disabilities and 20% have an IQ slightly below the normal range

Company: Use of fenfluramine is unlikely to raise any equality issues. However significant heterogeneity in clinical presentations of LGS and low prevalence, so data collection difficult.

Clinical experts:

- Adult population with LGS may not be under care of specialist so may not have access to new treatments
- Support from advocate required in people with intellectual disabilities, such as LGS

Patient expert: If tests are required to initiate fenfluramine then need to consider the impact on people with LGS. For example, regular blood tests traumatic for people with sensory issues

Key issues

NICE National Institute for Health and Care Excellence

Key issues

Table: Key issues

Issue	Resolved?	ICER impact
Relevant comparators	No, to discuss	Unknown
Appropriateness of model structure based on relative reduction in drop seizures	No, to discuss	Unknown
Extrapolation of fenfluramine treatment effect	No, to discuss	Very large*
Utility values		
• Uncertainty in the modelling of patient HRQoL	No, to discuss	Likely large
• Plausibility of approach for modelling caregiver HRQoL	No, to discuss	Moderate
Application of severity modifier to caregiver QALYs	No, to discuss	Large
Maintenance doses of fenfluramine and cannabidiol	No, to discuss	Moderate

* FFA+SoC more total QALYs in company base case, whereas CBD+CLB+SoC more total QALYs in EAG base case

CBD, Cannabidiol; CLB, Clobazam; FFA, Fenfluramine; HRQoL, Health-related quality of life; ICER, Incremental cost-effectiveness ratio; QALYs, Quality-adjusted life years; SoC, Standard of care

Key issues

Table: Key issues

Issue	Resolved?	ICER impact
Modelling institutionalisation		
• Impact of institutionalisation on caregiver HRQoL	No, to discuss	Moderate
• Inclusion of institutionalisation costs	No, to discuss	Small
Discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC	No, in appendix	Small
Inclusion of seizure frequency and seizure severity	No, in appendix	Unknown
Study validity		
• Measurement validity of eDiary	No, in appendix	Unknown
• External validity of trial – age, gender, ethnicity	No, in appendix	Unknown
• Internal and external validity of trial – concomitant treatments	No, in appendix	Unknown

NICE

ICER, Incremental cost-effectiveness ratio; SoC, Standard of Care; QALYs, Quality-adjusted life years

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Fenfluramine (Fintepla, UCB)

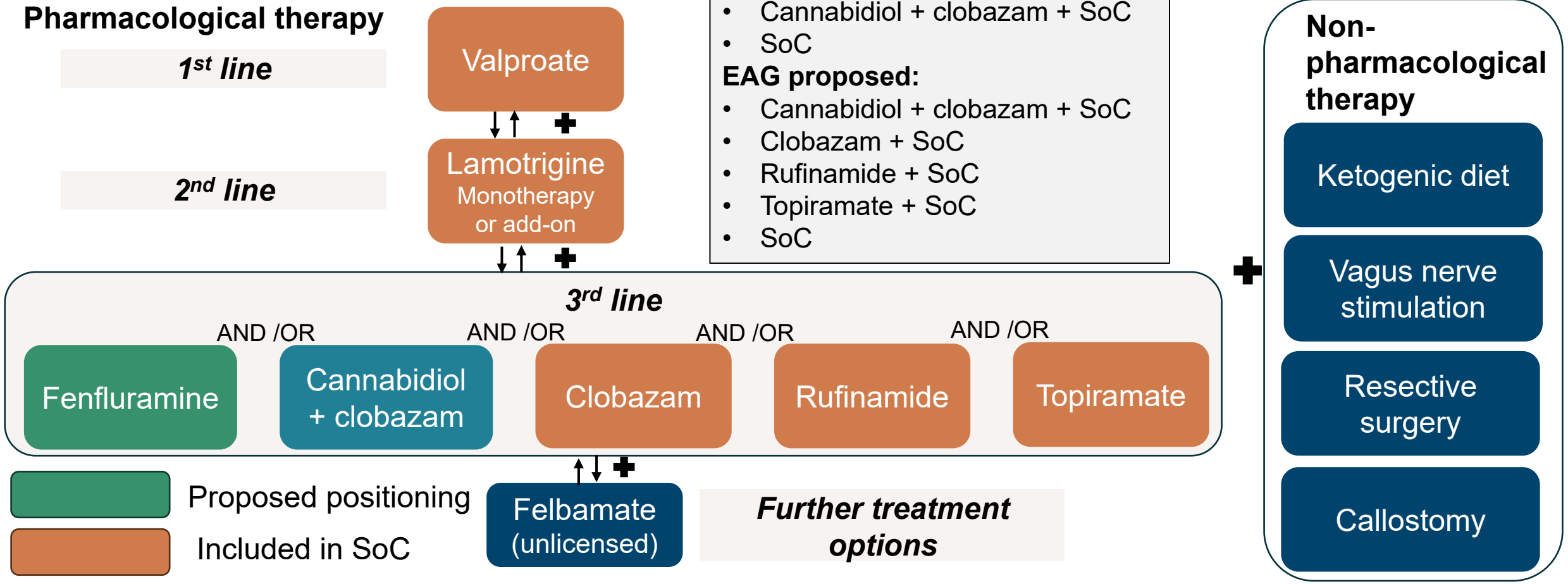
Table: Fenfluramine key information

Marketing authorisation	• Indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome as an add-on therapy to other antiepileptic medicines for patients aged 2 years and older • GB marketing authorisation: July 2023
Mechanism of action	• Precise anticonvulsant mechanism not known • Serotonin-releasing agent → may reduce seizures by acting as an agonist at specific serotonin receptors in the brain
Administration	• Oral solution • Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day) • After 7 days for people who are tolerating fenfluramine and require a further reduction of seizures, dose can be increased to 0.2 mg/kg twice daily (0.4 mg/kg/day) • After additional 7 days, dose can be increased to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day). Dose should not exceed 13 mg twice daily (26 mg/day)
Price	• List price £1,802.88 for 120 ml (2.2 mg/ml) bottle; £5,408.65 for 360 ml (2.2 mg/ml) bottle • Confidential patient access scheme in place

Treatment pathway

Fenfluramine positioned at 3rd line, same place in pathway as cannabidiol + clobazam

Figure: LGS treatment pathway



Relevant comparators:

Company:

- Cannabidiol + clobazam + SoC
- SoC

EAG proposed:

- Cannabidiol + clobazam + SoC
- Clobazam + SoC
- Rufinamide + SoC
- Topiramate + SoC
- SoC

↓↑ Switch treatment upon failure to reduce seizures
+ Add-on treatment upon failure to reduce seizures

Q for clinical experts: Does treatment pathway align with your experience of clinical practice?

NICE SoC, Standard of care

Key clinical trials

Table: Study 1601 RCT and OLE key trial information

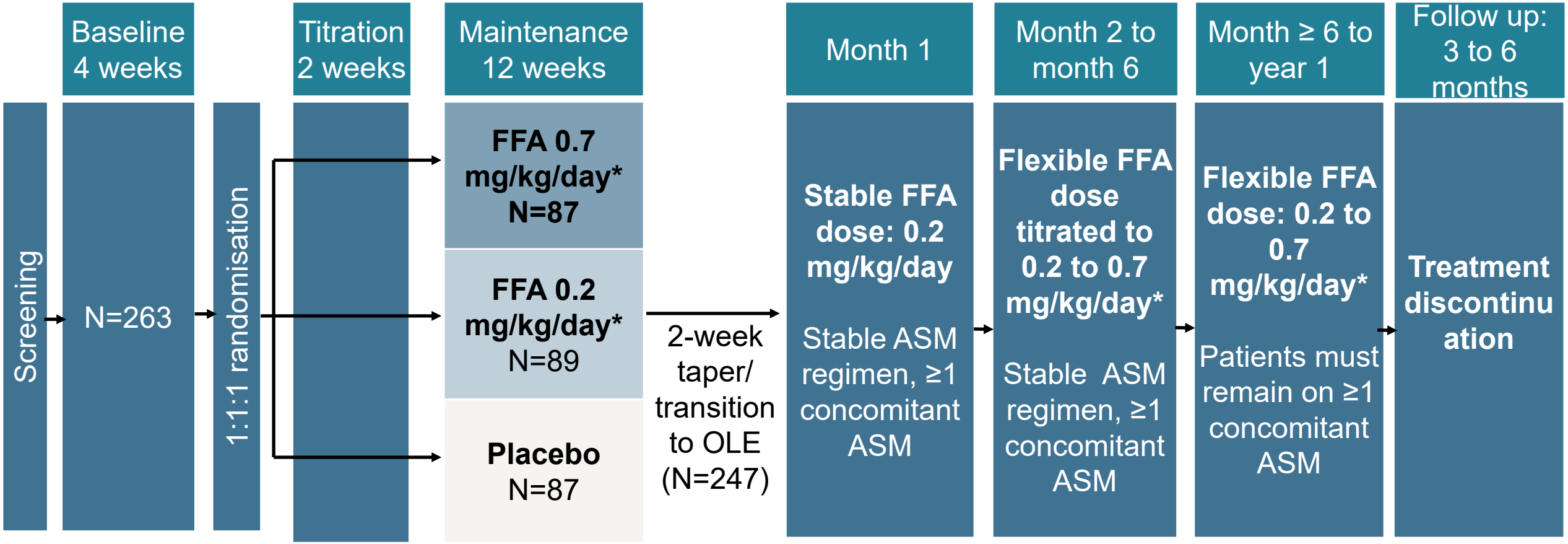
	Study 1601 RCT	Study 1601 OLE (ongoing)
Design	Phase 3 double-blind, placebo-controlled, multinational RCT	OLE study
Population	People aged between 2 to 35 years with ESC-confirmed LGS diagnosis, using stable ASMs	People who completed study 1601 RCT
Intervention	Fenfluramine (0.2 or 0.7 mg/kg/day) + SoC	Fenfluramine (0.2 to 0.7 mg/kg/day) + SoC
Comparator	Placebo + SoC	None
Duration	20 weeks (including 2-week taper or transition period)	12 months + safety follow-up visits up to 6 months after last dose*
Primary outcome	Percentage change in DSF from baseline in 0.7 mg/kg/day group vs placebo	N/A
Key secondary outcomes	Percentage change in DSF from baseline in 0.2 mg/kg/day group vs placebo, proportion achieving a ≥50% reduction from baseline in DSF, proportion experiencing improvement in CGI-scale	N/A
Locations	65 study sites: 34 in North America, 29 in Europe (0 in UK) and 2 in Australia	
Used in model?	Yes	Yes

ASM, Anti-seizure medication; CGI, Clinical global impressions; DSF, Drop seizure frequency; ESC, Epilepsy study consortium; OLE, Open label extension; RCT, Randomised controlled trial; SoC, Standard of care

Study 1601 RCT and OLE design

Study 1601 included 4 phases: 4-week baseline period, 2-week titration period, 12-week maintenance phase, 2-week taper or transition period

Figure: Study 1601 and OLE design



* Maximum daily dose: 26 mg fenfluramine. Mean maintenance dose in OLE: [redacted] mg/kg/day

NICE ASM, Anti-seizure medication; FFA, Fenfluramine; OLE, Open label extension; RCT, Randomised controlled trial

Study 1601 and OLE key results

Fenfluramine + SoC significantly improved the percentage change from baseline in DSF compared with placebo

Table: Study 1601 key results

	Placebo (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Fenfluramine 0.7 mg/kg/day (n=89)
DSF per 28 days: median (IQR)	53 (2 to 1,761)	85 (4 to 2,943)	83 (7 to 1,803)
Efficacy endpoint			
Median percentage change from BL in DSF during T+M	-7.59%	-14.16%	-26.49%
Estimated median difference vs placebo, HL estimator		10.5%	19.9%
p-value for comparison with placebo		0.0939	0.0013
Percentage of patients with ≥50% reduction from BL in DSF during T+M	10.3%	28.1%	25.3%
p-value for comparison with placebo		0.0051	0.0150

OLE

- At year 1 of the OLE the median percentage reduction from baseline in DSF was 51.8% (p<0.0001)

EAG highlighted that seizure frequency restricted to drop seizures; and outcome of seizure severity not included in CS – see further details in appendix

EAG highlighted potential issues with the validity of Study 1601:

- Measurement validity of eDiary used to record seizures – see further details in appendix
- External validity of trial in terms of age, gender and ethnicity – see further details in appendix
- Internal and external validity of trial in terms of concomitant treatments – see further details in appendix

BL, Baseline; DSF, Drop seizure frequency; EMD, Estimated mean difference; HL, Hodges-Lehman; IQR, Interquartile range; OLE, Open label extension; SoC standard of Care; T+M, Titration+maintenance

NMA summary

NMA suggests that fenfluramine is superior to placebo and cannabidiol + clobazam for key efficacy outcomes except for the ≥75% reduction in DSF outcome

Methodology overview

- Company's base case NMA analysis used data from clinical trial ITT population and from GBA (German HTA body)
  - **ITT data NMA:** Included 3 RCTs (including fenfluramine, cannabidiol and placebo). However, cannabidiol data included patients not systematically also receiving clobazam so GBA data NMA preferred
  - **GBA data NMA:** Data available for for cannabidiol + clobazam subgroup. GBA data not suitable for median reduction in frequency of GTC seizures or the discontinuation due to AEs, so ITT data NMA used for these outcomes
- Company also shared extended NMA (including 9 RCTs), which also included clobazam, lamotrigine, rufinamide and topiramate

Base case NMA analysis results overview

- 4 treatments compared in base case analysis: Fenfluramine (0.7 mg/kg), cannabidiol + clobazam (10 mg/kg), cannabidiol + clobazam (20 mg/kg), placebo
- Fenfluramine (0.7 mg/kg) ranked 1st of 4 treatments for median percent reduction in frequency of GTC seizure, ≥25%, and ≥50% reduction in DSF
- Fenfluramine (0.7 mg/kg) ranked 3rd of 4 treatments for ≥75% reduction in DSF

See appendix for further information

DSF, Drop seizure frequency; GBA, The Federal Joint Committee; GTC, Generalised tonic-clonic; ITT, Intention to treat; NMA, Network meta-analysis

Key issue: Relevant comparators

EAG: Rufinamide, topiramate and clobazam should be considered separately as comparators

Background

- Final scope comparators: ECM without fenfluramine, which may include combinations of: ASMs, ketogenic diet, vagus nerve stimulation and surgery
- Comparators in company submission: cannabidiol with clobazam + SoC and SoC alone (other ASMs and non-pharmaceutical treatments are not considered as comparators but constitute SoC 'basket')

Company

- SoC varies due to the refractory nature of LGS. Given the heterogeneity of LGS, not clinically or statistically meaningful to compare to individual or specific combinations of ASMs beside cannabidiol with clobazam + SoC
- Cannabidiol with clobazam is the only established clinical add-on therapy appraised by NICE, and only therapy with sufficient trial data to permit a robust comparison (6 out of 9 RCTs failed feasibility assessment)
- Other ASMs considered as separate 3rd line treatment options are not necessarily used at 3rd line in practice
- In TA615, cannabidiol with clobazam + SoC is compared to "SoC" defined as a 'basket' of choice of ASMs

EAG comments

- Rufinamide, topiramate and clobazam recommended as 3rd line medications in NG217 so these should be considered separately as comparators → rationale for exclusion not sufficiently convincing
- Results from this extended NMA (including all 9 RCTs) suggest that some of these alternative treatments may have greater efficacy than fenfluramine → likely reduction of cost-effectiveness of fenfluramine

What are the most appropriate comparators for fenfluramine?

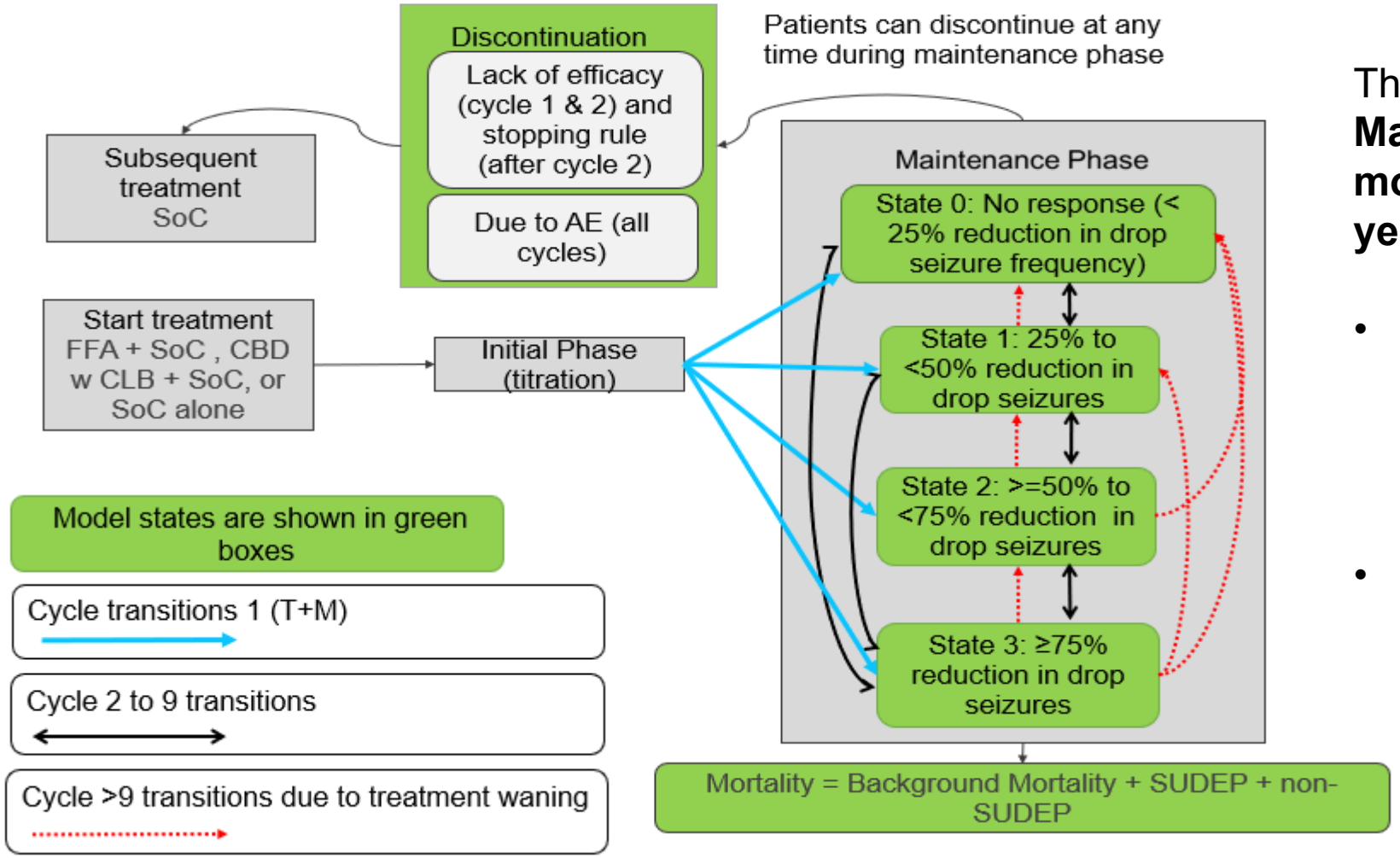
ASM, Anti-seizure medication; EAG, Evidence Assessment Group; ECM, Established clinical management; LGS, Lennox-Gastaut syndrome; RCT, Randomised controlled trial; SoC, Standard of care

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Figure: Company's model structure



The company presented a **cohort-based Markov model** with a **cycle length of 3 months** and a **lifetime time horizon of 86 years**

- Overall, technology primarily affects **costs** by:
  - the higher treatment costs for fenfluramine
- Technology primarily affects **QALYs** by:
  - reduction in frequency of drop seizures
  - reduction in caregiver burden

AE, Adverse event; CBD, Cannabidiol; CLB, Clobazam; FFA, Fenfluramine; SoC, Standard of care; T+M, Titration and Maintenance; QALY, Quality-adjusted life year; SUDEP, Sudden unexpected death in epilepsy

How company incorporated evidence into model

See appendix for full list of assumptions and evidence sources

Table: Key assumptions and evidence sources in company's base case model

Input	Assumption and evidence source
Baseline inputs	Study 1601
Fenfluramine + SoC efficacy	**Cycle 1**: TPs based on RR derived from NMA results **Cycles 2-5**: TPs based on Study 1601 OLE **Cycles 6-9**: TPs assumed to equal TPs observed in cycle 4-5 **Cycles 10+:** Change in state occupancy based on treatment waning, discontinuation and death
Cannabidiol + clobazam + SoC efficacy	**Cycle 1**: TPs based on a RR derived from the NMA results using a weighted average of the 10 mg/kg/day and 20 mg/kg/day subgroups **Cycles 2-5**: State occupancy based on cannabidiol + clobazam + SoC trial OLE **Cycles 6-9**: Assumed no change in state occupancy (except discontinuation and death) **Cycles 10+:** Change in state occupancy based on treatment waning, discontinuation and death
SoC efficacy	**Cycle 1**: TPs directly derived from SoC arm of Study 1601 **Cycles 2+**: Assumed no change in state occupancy (except death)
Treatment waning	After cycle 9, treatment waning implemented considering 2 main elements: 1) Proportion of people that experienced treatment waning, which was 5.2% (for both fenfluramine and cannabidiol arms) based on last 3 months of study 1601 OLE 2) Applying last deteriorating TP (i.e. TPs calculated only including people that stayed in their health state or deteriorated to a worse health state) observed from last 3 months of study 1601 OLE to 5.2% of fenfluramine and cannabidiol arms

NICE

NMA, Network meta-analysis; OLE, Open label extension; RR, Relative risk; SoC, Standard of care; TP, Transition probability

Key issue: Model structure

Company model based on relative reductions in DSF, EAG prefer model based on absolute seizure frequency

Background

- Company's model structure based on relative reductions in DSF rather than absolute DSF

Company

- Relative reduction in DSF has been used in previously published models with a Markov structure in LGS
- Using absolute DSF values directly as health states not feasible as data not available for cannabidiol with clobazam + SoC. Possible in TA615 because ITC not used (only comparator being SoC [+placebo])
- Relative reduction in percentage of DSF translated into absolute DSF values by using the baseline number of drop seizures and changes in the median drop seizures frequency of each state, based on the midpoint method described in Neuberger et al. 2020

EAG comments

- Use of relative reductions in drop seizures will result in people with different numbers of absolute drop-seizures ending up in the same health state, although their HRQoL and costs and resource use could differ significantly in practice → lacks face validity
- Prefers a model structure based on absolute seizure frequency in line with NICE TA615

Is the company's model structure appropriate for decision making?

DSF, Drop seizure frequency; EAG, Evidence Assessment Group; HRQoL, Health-related quality of life; ITC, Indirect treatment comparison; LGS, Lennox-Gastaut syndrome; SoC, Standard of care

Key issue: Extrapolation of fenfluramine treatment effect (1)

Background

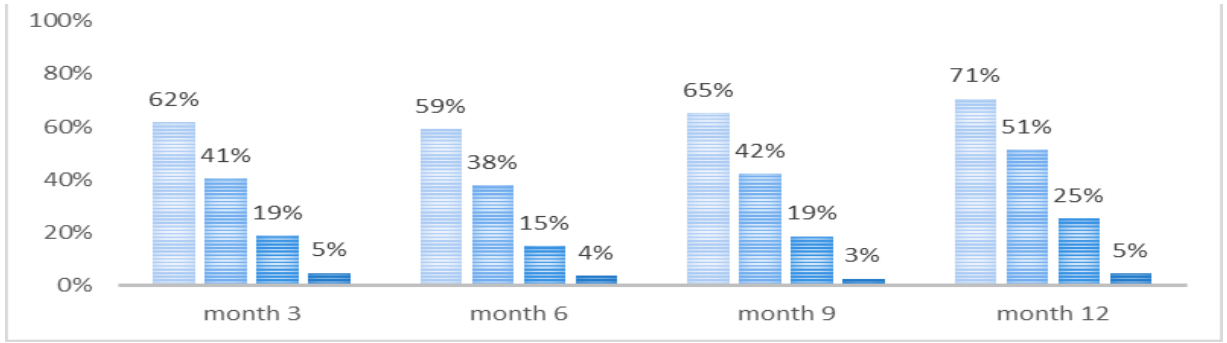
- Observed period data (15 months) extrapolated out to 86 year modelled time horizon
- In CS, treatment effectiveness for fenfluramine + SoC was assumed to increase after observed study period (cycle 5 to 9), while the treatment effectiveness for cannabidiol + clobazam + SoC was assumed to be stable

Company

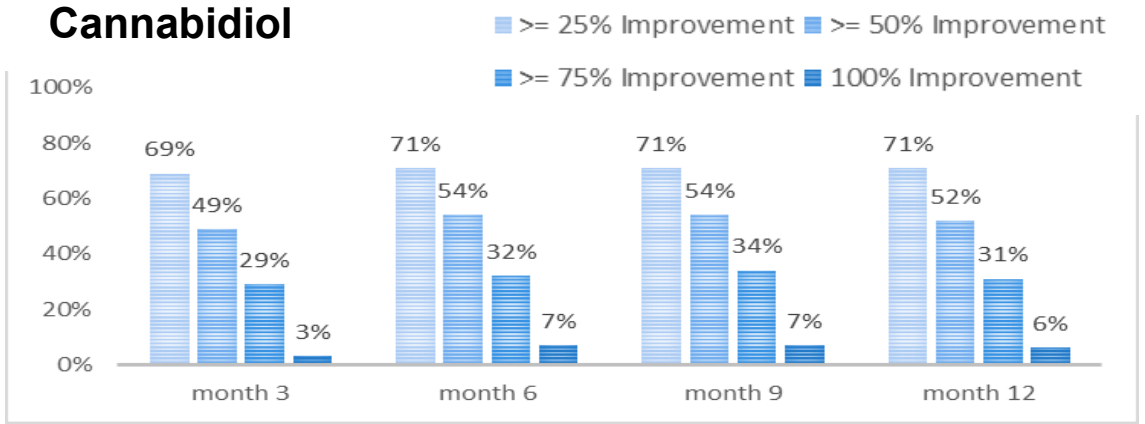
- Trial data shows fenfluramine treatment is sustained and increasing, represented by increasing percentage of people showing improvement in seizure outcomes of varying degrees over time. Whereas cannabidiol's efficacy plateaus – state occupancy remained fixed for almost 6 months (from month 6 to 12) – see **figure**
- Evidence from Dravet syndrome suggests efficacy of fenfluramine continues to improve up to ~month 25 to 30
- Clinicians consider long-term efficacy improvements of fenfluramine in Dravet syndrome would also apply in LGS

Figures: State occupancy of fenfluramine and cannabidiol arms in 1st year follow-up after T+M (data from OLE studies) based on people with calculable state at respective timepoints

Fenfluramine



Cannabidiol



See appendix for median change in drop seizure frequency over time in trial and OLE

CS, Company submission; LGS, Lennox-Gastaut syndrome; OLE, Open label extension; SoC, Standard of care

Key issue: Extrapolation of fenfluramine treatment effect (2)

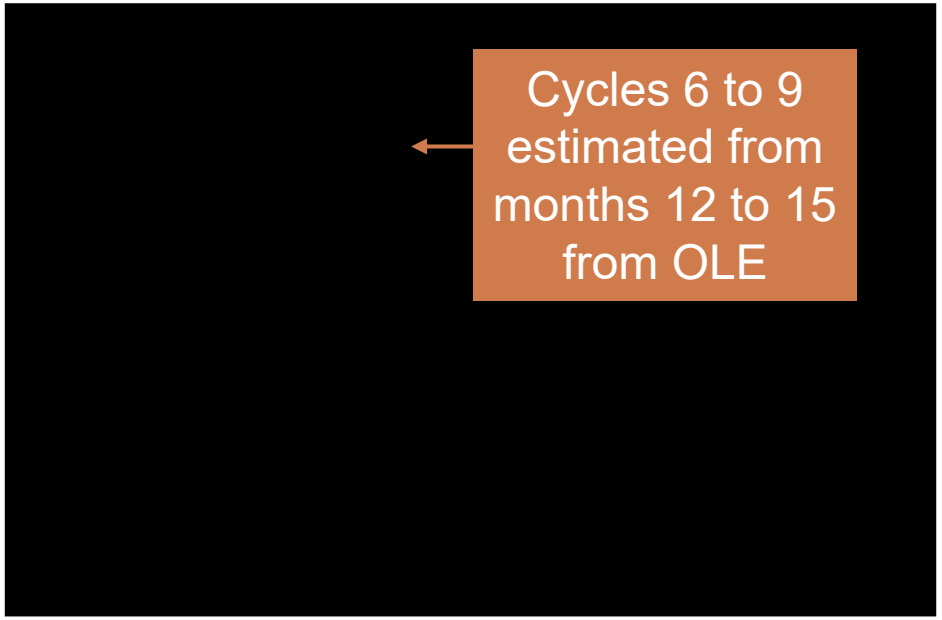
Distribution of health states over time (Markov trace)

Key
- State 0
- State 1
- State 2
- State 3
- Death + discontinuation

See appendix for SoC arm Markov trace

CBD, Cannabidiol; CLB, Clobazam; FFA, Fenfluramine; SoC, Standard of care

Company base case – FFA + SoC



Company base case – CBD + CLB + SoC

EAG base case – FFA + SoC

EAG base case – CBD + CLB + SoC

Key issue: Extrapolation of fenfluramine treatment effect (3)

EAG comments

- Agrees that effectiveness of fenfluramine + SoC seems to increase over time **during trial** period
- Uncertain about the prolongation of treatment effect **after trial** period.
  - Long-term efficacy data of fenfluramine in Dravet syndrome shows treatment effect maintained until month 15 of OLE study but does not show an increased treatment effect
  - Maintained treatment effect modelled in TA808 (fenfluramine for Dravet syndrome)→ so company's assumption inconsistent with assumption in TA808
- In company base case, incremental QALY gains for fenfluramine + SoC obtained only in unobserved period (see **table**)
- Preferred to model maintenance of fenfluramine treatment effect after the observed period in base case
- Also noted concerns with:
  - company's method to calculate treatment waning (see appendix)
  - discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC in 1st year of model (see appendix)

Table: Observed vs extrapolated QALYs in company base case

	Observed	Total (Observed and extrapolated)
Fenfluramine + SoC	0.73	3.68
CBD + CLB + SoC	0.75	2.86
SoC	0.47	1.63

Is it appropriate to assume the treatment effectiveness for fenfluramine will increase after the observed study period or stay the same?

CS, Company submission; LGS, Lennox-Gastaut syndrome; OLE, Open label extension; QALY, Quality-adjusted life year; SoC, Standard of care

Key issue: Patient utilities

EAG: none of the utility values provided in the company submission are ideal for informing patient HRQoL

Background

- QOLCE-16 data collected in Study 1601 and OLE but company did not use these data in economic model because QOLCE-16 is a disease-specific measure and long-term data were not yet available

Company

- EQ-5D utilities from vignette-based study, Verdian et al. used to inform base case – matched NICE's EQ-5D reporting requirements, used in similar LGS models and aligned with model's relative health state structure
- Vignettes useful in rare diseases such as LGS where difficult to recruit large enough representative sample
- 2 other studies reporting relevant UK utility values deemed less appropriate (see appendix):
  - Auvin et al. did not align with patient population
  - Lo et al. described health states based on absolute DSF per month rather than treatment response

EAG comments

- Approach condition-oriented (vignette may not provide enough detail on all dimensions of EQ-5D) so may not capture other aspects that influence HRQoL
- Verdian et al. values not directly from people living with LGS
- Utility values from Verdian et al. relatively low (see **table**) → lack face validity compared to QOLCE-16 data from Study 1601 and OLE
- Uses Verdian et al. in base case but noted none of utilities in CS are ideal for informing patient HRQoL

Table: Utility values in model

Health state	Utility value
0	0.02
1	0.1
2	0.5
3	0.596

What utility values should be used in the model?

DSF, Drop seizure frequency; EQ-5D, EuroQol-5 dimensions; HRQoL, Health-related quality of life; OLE, Open label extension; LGS, Lennox-Gastaut syndrome; QOLCE-16, Quality of Life in Childhood Epilepsy-16 item

Key issue: Caregiver utilities

Company base case uses caregiver utility approach, EAG prefers caregiver disutility approach

Background

- Company included caregiver utilities in model and assumed 1.8 caregivers per LGS patient (in line with TA615)

Company

- Assumed caregiver utilities same as patient utilities due to lack of caregiver utility values in literature and substantial impact of LGS on caregivers who provide round-the-clock care
- Evidence suggests utility values for caregivers are also relatively low. Lo et al. indicates that utility values for people with LGS and LGS caregivers are highly correlated and sensitive to seizure frequency
- Provided a scenario analyses modelling caregiver disutility (rather than caregiver utility) based on Auvin et al.

EAG comments

- Unrealistic to assume same utility values for people with LGS and caregivers. Auvin et al. and Lo et al. report higher utility values for caregivers than patients
- Zarit Caregiver Burden Inventory results in Study 1601 suggest a mild to moderate caregiver burden and that caregiver burden may not be sensitive to changes in seizure frequency
- Company assumed that when a patient in model died, corresponding carer utility was also set to 0→ overestimates the impact of mortality on caregivers
- Applied caregiver disutility values in base case* (calculated as difference between UK general population and UK caregiver utility scores for LGS in Lo et al.). See appendix for caregiver utilities from Auvin et al and Lo et al

Do the committee prefer the caregiver utility or disutility approach for modelling?
What is the committee's preferred choice of caregiver (dis)utility values for use in the economic model?

LGS, Lennox-Gastaut syndrome

QALY weighting for severity

Table: Key for applying severity modifier

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

Table: QALY shortfall analysis

Treatment	Expected total QALYs without disease	Total QALYs with condition, under current treatment	Absolute shortfall	Proportional shortfall	QALY weight
Company base case assumptions					
SoC	23.55	0.58	22.98	97.54%	1.7
CBD+CLB+SoC	23.55	1.01	22.54	95.71%	1.7
EAG base case assumptions					
SoC	23.55	0.60	22.95	97.45%	1.7
CBD+CLB+SoC	23.55	1.23	22.32	94.78%	1.7

Key issue- application of severity modifier to caregiver QALYs

NICE defines severity as "future health lost by people living with the condition with standard care in the NHS".

Company: Considers that this applies to both patients and caregivers

EAG: Considers that severity modifier should be applied solely to patient QALYs

NICE: Caregiver QALYs should not be weighted- but flexibility to consider weighting in exceptional circumstances

CBD, Cannabidiol; CLB, Clobazam; EAG, Evidence Assessment Group; QALY, Quality-adjusted life year; SoC, Standard of care

Key issue: Maintenance doses of fenfluramine and cannabidiol

At clarification stage, company changed maintenance doses of fenfluramine and cannabidiol

Table: Company and EAG base rationale for base case maintenance doses of fenfluramine and cannabidiol

Treatment	Dose	Rationale
Fenfluramine	**Company:** [redacted] mg/kg/day	• Based on real-world data and supported by clinical expert opinion • In OLE, efficacy continued to improve at lower average doses than used in Study 1601 • Doses in OLE titrated based on tolerability and safety→ more reflective of practice
	EAG: 0.5 mg/kg/day	• In CS, clinical experts said that average dose of 0.5 mg/kg/day is realistic • Company dose lower than maintenance dose in SmPC (0.7 mg/kg/day) and different from the doses received in Study 1601 (which was used to inform ITC)
Cannabidiol	**Company:** 16 mg/kg/day	• Clinical experts said dose closer to 20 mg/kg/day in clinical practice • Mean modal dose in cannabidiol OLE study was 24 mg/kg/day. OLE more reflective of practice • Adequate reductions in DSF rarely seen at lower cannabidiol doses
	EAG: 12 mg/kg/day	• 12 mg/kg/day used in NICE TA615 • Cannabidiol treatment effectiveness based on same data as TA615

Note: weights used to inform dose in economic model based on mean weight for each age category (2-5 years, 6-11 years, 12-17 years, 18-35 years and >35 years*) in Study 1601. Wastage not included in model. Dose cap of 26 mg/day for fenfluramine, no dose cap applied to cannabidiol.

What maintenance doses for fenfluramine and cannabidiol should be used in model?

CS, Company submission; DSF, Drop seizure frequency; FFA, Fenfluramine; ITC, Indirect treatment comparison; OLE, Open label extension; SmPC, Summary of Product Characteristic; SoC, Standard of care

Key issue: Modelling institutionalisation

Company did not model impact of institutionalisation on costs and caregiver HRQoL, EAG prefer to include

Background

- Stated in CS "outcomes for patients with LGS are typically very poor; the majority of patients will require home care or institutionalisation" but impact on institutionalisation not included in economic model
- EAG asked company to provide scenario analysis including costs of institutionalisation and home care

Company

- Institutionalisation costs not included in base case as difficult to determine the percentage of people institutionalised according to the reduction of seizure frequency
- Provided scenario including institutionalisation costs applied to 10% of people reaching 18 years, similar to TA615*

EAG comments

- Assuming an institutionalisation rate of 10% adopted by the EAG in its base case but unclear if representative of UK clinical practice→ further evidence should be provided to support this assumption
- Caregiver (dis)utilities should also be adjusted for fact that a proportion of people with LGS will be institutionalised
- In base case assumed 0.7 caregivers for people institutionalised (based on proportion of days per year that institutionalised people are expected to be home)

Should the costs and caregiver HRQoL impact of institutionalisation be included in the economic model?
Is it appropriate to assume an institutionalisation rate of 10% of all people reaching 18 years old?
Is it more appropriate to assume 1.8 or 0.7 caregivers for institutionalised people with LGS?

CS, Company submission; EAG, Evidence Assessment Group; HRQoL, Health-related quality of life; LGS, Lennox-Gastaut syndrome; TTO, Time trade off

Other issues

Further to the key issues, the EAG's base case differed from the company base case in the preferred stopping rule

Stopping rule

Company modelled a stopping rule for patients with a <25% reduction in DSF based on clinical expert opinion, assessed every 3 months

EAG: in TA808 (fenfluramine for treating seizures associated with Dravet syndrome) Committee deemed a stopping rule of "30% at 6 months", i.e. patients stopped treatment if they had <30% reduction in DSF over a period of 6 months, most appropriate→ prefers this stopping rule in its base case

Which stopping rule is most appropriate for clinical practice?

Lead team issues

- Known association between fenfluramine and pulmonary hypertension – median of 4.5 years to develop in previous study (Souza et al.). No confirmed cases of pulmonary hypertension in study 1601 or OLE, but only 12 months of follow-up in OLE → possibility that cases may emerge in the future? **Should treatment for pulmonary hypertension be included in model?**
- Most common TEAE for fenfluramine is decreased appetite (as per study 1601 safety data). **Would some people receiving fenfluramine require a gastric tube due to decreased appetite?**
- **When will data from long-term safety study of fenfluramine in LGS and Dravet syndrome be available?**

DSF, Drop seizure frequency; EAG, Evidence Assessment Group; LGS, Lennox-Gastaut syndrome; TEAE, Treatment-emergent adverse event

Summary of company and EAG base case assumptions (1)

Table: Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Fenfluramine treatment effect extrapolation	Treatment effect assumed to increase after observed study period	Assumed maintenance of treatment effect after observed study period
Patient utility	Verdian et al.	Verdian et al.
Carer (dis)utility approach	Utility approach using Verdian et al.	Disutility approach using Lo et al.
Application of severity modifier	Modifier of 1.7 applied to patient and caregiver QALYs	Modifier of 1.7 applied to only patient QALYs
Fenfluramine maintenance dose	[redacted] mg/kg/day	0.5 mg/kg/day
Cannabidiol maintenance dose	16 mg/kg/day	12 mg/kg/day
Impact of institutionalisation on caregiver dis(utility)	Excluded	Reduced caregiver disutility
Institutionalisation costs	Excluded	Included

NICE

EAG, Evidence Assessment Group; QALYs, Quality-adjusted life years

Summary of company and EAG base case assumptions (2)

Table: Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Fenfluramine model state occupancy cycles 2-5	Calculated transition probabilities between states based on Study 1601 OLE	Based on state occupancies in ITT population of Study 1601 OLE
Stopping rule	<25% reduction in DSF assessed every 3 months	<30% reduction in DSF assessed every 6 months
Treatment waning transition probabilities	Calculated only using patients that stayed in health state or deteriorated from month 9 to month 12	Calculated using all patients on treatment from month 9 to 12

NICE

DSF, Drop seizure frequency; EAG, Evidence Assessment Group; ITT, Intention to treat; OLE, Open-label extension

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Results presented in part 2:

- Company base case* – below the threshold usually considered an acceptable use of NHS resources
- EAG base case – dominated versus cannabidiol + clobazam + SoC; above the threshold usually considered an acceptable use of NHS resources versus SoC

Scenarios in which each of the company's preferred assumptions (where different from EAG's preferred assumptions) are applied individually to EAG base case will also be considered

*probabilistic ICER versus cannabidiol + clobazam + SoC is significantly lower than deterministic ICER due to application of a dose cap of 26 mg/day to fenfluramine with no dose cap applied to cannabidiol

EAG, Evidence Assessment Group; PAS, Patient access scheme

NICE National Institute for Health and Care Excellence

Supplementary Appendix

Decision problem (1)

Table: Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	People aged 2 and over with LGS whose seizures are inadequately controlled by ECM	As per final NICE scope	Positioning more specifically as 3rd line treatment (where cannabidiol is currently recommended)
Intervention	Fenfluramine hydrochloride	After clarification company amended to fenfluramine + SoC	Fenfluramine would not be given alone; correctly amended to fenfluramine + SoC
Comparators	ECM without fenfluramine hydrochloride, which may include combinations of: ASMs, ketogenic diet, vagus nerve stimulation and surgery	After clarification, company amended decision problem comparators from SoC treatment (or ECM) to the more specific CBD + CLB + SoC, or SoC	In addition to CBD + CLB, NG217 recommends three alternative 3rd line add-on therapies: clobazam, rufinamide and topiramate. All these should also be considered as specific comparators alongside CBD + CLB

ASM, Anti-seizure medication; CBD, Cannabidiol; CLB, Clobazam; ECM, Established clinical management; LGS, Lennox-Gastaut syndrome; SoC, Standard of care; VAT, Value added tax

Decision problem (2)

Table: Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Outcomes	Measures to be considered include: • seizure frequency (overall and by seizure type) • proportion of people seizure-free (overall and by seizure type) • response rate (overall and by seizure type) • seizure severity • incidence of status epilepticus • mortality • adverse events of treatment • HRQoL (patients and carers)	As per final NICE scope except: • Only drop seizures (and tonic-clonic) considered because drop seizures characteristic of LGS and primary and key secondary endpoints of RCT • Seizure severity captured through types of seizures • Proportion seizure free not considered in model as proportion seizure free very low in phase 3 trials of fenfluramine and cannabidiol • Incidence of status epilepticus not a model outcome per se but non-SUDEP was considered including status epilepticus deaths	• Seizure severity included despite inclusion in NICE scope • Mortality not included as trial outcome but included in model through SUDEP and non-SUDEP • Seizure frequency restricted to drop seizures (and tonic-clonic) but other seizure types not included

HRQoL, Health-related quality of life; LGS, Lennox-Gastaut syndrome; RCT, Randomised controlled trial; SUDEP, Sudden unexpected death in epilepsy

Study 1601 baseline characteristics (1)

Table: Study 1601 baseline characteristics

Characteristic	Placebo (n=87)	Fenfluramine 0.2mg/kg/day (n=89)	Fenfluramine 0.7mg/kg/day (n=87)
Age, mean (SD), y	14 (8)	13 (8)	13 (7)
Sex (%)	46 (53) male	46 (52) male	54 (62) male
Ethnicity Asian Black or African American White Other Unknown, not reported	 2 (2) 4 (5) 71 (82) 0 10 (11)	 3 (3) 5 (6) 67 (75) 1 (1) 13 (15)	 4 (5) 3 (3) 70 (80) 0 10 (11)
Motor seizure frequency per 28 days: median (IQR)	68 (14 to 1,761)	106 (4 to 2,943)	111 (10 to 1,897)
Total (motor and non-motor) seizure frequency per 28 days: median (IQR)	120 (14 to 1,761)	138 (14 to 2,967)	152 (10 to 5,472)
DSF per 28 days: median (IQR)	53 (2 to 1,761)	85 (4 to 2,943)	83 (7 to 1,803)

DSF, Drop seizure frequency; IQR, Interquartile range; SD, Standard deviation; RCT, Randomised controlled trial; y, Years

Study 1601 baseline characteristics (2)

Table: Study 1601 baseline characteristics

Characteristic	Placebo (n=87)	Fenfluramine 0.2mg/kg/day (n=89)	Fenfluramine 0.7mg/kg/day (n=87)
Number or previous ASM use Mean (SD) Median (Range)	 7 (4) 6 (1 to 19)	 7 (4) 7 (1 to 18)	 8 (4) 7 (1 to 20)
Concurrent ASM use Total mean (SD) Total median (Range)	 3(1) 3 (1 to 4)	 3 (1) 3 (1 to 5)	 3 (1) 3 (1 to 4)
Number of patients taking each concomitant medication (%)	Valproate: 49 (56) Clobazam: 38 (44) Lamotrigine: 29 (33) Levetiracetam: 20 (23) Rufinamide: 18 (21)	Valproate: 52 (58) Clobazam: 36 (40) Lamotrigine: 30 (34) Levetiracetam: 17 (19) Rufinamide: 17 (19)	Valproate: 46 (53) Clobazam: 45 (52) Lamotrigine: 29 (33) Levetiracetam: 23 (26) Rufinamide: 18 (21)

SD, Standard deviation

Adverse events

Overall, fenfluramine showed a good safety and tolerability profile and sustained retention rates in the use of fenfluramine during the OLE

Table: Study 1601 TEAEs, serious TEAEs and discontinuation

	Fenfluramine 0.7 mg/kg/day (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Placebo (n=87)	Overall (N=263)
Most common TEAEs				
Any TEAE, n (%)	78 (90)	69 (78)	65 (75)	212 (81)
Decreased appetite, n (%)	31 (36)	18 (20)	10 (11)	59 (22)
Somnolence, n (%)	15 (17)	9 (10)	9 (10)	33 (13)
Fatigue, n (%)	16 (18)	8 (9)	9 (10)	33 (13)
Serious TEAEs and treatment discontinuation				
≥1 serious TEAE, n (%)	10 (11.5)	4 (4.5)	4 (4.6)	18 (6.8)
Discontinuation due to AE, n (%)	5 (5.7)	4 (4.5)	1 (1.1)	10 (3.8)
Discontinuation all cause, n (%)	10 (11.5)	7 (8.0)	4 (4.6)	21 (8.0)

OLE: - TEAEs were experienced in 203/247 people (82.2%). Most common TEAEs were decreased appetite (16.2%) and fatigue (13.4%)

- 16.2% experienced a serious TEAE, 4.9% experienced a TEAE that led to study discontinuation

NICE

OLE, Open label extension; TEAE, Treatment-emergent adverse event

NMA methodology

The company conducted 2 NMAs for use in the economic modelling

- Following completion of SLR and subsequent feasibility assessment, 3 RCTs (including fenfluramine, cannabidiol and placebo) were included in 1 of company's NMA analyses (ITT data NMA).
  - In the UK cannabidiol's approved indication is for treating LGS patients in conjunction with clobazam but clinical trial data for cannabidiol included patients not systematically receiving clobazam with cannabidiol
  - Therefore a second NMA analysis was performed on cannabidiol + clobazam subgroup, based on data published by the German HTA body, GBA (GBA data NMA)
  - However, GBA data did not include sufficient data on the median reduction in frequency of GTC seizures or the discontinuation due to AEs so ITT data NMA was used for these outcomes
  - Together, the 'ITT data NMA' and the 'GBA data NMA' form company's base case NMA analysis. Note an extended NMA was also conducted (9RCTs) but not used for base case following feasibility assessment
- In Study 1601, primary outcomes were captured through the 14-week treatment period (2-week titration and 12-week maintenance period). Trials for other ASMs have used different treatment durations so outcomes captured between 10- and 20-week timepoints were considered in NMA
- Both fixed effects and random effects models were performed - fixed effects models were presented as a base case to accommodate the small number of studies and simple networks
- Covariate adjustment via meta-regression not used due to the limited number of studies for each treatment.

ASM, Anti-seizure medication; GBA, The Federal Joint Committee; GTC, Generalised tonic-clonic; ITT, Intention to treat; NMA, Network meta-analysis

NMA results

NMA results suggest that fenfluramine is superior to placebo treatment and cannabidiol treatment for key efficacy outcomes except for the ≥75% reduction in DSF outcome

The effect measures of the fixed effects model are presented below for the key outcomes used in the economic analysis

Table: Company base case NMA analysis results summary

NMA outcome	Corresponding trial network	Summary result
Median percent reduction in frequency of GTC seizures	ITT data: FFA-PBO-CBD	Relative effect estimates: FFA (0.7 mg/kg), CBD (10 mg/kg), and CBD (20 mg/kg) significantly superior versus placebo SUCRA: FFA (0.7 mg/kg) ranked first
≥25% reduction in drop seizure frequency	GBA data: (FFA-PBO-CBD+CLB (GBA))	
≥50% reduction in drop seizure frequency	GBA data: (FFA-PBO-CBD+CLB (GBA))	
≥75% reduction in drop seizure frequency	GBA data: (FFA-PBO-CBD+CLB (GBA))	Relative effect estimates: solely CBD (20 mg/kg) significantly superior versus placebo SUCRA: FFA (0.7 mg/kg) ranked third
Discontinuation due to adverse events	ITT data: FFA-PBO-CBD	Relative effect estimates: solely CBD (20 mg/kg) significantly higher probability of discontinuation due to AEs versus placebo SUCRA: CBD (20 mg/kg) ranked last

ASM, Anti-seizure medication; CBD, Cannabidiol; CLB, Clobazam; DSF, Drop seizure frequency; ECM, Established clinical management; FFA, Fenfluramine; GBA, The Federal Joint Committee; GTC, Generalised tonic-clonic; ITT, Intention to treat; NMA, Network meta-analysis; PBO, Placebo; SUCRA, Surface under the cumulative ranking curve

Extended NMA results summary

Table: Extended NMA results summary

NMA outcome	Corresponding trial network	Summary result
≥25% reduction in drop seizure frequency	FFA-PBO-CBD-CLB-TPM-RFM-LTG	SUCRA: Fenfluramine (0.7 mg/kg) ranked fourth among 9 treatments
≥50% reduction in drop seizure frequency	FFA-PBO-CBD-CLB-TPM-RFM-LTG	SUCRA: Fenfluramine (0.7 mg/kg) ranked first among 10 treatments
≥75% reduction in drop seizure frequency	FFA-PBO-CBD-CLB-TPM-RFM	SUCRA: fenfluramine (0.7 mg/kg) ranked seventh among 9 treatments.
≥50% reduction in frequency of GTC seizures	FFA-PBO-CBD-LTG	SUCRA: fenfluramine (0.7 mg/kg) ranked first among 4 treatments
Discontinuation due to adverse events	FFA-PBO-CBD-CLB-RFM-LTG-FLB	SUCRA: fenfluramine (0.7 mg/kg) ranked seventh among 10 treatments (i.e. 6 treatments likely to have lower rate of discontinuation due to AEs than fenfluramine

CBD, Cannabidiol; CLB, Clobazam; FFA, Fenfluramine; FLB, Felbamate; GTC, Generalised tonic-clonic; LTG, Lamotrigine; NMA, Network meta-analysis; PBO, Placebo; RFM, Rufinamide; SUCRA, Surface under the cumulative ranking curve; TPM, Topiramate

Key issue: Inclusion of seizure frequency and seizure severity

Background

- Final scope outcomes included seizure frequency (overall and by seizure type) and seizure severity
- In CS, outcome of seizure frequency restricted to drop seizures; and outcome of seizure severity not included

Company

- Drop seizures characteristic seizures of LGS, and primary and key secondary endpoints in Study 1601
- In Study 1601, drop seizures are classified as GTC, secondary generalised tonic-clonic, tonic, atonic, or tonic/atonic → utilising drop seizures encompasses multiple seizure types
- Since drop seizures result in physical events such as falls, data collection for these seizures is considered more easily identifiable, and accuracy of measurement can be better compared to other seizures
- Seizure severity captured through seizure type. GTC seizures leading to drops associated with higher healthcare resource use→ use of GTC best proxy to capture severity as severity not collected in Study 1601

EAG comments

- Accept logic of using most easily measured and verified seizure outcome available (drop seizure) but exclusion of non-drop seizures prevents any evaluation of effects of fenfluramine on less severe seizures, which are also important to patients
- Accepts value of GTC drop seizures as proxy for seizure severity, but thinks a continuous measure might be more useful

Is it appropriate to exclude non-drop seizures from the model?
Is it appropriate to use GTC seizures as a proxy for seizure severity?

CS, Company submission; EAG, Evidence Assessment Group; ECM, Established clinical management; GTC, Generalised tonic-clonic; LGS, Lennox-Gastaut syndrome; SoC, Standard of Care

Key issues: study 1601 eDiary measurement validity and external validity

EAG raised several key issues relating to the validity of study 1601- summarised below

Measurement validity of eDiary

EAG: validity of efficacy measures depends on the measurement validity of eDiary, an electronic, homebased handheld device provided to every subject, and used for recording of seizures. Company did not present convincing evidence of validity of eDiary as measurement device→ validity of much of trial evidence unclear

Company: use of diary data (either paper or electronic) has been the gold standard for data collection in epilepsy trials and various studies have demonstrated the accuracy of using eDiaries in epilepsy trials

Does the use of an eDiary used for recording seizures in Study 1601 result in uncertainty?

External validity of trial- age, gender, ethnicity

EAG: external validity of trial unclear in terms of age, gender and ethnicity→ information required from subgroup analyses investigating whether age, gender or ethnicity affect outcome, and about the similarity of age, gender and ethnicity in the trial and in UK target population

Company: 1) subgroup analyses conducted were not adequately powered - generally, analysis results consistent across all relevant subgroups so not presented in CS

2) Clinicians consulted stated that baseline characteristics match characteristics within UK clinical practice

Are age, gender and ethnicity potential treatment effect modifiers for fenfluramine?
Is Study 1601 generalisable to the UK target population in terms of age, gender and ethnicity?

CS, Company submission; EAG, Evidence Assessment Group; eDiary, Electronic diary

Key issue: study 1601 internal validity and external validity

EAG raised several key issues relating to the validity of study 1601- summarised below

Internal and external validity of trial- concomitant treatments

EAG: 1) Per-arm use of non-pharmacological treatments unclear→ uncertainty about internal validity of trial data
2) External validity of trial unclear in terms of the exact combinations of concomitant medications used → information required from subgroup analyses investigating whether particular combinations of concomitant ASMs used affect outcome, and about the similarity of such combinations in the trial and in UK target population

Company: 1) difficult to perform meaningful analysis→ would be very complex and potentially lead to implausible conclusions on a small group of heterogenous patients
2) Clinicians consulted stated that no ASM combinations have been seen to be more effective than others and that combinations in Study 1601 reflect UK clinical practice

Does the lack of data about per-arm use of non-pharmacological treatments result in uncertainty?
Do committee expect particular combinations of concomitant ASMs to affect outcome?
Is study 1601 generalisable to the UK target population in terms of concomitant ASMs?

ASM, Anti-seizure medication; CS, Company submission; EAG, Evidence Assessment Group

How company incorporated evidence into model (2)

Table: Assumptions and evidence sources in company's base case model

Input	Assumption and evidence source
Discontinuation due to lack of efficacy and stopping rule	**Lack of efficacy**: 0% in cycle 1 and 7.3% in cycle 2, for fenfluramine + SoC arm based on Study 1601 and OLE (assumed to be same for cannabidiol + clobazam + SoC) **Stopping rule**: After cycle 2, stopping rule applied whereby all people in state 0 (<25% reduction in drop seizure frequency) discontinued treatment after 3 months
Mortality	**General population mortality**: informed by age and sex-adjusted life tables in UK **Baseline SUDEP mortality**: informed by Dravet syndrome publication (due to lack of LGS data). A higher number of drop seizures incurred an increased risk of SUDEP **Non-SUDEP mortality**: captured status epilepticus and accidental mortality. Status mortality informed by Dravet Syndrome publication (due to lack of LGS data). Accidental mortality calculated as 21.40% of SUDEP and status epilepticus mortality combined informed by Dravet syndrome publication
AEs	Included most commonly reported TEAEs of special interest in fenfluramine and cannabidiol trials (i.e diarrhoea, somnolence, pyrexia, decreased appetite and vomiting); AEs assumed to occur once in initial cycle AE rates for fenfluramine + SoC and SoC alone based on Study 1601 AE rates for cannabidiol + clobazam + SoC based on GWPCARE4 trial

AE, Adverse event; BNF, British National Formulary; LGS, Lennox-Gastaut syndrome; PSSRU, Personal Social Services Research Unit; SoC, Standard of care; SUDEP, Sudden unexpected death in epilepsy; TEAE, Treatment-emergent adverse event

How company incorporated evidence into model (3)

Table: Assumptions and evidence sources in company's base case model

Input	Assumption and evidence source
Utilities	**Health state utilities**: Verdian et al. **Caregiver utilities**: same utility value assumed as for patients; assumed 1.8 carers per patient **AE disutilities**: fatigue disutility of -0.060 from Matza et al. applied to all TEAEs
Costs	**Categories included**: acquisition costs, subsequent treatment costs, health state costs, monitoring costs, cost of managing AEs and mortality costs **Unit prices based on**: NHS reference prices, BNF, and PSSRU
Resource use	**Drug acquisition**: For dosing of weight-dependent drugs, fixed weight approach used, based on inputted patients' mean weight by age group based on Study 1601 **Subsequent treatments**: for people on fenfluramine or cannabidiol that discontinue treatment, subsequent treatment assumed to be same as SoC arm of study 1601 **Health state**: primary care resource use (i.e. LGS routine care) based on seizure frequency by matching the median number of drop seizures in health states 0, 1, 2, and 3 to the categories of mean number of drop seizures from NICE TA615. Secondary care resource use (i.e. seizure-associated care) estimated separately for GTC and other drop seizure types **Monitoring**: people receiving fenfluramine modelled to have ECG every 6 months for first 2 years, annually thereafter and once upon treatment discontinuation **AEs**: Assumed to equal that of one specialised nurse visit **Mortality**: Assumed to equal that of 1 emergency department visit and 1 ICU visit

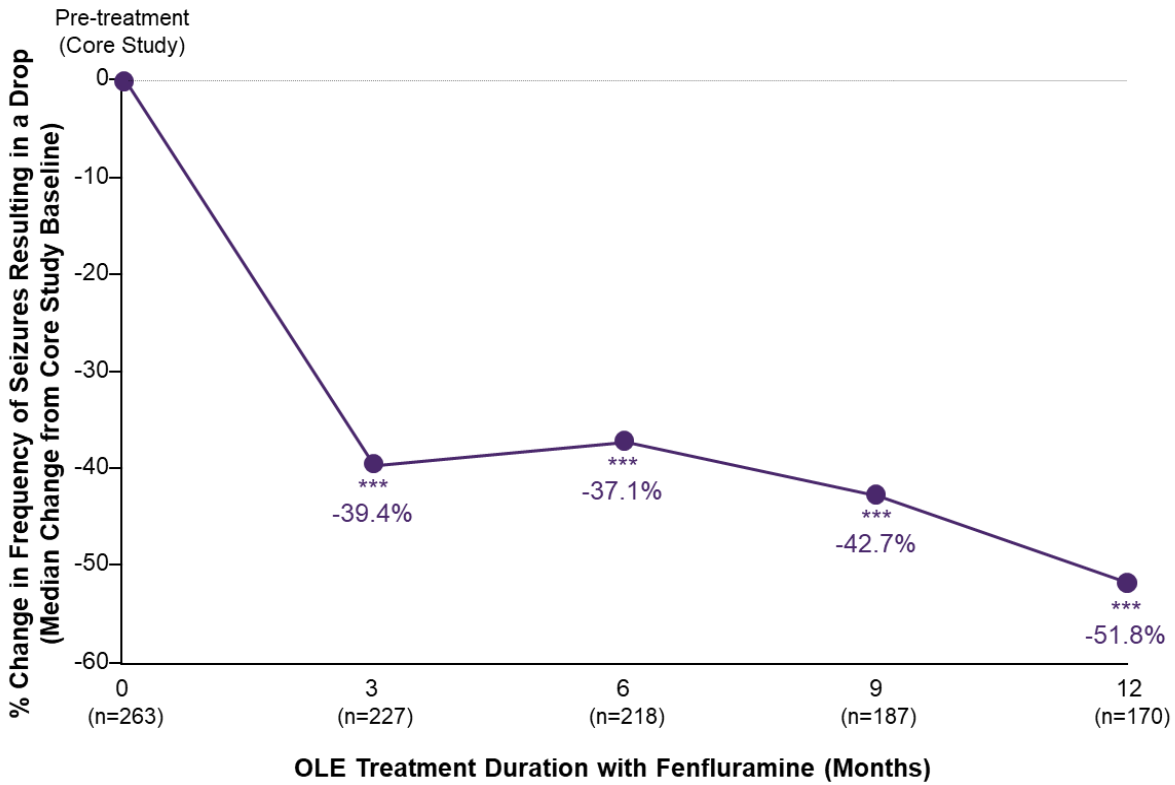
AE, Adverse event; ECG, Electrocardiogram; GTC, Generalised tonic-clonic; ICU, Intensive care unit; LGS, Lennox-Gastaut syndrome; SoC, Standard of care

Key issue: Extrapolation of fenfluramine treatment effect

Figure: Median percentage Change in Drop Seizure Frequency (mITT Population) over time

[redacted]

Figure: Median percentage change from baseline in drop seizure frequency in Study 1601 OLE



CS, Company submission; LGS, Lennox-Gastaut syndrome; mITT, Modified intention to treat; OLE, Open label extension; QALY, Quality-adjusted life year; SoC, Standard of care

Key issue: Extrapolation of fenfluramine treatment effect

Distribution of health states over time (Markov trace)

Key
- State 0
- State 1
- State 2
- State 3
- Death + discontinuation

Company base case – SoC

[redacted]

EAG base case – SoC

[redacted]

EAG, Evidence Assessment Group; SoC, Standard of care

Key issue: Discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC

Background

- Overview of clinical trial versus modelled health state occupancies in first year shows a discrepancy between clinical trial state occupancy and the modelled state occupancy for fenfluramine + SoC

Company

- Differences partly due to state occupancy in the model being determined from TPs between states, and not based on state occupancies reported by clinical trial data (as was done for cannabidiol [for cycles 2-5] due to lack of TP data, and for SoC (assumed patients remain in baseline states)
- Clinical trial data is ITT population, whereas the model health states (HS0, HS1, HS2 and HS3) are for treated population (model has separate health state for discontinuation to accommodate patients that have discontinued treatment due to AE or lack of efficacy, including stopping rule)

EAG comments

- Inconsistent to considering only the treated population for fenfluramine + SoC, while ITT populations were used for cannabidiol + clobazam + SoC and SoC alone
- Difference in modelling approach between treatments causes an overestimation of fenfluramine + SoC treatment effect as compared to cannabidiol + clobazam + SoC and SoC alone
- Preferred to use clinical trial state occupancy of fenfluramine + SoC in the model (for cycles 2-5) in base case

Is it more appropriate to determine model state occupancy for fenfluramine + SoC using clinical trial state occupancy data or by calculating transition probabilities as per the company base case?

EAG, Evidence Assessment Group; HS, Health state; ITT, Intention to treat; SoC, Standard of care; TP, Transition probability

Key issue: Discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC

Table: Fenfluramine state occupancy- OLE trial data and model data

Fenfluramine				
Clinical trial state occupancy				
Health State	**month 3**	**month 6**	**month 9**	**month 12**
State 0: < 25%	38.3%	40.8%	34.8%	29.4%
State 1: 25% to <50%	21.1%	21.1%	23.0%	19.4%
State 2: 50% to <75%	21.6%	22.9%	23.5%	25.9%
State 3: >=75%	18.9%	15.1%	18.7%	25.3%
Model state occupancy				
Health State	**month 3**	**month 6**	**month 9**	**month 12**
State 0: < 25%	34.7%	34.7%	33.1%	25.0%
State 1: 25% to <50%	21.5%	20.3%	20.6%	19.8%
State 2: 50% to <75%	20.8%	23.3%	17.5%	23.1%
State 3: >=75%	23.0%	21.7%	28.7%	32.0%

Other issue: Treatment waning

Further to the key issues, the EAG's base case analysis differed from the company base case in the method used to calculate treatment waning

Treatment waning

Company calculated the deteriorating transition probabilities used to inform transitions for patients who experience treatment waning by only including patients that stayed in their health state or deteriorated and excluded patients that improved from month 9 to 12 (last cycle of observed data)
EAG: percentage of patients with deteriorating transition probabilities is overestimated as it is not calculated over the total number of patients on treatment→ preferred to use all patients on treatment from month 9 to 12 (last cycle of observed data) to calculate the treatment waning probability in the next cycles in its base case

What is the committee's preferred method for incorporating treatment waning?

Key issue: Patient utilities

Table: Verdian et al. patient utility values (used in company and EAG base case)

Model health states	Matched Verdian Health state (HS)	EQ-5D mean	TTO mean	VAS mean
state 0: No response (< 25% reduction)	HS-1	0.020	0.393	0.020
state 1: Response group 1: 25% to <50% reduction	HS-2	0.100	0.461	0.414
state 2: Response group 2: 50% to <75% reduction	HS-3	0.500	0.605	0.556
state 3: Response group 3: >=75% response	HS-4	0.596	0.699	0.677

Table: Lo et al. patient utility values

No. of drop-seizures per month	No. of seizure-free days	TTO weights	VAS ratings
		Mean (SD)	Mean (SD)
Drop seizure free	>15	0.754 (0.371)	0.687(0.16)
≤45	>3 to ≤15	0.375 (0.575)	0.423 (0.21)
>45 to ≤110	>15	0.228 (0.598)	0.317 (0.19)
>45 to ≤110	≤3	-0.008 (0.613)	0.219 (0.18)
>110	>15	0.032 (0.626)	0.219(0.20)
>110	≤3	-0.186 (0.623)	0.118 (0.19)

DSF, Drop seizure frequency; EQ-5D, EuroQol-5 dimensions; HS, Health state; TTO, Time trade off; VAS, Visual analogue scale

Key issue: Patient utilities

Table: Auvin et al. patient utility values

No. of Seizure-Free Days	No. of Drop Seizures Per Month - UK (mean)						
	110-130	80-110	60-80	45-60	20-45	0-20	0
1	0.210	0.240	0.290	0.300	0.330	-	-
3	0.260	0.280	0.320	0.300	0.330	-	-
6	0.350	0.290	0.370	0.370	0.370	-	-
9	0.360	0.390	0.380	0.400	0.390	-	-
12	0.410	0.350	0.430	0.430	0.410	0.520	-
15	0.430	0.440	0.480	0.490	0.490	0.540	-
18	0.460	0.470	0.450	0.490	0.530	0.590	-
30	-	-	-	-	-	-	0.830

Key issue: Caregiver utilities

Table: Lo et al. caregiver utility values

No. of drop-seizures per month	No. of seizure-free days	TTO weights	VAS ratings
		Mean (SD)	Mean (SD)
Drop seizure free	>15	0.810(0.281)	0.702 (0.18)
≤45	>3 to ≤15	0.572(0.479)	0.492 (0.23)
>45 to ≤110	>15	0.424(0.554)	0.397 (0.22)
>45 to ≤110	≤3	0.205(0.613)	0.280 (0.20)
>110	>15	0.318(0.643)	0.317 (0.22)
>110	≤3	0.032(0.688)	0.198 (0.20)

Table: Auvin et al. caregiver utility values

Number of seizures in an average month	Number of seizure-free days in an average month	VAS score, mean (SD)	Utility value
130	3	38.1 (28.1)	0.38
80	15	51.6 (20.1)	0.52
0	30	78.3 (17.3)	0.78

DSF, Drop seizure frequency; EQ-5D, EuroQol-5 dimensions; HS, Health state; TTO, Time trade off; VAS, Visual analogue scale

Key issue: Caregiver utilities

Table: Lo et al. calculated caregiver TTO disutility values – EAG base case

Number of seizures	No. of Seizure-Free Days		
	≤ 3 days	> 3 to ≤ 15 days	> 15 days
Drop seizure free	-0.046	-0.046	-0.046
≤45	-0.284	-0.284	-0.284
>45–≤110	-0.651	-0.542	-0.432
>110	-0.824	-0.681	-0.538

Table: Auvin et al. calculated caregiver disutility values – company scenario analysis

Number of seizures	No. of Seizure-Free Days		
	≤ 3 days	> 3 to ≤ 15 days	> 15 days
Drop seizure free	-0.048	-0.048	-0.048
≤45	-0.048	-0.048	-0.048
>45–≤110	-0.308	-0.308	-0.308
>110	-0.448	-0.448	-0.448

DSF, Drop seizure frequency; EQ-5D, EuroQol-5 dimensions; HS, Health state; TTO, Time trade off; VAS, Visual analogue scale

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.