Single Technology Appraisal

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from UCB Pharma:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response
   b. Addendum to response

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Tuberous Sclerosis Association
   b. NHS England

4. **Expert personal perspectives** from:
   a. Professor Helen Cross, Director of the UCL Great Ormond Street Institute of Child Health – clinical expert, nominated by UCB Pharma
   b. Dr Rhys Thomas, Clinical Senior Lecturer, Honorary Consultant in Epilepsy – clinical expert nominated by UCB Pharma
   c. Victoria Tsang, Highly Specialist Paediatric Pharmacist – Neuroscience – clinical expert nominated by Neonatal & Paediatric Pharmacists Group (NPPG)
   d. Lisa Suchet – patient expert, nominated by Tuberous Sclerosis Association

5. **External Assessment Report** prepared by Kleijnen Systematic Reviews

6. **External Assessment Report – factual accuracy check**

7. **Additional scenarios post-EAG report** prepared by Kleijnen Systematic Reviews

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Document B

Company evidence submission

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Content

Content 2
Tables 6
Figures 9
Abbreviations 11
B.1 Decision problem, description of the technology and clinical care pathway 15
B.1.1 Decision problem 16
B.1.2 Description of the technology being evaluated 18
B.1.3 Health condition and position of the technology in the treatment pathway 21
B.1.3.1 Disease overview 21
B.1.3.1.1 Definition of LGS 21
B.1.3.1.2 Particularity of a DEE 21
B.1.3.1.3 Heterogenous aetiology of LGS 22
B.1.3.1.4 Diagnosis 22
B.1.3.2 Disease burden 22
B.1.3.2.1 Epidemiology 22
B.1.3.2.2 Clinical burden 22
B.1.3.2.3 Quality of life burden 25
B.1.3.2.4 Economic burden 25
B.1.3.3 LGS clinical care pathway 26
B.1.3.3.1 Treatment objectives 26
B.1.3.3.2 Current clinical pathway of care in England 27
B.1.3.4 Remaining unmet need 30
B.1.3.5 Proposed positioning of fenfluramine within the current treatment pathway 31
B.1.4 Equality considerations 32
B.2 Clinical effectiveness 33
B.2.1 Identification and selection of relevant studies 34
B.2.2 List of relevant clinical effectiveness evidence 34
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence 37
B.2.3.1 Trial design 40
B.2.3.2 Eligibility criteria 41
B.2.3.3 Settings and locations where the data were collected 42
B.2.3.4 Patient flow in the studies 42
B.2.3.5 Endpoints 43
B.2.3.6 Baseline patient characteristics 44
B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence 47
B.2.4.1 Efficacy 47
B.2.4.2 Safety 48
B.2.5 Critical appraisal of the relevant clinical effectiveness evidence 50
B.2.6 Clinical effectiveness results of the relevant studies 51
B.2.6.1 Double blind RCT – Study 1601 51
B.2.6.1.1 Primary endpoint: Percent change from baseline in drop seizure frequency in T+M versus placebo in the fenfluramine 0.7 mg/kg/day arm 55
B.2.6.1.2 Key secondary endpoint: Percent change from baseline in drop seizure frequency in T+M versus placebo in the fenfluramine 0.2 mg/kg/day arm 56

B.2.6.1.3 Key secondary endpoints: Proportion of patients achieving ≥25%, ≥50% or ≥75% reduction in drop seizure frequency 57
B.2.6.1.4 GTC seizures 58
B.2.6.1.5 Proportion of patients seizure-free T+M and Maintenance only 58
B.2.6.1.6 Number of drop seizure-free days per 28 days 59
B.2.6.1.7 Incidence of status epilepticus on rescue medication use and hospitalisation 59
B.2.6.2 Patient reported outcomes and Quality of Life 59
B.2.6.2.1 Clinical Global Impression of Change – Improvement (CGI-I) rating 59
B.2.6.2.2 Quality of Life in Childhood Epilepsy Scale (QOLCE) Paediatric QoL inventory 60
B.2.6.2.3 Caregiver quality of life, anxiety and depression 60
B.2.6.3 Open label extension study 60
B.2.6.3.1 Proportion of patients seizure-free 62
B.2.6.3.2 Seizure-free days 62
B.2.6.3.3 Responder analysis 63
B.2.6.3.4 Additional endpoints 63
B.2.7 Subgroup analysis 64
B.2.8 Meta-analysis 64
B.2.9 Indirect and mixed treatment comparisons 64
B.2.9.1 Identification of relevant studies 65
B.2.9.2 NMA feasibility assessment 67
B.2.9.2.1 Comparison of study designs and characteristics 67
B.2.9.2.2 Comparison of patient baseline characteristics 70
B.2.9.2.3 Feasibility assessment conclusion 74
B.2.9.3 Methods of the NMA 76
B.2.9.3.1 Trial data used in the base case (selected endpoints) 76
B.2.9.4 Results of the NMA of fenfluramine versus cannabidiol 78
B.2.9.4.1 Trial networks 78
B.2.9.4.2 Fenfluramine versus cannabidiol: selected efficacy and safety outcomes results 79
B.2.9.5 Conclusions of the NMA 87
B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons 87
B.2.10 Adverse reactions 88
B.2.10.1 Adverse reactions in Study 1601 89
B.2.10.1.1 Most common treatment-emergent adverse events (≥10%) in Study 1601 89
B.2.10.1.2 Serious Adverse Events and treatment discontinuation in Study 1601 89
B.2.10.2 Adverse reactions in OLE study 90
B.2.10.2.1 Most common treatment-emergent adverse events in OLE study 90
B.2.10.2.2 Serious adverse events and treatment discontinuation 90
B.2.10.3 Adverse events of special interest 91
B.2.10.4 Other observations related to the cognition and executive function 91
B.2.10.5 Confirmation of safety and tolerance observations from the Dravet syndrome (DS) safety data 92
B.2.11 Ongoing studies 93
B.2.12 Interpretation of clinical effectiveness and safety evidence 93
B.2.12.1 Summary of clinical evidence base 93
B.2.12.1.1 Efficacy and safety in phase 3 RCT and OLE study 93
B.2.12.1.2 Comparative evidence versus NICE-recommended add-on therapies 94
B.2.12.2 Generalisability and relevance of the clinical evidence base 94

B.2.12.2.1 Patient population ... 94
B.2.12.2.2 Intervention ... 95
B.2.12.2.3 Comparators ... 95
B.2.12.2.4 Outcomes ... 95
B.3 Cost-effectiveness ... 96
Cost-utility analysis of fenfluramine ... 96
Model features ... 96
Conclusion ... 97
B.3.1 Published cost-effectiveness studies ... 98
B.3.1.1 Identification of the studies ... 98
B.3.1.2 Description of the identified studies ... 99
B.3.1.3 Summary of published cost-effectiveness results ... 101
Clobazam ... 101
Cannabidiol ... 101
Rufinamide, topiramate, lamotrigine ... 101
B.3.2 Economic analysis ... 102
B.3.2.1 Patient population ... 102
B.3.2.2 Model structure ... 102
B.3.2.3 Intervention technology and comparators ... 109
B.3.3 Clinical parameters and variables ... 110
B.3.3.1 Baseline patient characteristics ... 110
B.3.3.2 Transition probabilities ... 113
B.3.3.2.1 Transition probabilities for T+M period (ITC of pivotal trial results) ... 113
B.3.3.2.2 Transition probabilities for cycle 2 to cycle 5 (analysis of OLE studies) ... 114
B.3.3.2.3 Transition probabilities from cycle 6 to cycle 9 (Long-term efficacy) ... 114
B.3.3.2.4 Transition probabilities from cycle 10 (Long-term efficacy) ... 114
B.3.3.3 Supplementary efficacy outcomes ... 117
B.3.3.3.1 Reduction in GTC seizures to inform healthcare resource use costs ... 117
B.3.3.4 Treatment discontinuation ... 118
B.3.3.4.1 Treatment discontinuation due to AE ... 118
Discontinuation due to AE at titration ... 118
Discontinuation due to AE at cycle 1 (T+M) ... 119
Discontinuation due to AE at follow-up (>cycle 2) ... 119
B.3.3.4.2 Treatment discontinuation due to lack of efficacy and stopping rule ... 120
B.3.3.5 Treatment waning ... 120
B.3.3.6 Treatment-emergent adverse events ... 121
B.3.3.7 Mortality ... 121
B.3.3.8 Validation of the clinical parameters ... 122
B.3.4 Measurement and valuation of health effects ... 123
B.3.4.1 Health-related quality-of-life data from clinical trials ... 123
B.3.4.2 Mapping ... 123
B.3.4.3 Health-related quality-of-life studies ... 123
B.3.4.3.1 Identification and key characteristics of the HrQoL studies ... 123
B.3.4.3.2 Baseline patient characteristics for the selected HrQoL studies ... 124
B.3.4.3.3 Summary of the HrQoL studies' results ... 128
B.3.4.4 Adverse reactions ... 130
B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis ... 130
B.3.5 Cost and healthcare resource use identification, measurement, and valuation ... 132
B.3.5.1 Cost and healthcare resource use studies ... 132
B.3.5.2 Intervention and comparators' costs and resource use ... 133

B.3.5.2.1 Drug dosing 133
B.3.5.2.2 Drug costs 136
B.3.5.3 Subsequent treatment costs 139
B.3.5.4 Health-state unit costs and resource use 139
B.3.5.4.1 Primary care 140
B.3.5.4.2 Secondary care 144
B.3.5.5 Drug monitoring 147
B.3.5.6 Adverse reaction unit costs and resource use 147
B.3.5.7 Mortality costs 148
B.3.6 Severity modifier eligibility 148
B.3.6.1 QALY shortfall calculation 148
B.3.6.2 Estimated QALY Weight 150
B.3.7 Uncertainty 152
B.3.8 Managed access proposal 153
B.3.9 Summary of base-case analysis inputs and assumptions 153
B.3.9.1 Summary of base-case analysis inputs 153
B.3.9.2 Assumptions 163
B.3.10 Base-case results 166
B.3.10.1 Base-case incremental cost-effectiveness analysis results 166
B.3.10.1.1 Deterministic results 166
B.3.10.1.2 Complementary analysis: cost-effectiveness in comparison of SoC 168
B.3.11 Exploring uncertainty 168
B.3.11.1 Probabilistic sensitivity analysis 168
Cost-effectiveness plane 170
Cost-effectiveness acceptability curves 171
B.3.11.2 Deterministic sensitivity analysis 172
B.3.11.3 Scenario analysis 174
B.3.12 Subgroup analysis 181
B.3.13 Benefits not captured in the QALY calculation 181
B.3.14 Validation 181
B.3.14.1 Validation of cost-effectiveness analysis 181
B.3.14.2 Quality control 182
B.3.15 Interpretation and conclusions of economic evidence 183
B.3.15.1 Results summary 183
B.3.15.2 Strengths and limitations 184
B.3.15.3 Conclusion 185
References 186

Tables

Table 1. The decision problem 17
Table 2. Description of fenfluramine (Fintepla®) 19
Table 3. Treatments with specific marketing for LGS 28
Table 4. Clinical effectiveness evidence 35
Table 5. Summary of trial methodology 37
Table 6. Baseline characteristics of patients included in Study 1601 45
Table 7. Baseline characteristics of patients included in OLE study 46
Table 8. Statistical methodology used 49
Table 9. Summary of quality assessment of Study 1601 50
Table 10. Primary, key secondary and selected additional endpoints from Study 1601 52
Table 11. Additional secondary and exploratory endpoints relating to condition ratings and quality of life in Study 1601 54
Table 12. Key effectiveness endpoint: Change from Baseline in DSF per 28 days during the OLE Treatment Period Responder analysis (mITT) 61
Table 13. Summary of the trials used to carry out the indirect or mixed treatment comparison 66
Table 14. Summary of study designs and characteristics 68
Table 15. Patient baseline characteristics 71
Table 16. Summary of feasibility assessment 75
Table 17. Selected outcomes of interest from the network meta-analysis 76
Table 18. NMA models for continuous and binary outcomes 77
Table 19. Summary of the efficacy and safety outcomes available 79
Table 20. Network meta-analysis selected outcomes with their corresponding trial network 79
Table 21. Mean difference, probability of being the best, and SUCRA for median percent reductions in frequency of GTC seizures, fixed effects (FFA-PBO-CBD) 81
Table 22. Risk ratios, probability of being the best, and SUCRA for ≥25%, 50% and 75% reduction in DSF, fixed effects FFA-PBO-CBD w CLB (GBA)) 83
Table 23. Risk ratios, probability of being the best, and SUCRA for discontinuation due to AEs, fixed effects (FFA-PBO-CBD) 85
Table 24. Summary of ITT scenario results 86
Table 25. Summary of results for (FFA-PBO-CBD w CLB (GBA)) network 86
Table 26. Most common treatment-emergent adverse events (Study 1601) 89
Table 27. Serious TEAEs and treatment discontinuation (Study 1601) 90
Table 28. Most common treatment-emergent adverse events OLE study 90
Table 29. Adverse events of special interest in Study 1601 91
Table 30. Summary of information sources 98
Table 31. Summary of study characteristics – economic evaluations 100
Table 32. Model description 105
Table 33. Estimated mid-point and number of drop seizures per 28 days per model health state 107
Table 34. Features of the economic analysis 108
Table 35. Baseline patient characteristics included in Study 1601 (aggregate across treatment arms FFA 0.2mg/kg/day, FFA 0.7mg/kg/day, and placebo) 111

Table 36. Weight parameters 112
Table 37. Binomial relative risks for proportion in each state - Binomial relative risks at cycle 1 (T+M), FFA-PBO-CBD w CLB (GBA) (NMA results) 113
Table 38. Calculated state occupancy at cycle 2 (after T+M) 114
Table 39. Transition probabilities after T+M 115
Table 40. Reduction in GTC seizures from baseline based on the ITC analysis 117
Table 41. Number of drop seizures and GTC seizures 118
Table 42. Discontinuation due to AE at Titration 118
Table 43. Discontinuation due to AE at T+M 119
Table 44. Discontinuation due to AE at follow-up 119
Table 45. Discontinuation proportion due to lack of efficacy at cycle 1 (T+M) and cycle 2 120
Table 46. Treatment waning per cycle (after cycle 9) 121
Table 47. Treatment-emergent adverse events at cycle 1(by treatment) 121
Table 48. SUDEP mortality 122
Table 49. Non-SUDEP: SE and accidental mortality 122
Table 50. Summary of baseline patient characteristics for selected HRQoL studies 125
Table 51. Patient utility measures 129
Table 52. Caregiver utility measures 129
Table 53. Utility measures used in the model for patients and caregivers 131
Table 54. Summary of utility values for cost-effectiveness analysis 131
Table 55. Age distribution at start of model and mean weights by age group 133
Table 56. Drug dosing - titration 134
Table 57. Drug dosing – maintenance phase 135
Table 58. Unit cost of the compared new adjunctive therapies (FFA & CBD) 136
Table 59. Unit cost of the standard of care drugs and PCA shares 137
Table 60. Distribution of patients taking SoC ASMs in each arm 139
Table 61. Patient distribution in subsequent treatment applied to all patients 139
Table 62. Mean number of drop seizures for each health state 140
Table 63. Number of annual primary care visits per seizure numbers and per age groups 140
Table 64. Healthcare unit costs for primary care 142
Table 65. Unit cost of the medications and PCA shares 143
Table 66. Drug dosing – rescue medication 143
Table 67. Routine care cost per patient per 3 months cycle 144
Table 68. Healthcare utilisation per year per LGS patient adjusted for age 145
Table 69. Healthcare utilisation per year for epileptic patients adjusted for seizure type 145
Table 70. Healthcare utilisation of LGS per patient per year per seizure type 145
Table 71. Healthcare unit costs for secondary care 146
Table 72. Secondary care costs per patient per 3 months cycle per seizure type 147
Table 73. Cost of echocardiogram 147
Table 74. Adverse event related costs 148
Table 75. Mortality costs 148
Table 76. Summary of utility values for QALY shortfall analysis 149

Table 77. Summary of health state benefits and utility values for QALY shortfall analysis 149
Table 78. Summary features of QALY shortfall analysis 150
Table 79. QALY weights for severity 150
Table 80. Summary of QALY shortfall analysis 151
Table 81. Summary of variables applied in the economic model 153
Table 82. Key assumptions used in the model (base case) 163
Table 83. Base-case results: FFA + SoC versus CBD w CLB + SoC..... 166
Table 84. Base-case results with severity modifier applied: FFA + SoC versus CBD w CLB + SoC..... 167
Table 85. Total costs by category of cost: FFA + SoC versus CBD w CLB + SoC. 167
Table 86. Base-case complementary results: FFA + SoC versus SoC 168
Table 87. Base-case complementary results with severity modifier applied: FFA + SoC versus SoC..... 168
Table 88. Summary of the parameter group evaluated, and distribution type applied in the PSA 168
Table 89. Average results from the probabilistic sensitivity analysis 171
Table 90. Summary of the parameter group evaluated, and range of variation applied in the DSA 173
Table 91. Patient utility measures – Lo et al. 2021..... 176
Table 92. Caregiver utility measures - Lo et al. 2021 177
Table 93. Patient utility measures - Auvin et al. 2021 177
Table 94. Distribution of seizure free days by health state at T+M (applied at all cycles)..... 177
Table 95. Summary of the scenario analyses explored and comparison to the base case..... 179
Table 96. Model checklist..... 183

Figures

Figure 1. Mechanism of action of fenfluramine 18
Figure 2. The clinical triad of LGS 21
Figure 3. Risk of SUDEP correlates with number of generalised tonic-clonic seizures (GTCs) experienced 24
Figure 4. Healthcare resource utilisation by number of drop seizures 26
Figure 5. Current clinical management of LGS 30
Figure 6. Position of fenfluramine in the clinical management of LGS 32
Figure 7. Study 1601 trial design 41
Figure 8. OLE trial design 41
Figure 9. Patient flow in Study 1601 and OLE Study 43
Figure 10. Reduction in median percentage of drop seizure frequency in the titration (2-weeks) and maintenance period (12-weeks) – Study 1601 55
Figure 11. Median percentage Change in Drop Seizure Frequency (mITT Population) over time 56
Figure 12. Primary and key secondary efficacy endpoint – Study 1601 57
Figure 13. Proportion of patients achieving ≥25%, ≥50% and ≥75% reductions from baseline in drop seizure frequency during the T+M period 58
Figure 14. Percentage reduction from baseline of GTC seizures in Study 1601 58
Figure 15. Median percentage change from baseline in drop seizure frequency 62
Figure 16. Responder rates for drop seizures after 1 year of fenfluramine treatment 63
Figure 17. Network diagram for median percent reductions in frequency of GTC seizures (FFA-PBO-CBD) 80
Figure 18. Forest plot for median percent reductions in frequency of GTC seizures, fixed effects (FFA-PBO-CBD) 80
Figure 19. Network diagram for ≥25%, ≥50% and ≥75% reduction in DSF (FFA-PBO-CBD w CLB (GBA)) 81
Figure 20. Forest plot for ≥25% reduction in drop seizure frequency, fixed effects (FFA-PBO-CBD w CLB (GBA)) 82
Figure 21. Forest plot for ≥50% reduction in DSF, fixed effects (FFA-PBO-CBD w CLB (GBA)) 82
Figure 22. Forest plot for ≥75% reduction in DSF, fixed effects (FFA-PBO-CBD w CLB (GBA)) 83
Figure 23. Network diagram for discontinuation due to AEs (FFA-PBO-CBD) 84
Figure 24. Forest plot for discontinuation due to AEs, fixed effects (FFA-PBO-CBD) 85
Figure 25. Clinically meaningful improvement (RCI ≥95% certainty) in BRIEF®2 indexes/composite (pooled analysis including 0.2 and 0.7 mg/kg dose of fenfluramine) 92
Figure 26. Schematic diagram of cost-effectiveness model (CEM) 104
Figure 27. State occupancy of treatment arms in the first-year follow-up after T+M (data from OLE studies) 116
Figure 28. Mean health state utility scores for a hypothetical patient with LGS 128
Figure 29. Cost-effectiveness plane FFA + SoC versus CBD w CLB + SoC 170
Figure 30. Cost-effectiveness acceptability curve 172

Figure 31. Cost-effectiveness acceptability curve with severity modifier 172
Figure 32. Tornado plot: deterministic sensitivity analyses: FFA + SoC versus CBD w CLB + SoC 174

Abbreviations

Abbreviation	Description
5-HT	5-Hydroxytryptamine, also known as serotonin
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALDVMM	Adjusted Limited Dependent Variable Mixture Mode
ANCOVA	Analysis Of Covariance
AR	Aortic Regurgitation
ASM	Antiseizure Medication
BIA	Budget-impact analysis
BL	Baseline
BMI	Body Mass Index
BNF	British National Formulary
BRI	Behaviour Regulation Index
BRIEF	Behaviour Rating Inventory of Executive Function
CBD	Cannabidiol
CBD w CLB	Cannabidiol with Clobazam
CCM	Current Clinical Management
CCT	Corpus Callosotomy
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEM	Cost-Effectiveness Model
CGI-I	Clinical Global Impression-Improvement
CHMP	Committee For Medicinal Products for Human Use
CI	Confidence Interval
CLB	Clobazam
CMH	Cochran-Mantel-Haenszel
CPRD	Clinical Practice Research Datalink
CrI	Credible Interval
CRI	Cognitive Regulation Index
CSR	Clinical Study Report
CUA	Cost-utility analysis
CVD	Cardiovascular Disease
DEE	Developmental Epileptic Encephalopathy
DHSC	Department of Health and Social Care
DIC	Deviance Information Criterion
DS	Dravet Syndrome
DSA	Deterministic Sensitivity Analysis
DSF	Drop Seizure Frequency
EAG	External Advisory Group
EBM	Evidence-Based Medicine
EC	European Commission

Abbreviation	Description
ECG	Electrocardiogram
ECHO	Echocardiogram
ED	Emergency Department
EEG	Electroencephalogram
EMA	European Medicine Agency
EMD	Estimated Median Difference
EOS	End Of Study
EQ-5D	EuroQoL-5 Dimensions
ERI	Emotion Regulation Index
ESC	Epilepsy Study Consortium
ESD	Extreme Studentised Deviant
EU	European Union
FEL	Felbamate
FFA	Fenfluramine
FS	Focal Seizure
GABA	Gamma-Aminobutyric Acid
GBA	Federal Joint Committee of Germany (*Gemeinsamer Bundesausschuss*)
GB	Great Britain
GBP	British Pound
GEC	Global Executive Composite
GP	General Practitioner
GTC	Generalised Tonic-Clonic
HADS	Hospital Anxiety and Depression Scale
HCRU	Health Care Resource Use
HES	Hospital Episode Statistics
HL	Hodges-Lehmann
HCS	Hemiclonic Seizure
HRQoL	Health-Related Quality of Life
HS	Health State
HSE	Health Survey for England
HSU	Health State Utility
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ILAE	International League Against Epilepsy
INAHTA	International HTA Database
IQR	Interquartile Range
ITC	Indirect Treatment Comparison
ITT	Intention-To-Treat
KD	Ketogenic Diet
kg	Kilogram
LAM	Lamotrigine
LEV	Levetiracetam

Abbreviation	Description
LGS	Lennox-Gastaut Syndrome
LOS	Length of Stay
MA	Marketing Authorisation
MD	Mean Difference
MHRA	Medical And Healthcare Products Regulatory Agency
mg	Milligram
mITT	Modified Intention-To-Treat
MR	Modified Release
MS	Myoclonic Seizure
MVH	Measurement and Valuation of Health
NA	Not Applicable
NHB	Net Health Benefit
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NR	Not Reported
OLE	Open Label Extension
ONS	Office for National Statistics
OR	Odds Ratio
OWSA	One-Way Sensitivity Analysis
PAH	Pulmonary Arterial Hypertension
PAS	Patient Access Scheme
PBO	Placebo
PCA	Prescription Cost Analysis
PICOS	Population, Intervention, Comparison, Outcomes and Study type
PLGB	Great Britain Product License
PP	Per Protocol
PPY	Per Patient-Year
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSSRU	Personal Social Services Research Unit
QALE	Quality-Adjusted Life Expectancy
QALY	Quality-Adjusted Life Year
QoL	Quality-of-Life
QOLCE	Quality-of-Life in Childhood Epilepsy
RCI	Reliable Change Index
RCT	Randomised Clinical Trial
RR	Risk Ratio
RUF	Rufinamide
RWE	Real World Evidence
SAE	Serious Adverse Event
SAF	Safety

Abbreviation	Description
SD	Standard Deviation
SE	Standard Error
SGTC	Secondarily Generalised Tonic-Clonic
SLR	Systematic Literature Review
SUCRA	Surface Under the Cumulative Ranking
SUDEP	Sudden Unexpected Death in Epilepsy
TA	Tonic Atonic
TEAE	Treatment Emergent Adverse Event
TOP	Topiramate
TP	Transition Probability
TTO	Time Trade-Off
TS	Tonic Seizure
UK	United Kingdom
US	United States
USD	United States Dollar
USA	United States of America
VAS	Visual Analog Scale
VAT	Value-Added Tax
VBA	Visual Basic for Applications
VHD	Valvular Heart Disease
VNS	Valgus Nerve Stimulation
WTP	Willingness-To-Pay
WHO	World Health Organisation

B.1 Decision problem, description of the technology and clinical care pathway

Lennox Gastaut syndrome (LGS)

- LGS is a severe, rare, difficult-to-treat childhood-onset epilepsy syndrome characterised by a high frequency of multiple types of uniquely resistant seizures, and cognitive deterioration with behavioural disturbances.
- Most commonly, patients with LGS experience frequent, dangerous, and debilitating drop seizures, which may result in falls, serious injury, pain, hospitalisation and death.
- Patients with LGS are at an increased risk of sudden unexpected death in epilepsy (SUDEP), which is highly correlated with the experience of multiple generalised tonic-clonic (GTC) seizures.
- LGS is burdensome to the health and social care system due to frequent seizures and difficult management. The significant impact of LGS extends beyond the patient, resulting in profound detrimental impact on the quality of life (QoL) of caregivers and a patient's families.
- LGS patients are extremely heterogenous in the type and frequency of seizures they experience as well as the treatment they receive.

Current treatment pathway and unmet need

- The goal of treatment is to reduce the seizure burden on the patient, caregivers, and the healthcare system. This can be achieved by decreasing the frequency and severity of disabling seizure types, such as drop seizures.
- The National Institute for Health and Care Excellence (NICE) NG217 recommends initial therapy with sodium valproate, followed by lamotrigine as add-on or monotherapy. Because seizure reduction is often insufficient, a 3rd line of adjunctive therapy is often given to patients as standard of care (SoC). Cannabidiol was recommended in 2019 by NICE (TA615) as a new adjunctive therapy to be tried in combination with clobazam in case of continued SoC treatment resistance, however, many patients still remain uncontrolled.
- Despite published guidelines, there is no existing standardised approach to treatment. Physicians' usual approach is to add on and/or switch treatments to build overall efficacy for seizure reduction. Individualised antiseizure therapy is initiated according to patients' syndrome type, treatment goals and preferences.
- There remains a high unmet need for additional treatment options with novel mechanisms of action for patients who have previously tried and failed multiple antiseizure medications (ASMs). Almost all patients continue to suffer daily with frequent debilitating seizures and remain uncontrolled on their current treatment regimen, resulting in increased risk of premature death. Considering the high burden of LGS on patients, their families, and the challenge of sustaining seizure control or achieving seizure freedom, it is vital to have access to additional, licensed treatments with proven efficacy.

Fenfluramine and its position in the treatment pathway

- Fenfluramine is a new add-on ASM for children and adults with hard-to-treat LGS that offers proven efficacy on the most disabling seizures regardless of prior treatment failures. It also has the flexibility to combine it with any existing add-on regimen.
- The ability to use fenfluramine irrespective of clobazam use is a distinctive benefit compared to cannabidiol, which means it may be used at any point in the add-on therapy pathway and has the potential to expand the available treatment options.

B.1.1 Decision problem

In January 2023, fenfluramine received marketing authorisation (MA) in the European Union (EU) 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. MHRA (Medical And Healthcare Products Regulatory Agency) approval for fenfluramine within the same indication has been received on July 5th, 2023 (1, 2).

This submission is solely based on the LGS indication, which is an extension to the technology's initial MA, obtained in December 2020, for the treatment of seizures associated with Dravet syndrome (DS) (3). In July 2022, NICE recommended fenfluramine as an add-on to other antiseizure medicines for treating seizures associated with DS in people aged 2 years and older (TA808) (4).

The decision problem addressed within this submission is consistent with the NICE final scope and is presented in Table 1, along with any differences between the decision problem in this submission and the NICE final scope.

Table 1. The decision problem

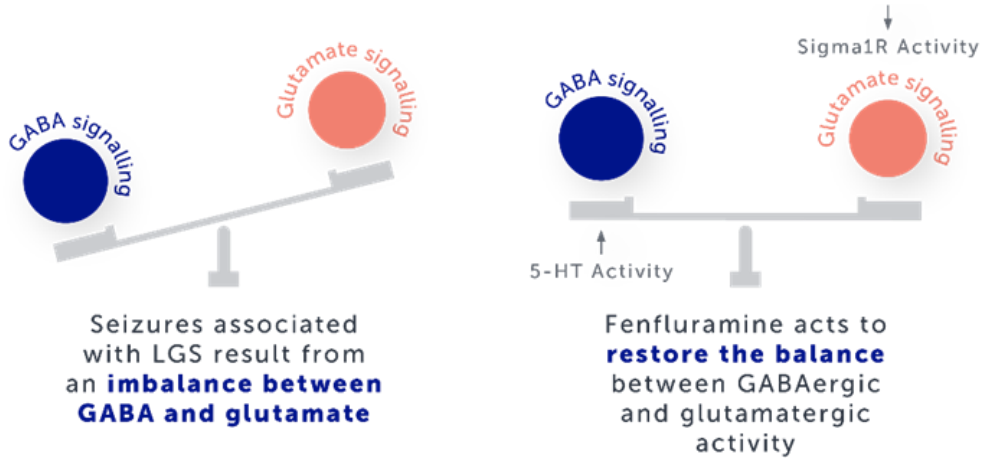
	Final scope issued by NICE	Part 2	Rationale if different from the final NICE scope
Population	People aged 2 and over with Lennox-Gastaut syndrome whose seizures are inadequately controlled by established clinical management.	People aged 2 and over with Lennox-Gastaut syndrome whose seizures are inadequately controlled by established clinical management.	As per final NICE scope
Intervention	Fenfluramine hydrochloride	Fenfluramine hydrochloride	As per final NICE scope
Comparators	Established clinical management without fenfluramine hydrochloride, which may include combinations of: • Antiseizure medications, including but not limited to: o cannabidiol with clobazam o sodium valproate o lamotrigine o rufinamide o topiramate o felbamate o clobazam o levetiracetam • ketogenic diet • vagus nerve stimulation • surgery	Established clinical management without fenfluramine hydrochloride, which may include combinations of: • Antiseizure medications, including but not limited to: o cannabidiol with clobazam o sodium valproate o lamotrigine o rufinamide o topiramate o felbamate o clobazam o levetiracetam • ketogenic diet • vagus nerve stimulation • surgery	As per final NICE scope
Outcomes	The outcome 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 • health-related quality of life (patients and carers)	The outcome measures to be considered include: • seizure frequency (drop seizure) • Response rate (percentage of reduction of drop seizures within these categories: <25%; 25-50%; 50-75%; >75%) • mortality (SUDEP and non-SUDEP including status epilepticus) • adverse events of treatment • health-related quality of life (patients and carers)	Only drop seizures, characteristic seizures of LGS and primary and key secondary endpoints in the RCT (Study 1601) for fenfluramine, are considered in the company submission. Proportion of people seizure-free is not considered in the model as the proportion of patients who are (drop) seizure-free was very low in the Phase 3 trials of fenfluramine and cannabidiol (either 0 or 1 patient per treatment arm). The severity of seizures was captured through the types of seizures: GTC seizures leading to drops are associated with higher healthcare resource use, and this was captured in the model. Incidence of status epilepticus is not a model outcome *per se* but non-SUDEP was considered including status epilepticus deaths.

Abbreviations: NICE, National Institute for Health and Care Excellence; SUDEP, Sudden Unexpected Death in Epilepsy. Note: All reference to 'cannabidiol' within this submission refers to the licensed and NICE-recommended pharmaceutical form branded as Epidyolex®.

B.1.2 Description of the technology being evaluated

Fenfluramine is licensed for use with or without concomitant clobazam and may be used without restriction at any point in the add-on therapy pathway. It is an additional treatment option for reducing seizures with a dual mode of action that aims to restore the balance between GABAergic and glutamatergic activity and effectively combines an agonistic impact on serotonin receptors with a modulating influence on Sigma1 receptors (Figure 1).

Figure 1. Mechanism of action of fenfluramine



Adapted from UCB Pharma S.A. Fintepla Summary of Product Characteristics. 2020 and Martin, P. et al. Int J Mol Sci 2021;22
Abbreviations: GABA, Gamma-Aminobutyric Acid; 5-HT, 5-hydroxytryptamine (serotonin); LGS, Lennox-Gastaut syndrome.

An imbalance between brain excitation and inhibition has been implicated as a cause for seizures (5): gamma-aminobutyric acid (GABA) plays an inhibitory role and glutamate is the major excitatory neurotransmitter in the central nervous system. Fenfluramine is a serotonin-releasing agent that may restore the inhibition/excitation imbalance through a dual action: (i) stimulation of multiple serotonin (5-HT) receptor subtypes via the release of serotonin, which increases inhibitory GABA signalling, and (ii) action at the Sigma1 receptors, which reduces excitatory glutamatergic signalling (6, 7), together, resulting in a reduction of seizures.

Preclinical studies have shown that, in addition to having a role in reducing seizures, the effect of fenfluramine on these two pathways (GABA signalling and Sigma1 receptors) may have a role in non-seizure outcomes, such as executive functions and sudden unexpected death in epilepsy (SUDEP) (8-11).

Fenfluramine presents a new therapeutic approach that acts on both seizure-related and non-seizure-related pathways (1). Fenfluramine may be particularly impactful in patients who have previously failed multiple antiseizure medications (ASMs) (1, 12). Fenfluramine may reduce the likelihood of treatment resistance often observed with single-action treatments, making it an appropriate treatment option for patients who have not responded well to other interventions (refractory patients) (13, 14).

Fenfluramine has a low risk of clinically significant drug-drug interactions, which means it can be combined with existing ASMs effectively (irrespective of clobazam use), multiplying possible treatment combinations for outcome optimisation (1).

Having demonstrated a substantial effect on seizure reduction when added to existing therapies (12, 15), fenfluramine is an innovative therapy that meaningfully extends the range of licensed therapy options for patients with LGS. A summary of fenfluramine is provided in Table 2 with the Summary of Product Characteristics (SmPC), labelling, and package leaflet provided in the reference pack (see Appendix C).

Table 2. Description of fenfluramine (Fintepla®)

UK approved name and brand name	Fenfluramine hydrochloride (Fintepla®)
Mechanism of action	Fenfluramine is a serotonin-releasing agent, and thereby stimulates multiple 5-HT receptor sub-types through the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor. The precise mode of action by which fenfluramine exerts its anticonvulsant effects in LGS is not known.
Marketing authorisation/CE mark status	Fenfluramine was granted a European marketing authorisation on January 24th 2023. Marketing authorisation for GB was granted on the 5th of July 2023.Fenfluramine was also granted orphan drug designation for the treatment of LGS (GB Orphan designation number: PLGB 00039/0804 – 0010OD2).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Fenfluramine is 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.
Method of administration and dosage	**Administration** Fenfluramine hydrochloride is presented as an oral solution containing 2.2mg/mL fenfluramine. It may be taken with or without food. **Dosage** The starting dose is 0.1 mg/kg twice daily (0.2mg/kg/day). After 7 days, for patients who are tolerating fenfluramine and require a further reduction of seizures, the dose can be increased to 0.2 mg/kg twice daily (0.4mg/kg/day). After an additional 7 days, for patients who are tolerating fenfluramine and require a further reduction of seizures, the dose can be increased to a maximum of 0.35 mg/kg twice daily (0.7mg/kg/day). Do not exceed a total dose of 13 mg (6 mL) twice daily (26mg/day). When discontinuing fenfluramine, the dose should be decreased gradually.
Additional tests or investigations	**Aortic or mitral valvular heart disease and pulmonary arterial hypertension** Because of reported cases of valvular heart disease that may have been caused by fenfluramine at historically higher doses when treating adult obesity, cardiac monitoring must be performed using echocardiography. Patients with valvular heart disease or pulmonary arterial hypertension were excluded from the controlled clinical studies of fenfluramine for the treatment of LGS. No valvular heart disease was observed during these studies.

	Decreased appetite and weight loss Fenfluramine can cause decreased appetite and weight loss. An additive effect on decreased appetite can occur when fenfluramine is combined with other ASMs. The decrease in weight appears to be dose-related. Most patients resumed weight gain over time while continuing treatment. The patient's weight should be monitored. A benefit risk evaluation should be undertaken prior to commencing treatment with fenfluramine in patients with a history of anorexia nervosa or bulimia nervosa.
List price and average cost of a course of treatment	Fenfluramine is presented as an oral solution containing 2.2mg/ml. The maximum NHS list price (excluding value-added tax [VAT]) submitted to the Department of Health and Social Care (DHSC) (20 July 2020) is: 120 mL bottle: £1,802.88 360 mL bottle: £5,408.65 Patients with LGS experience seizures during their entire lifetime. Treatment would be expected to be administered for the duration that their seizures persist and they receive a clinical benefit. Consistent with the average weight of patients in the fenfluramine Phase 3 trial, the annual maintenance treatment cost, based on the NHS maximum list price of Fintepla® (ex-VAT), is estimated as: [redacted] per patient.
Patient access scheme (if applicable)	A discount of [redacted] was applied to the list price average cost per mg of fenfluramine, [redacted].

Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); ASM, antiseizure medication; GB, Great Britain; LGS, Lennox-Gastaut Syndrome; MHRA, Medicines and Healthcare products Regulatory Agency; kg, Kilogram; mg, Milligram; PAS, Patient Access Scheme; PLGB, Great Britain Product License; SmPC, Summary of Product Characteristics; VAT, Value Added Tax.

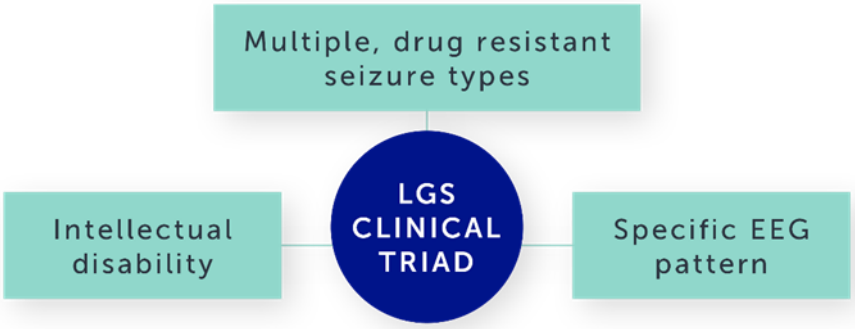
B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Definition of LGS

LGS is a rare, severe, lifelong, treatment-resistant form of epilepsy; its onset generally occurs in children under 8 years of age (16, 17). LGS is typically defined by a triad of symptoms (Figure 2): i) frequent, heterogeneous, and treatment-resistant seizures; ii) a specific epileptiform electroencephalogram (EEG) pattern (slow spikes, waves, and multifocal spikes); iii) developmental delay or cognitive impairment (18).

Figure 2. The clinical triad of LGS



Reference: Adapted from Asadi-Pooya, 2018(18)
Abbreviations: EEG, Electroencephalogram; LGS, Lennox Gastaut Syndrome.

In children with LGS, the dual impact from the developmental status and the ongoing, often treatment-resistant, epilepsy conforms with the definition of a developmental epileptic encephalopathy (DEE) as reported by the International League Against Epilepsy (ILAE) task force, is discussed in more detail below (19-21).

B.1.3.1.2 Particularity of a DEE

DEEs are a group of severe forms of epilepsy that are marked by recurring seizures and encephalopathy, leading to substantial delays or regression in developmental milestones (22, 23). Intense epileptiform activity interferes with brain development, resulting in cognitive slowing or intellectual regression, and is sometimes associated with psychiatric and behavioural consequences. Understanding this concept is crucial for both families and clinicians because it introduces the notion that early effective normalisation of the epileptic activity through early pharmaceutical intervention may improve cognition and behaviour, or at least prevent additional neurocognitive deterioration (19, 22, 23).

B.1.3.1.3 Heterogenous aetiology of LGS

Aetiologies can be symptomatic with an identifiable brain disorder, or cryptogenic without known causes. In about 20% of cases, LGS evolves from infantile seizure disorders. In other patients, sole onset occurs. Currently, no biological or genetic markers have clearly been identified (24, 25).

Causative gene mutations, most frequently arising *de novo*, are usually identified in 30–50% of infants with severe DEEs (22, 26). However, a genetic aetiology does not exclude an environmental contribution to an acquired cause. Thus, LGS may also be the direct result of a presumed or documented brain infection, brain malformation, inflammatory process, metabolic disorder, or traumatic brain injury (27). With such a range of different underlying causes, the extent to which a specific cause can be found depends on the extent of detailed evaluation of each patient (22, 23, 27, 28).

B.1.3.1.4 Diagnosis

Due to the diverse underlying causes of LGS, the seizure patterns and EEG results can be heterogeneous and may vary over time (29-31). LGS diagnosis typically occurs between 3 and 5 years (32). It is important to note that not all children with LGS display the characteristic triad of symptoms at onset or at any one time (18, 29). Therefore, the diagnosis of LGS can be challenging and may emerge only over several years (30, 32).

The types, frequency, and severity of seizures experienced by patients are subject to intra- and interpatient variability. LGS signs and symptoms evolve over time, including seizure presentation and EEG signatures, raising the risk of misdiagnosis and under-recognition in adulthood (29, 30). In a cohort from Nova Scotia, there were only four patients with LGS at the time of epilepsy diagnosis; however, 20 years later the number had increased to 17, with most of the new cases evolved from West syndrome (33). Risks of delayed diagnoses and patient heterogeneity were mentioned as key elements to consider for full understanding of the disease burden and treatment pathways by UK clinical opinion (34).

B.1.3.2 Disease burden

B.1.3.2.1 Epidemiology

LGS is a rare disease, accounting for 3 to 5% of childhood epilepsies, with a global incidence of approximately 2 per 100,000 children per year (35). In a recent UK study based on linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) data, the prevalence of LGS was estimated as 0.58 per 10,000 (36).

In the attached budget impact analysis of this submission, we have estimated that there are approximately 3,500 patients living with LGS in England and Wales. Among these patients, around 1,440 have received a confirmed diagnosis. As LGS is a rare disease, accurate epidemiology data can be difficult to obtain due to coding errors of the disease or misdiagnosis; therefore, the estimated number of LGS patients is likely to be underestimated.

B.1.3.2.2 Clinical burden

(i) High frequency and severe drop seizures that are resistant to classic ASMs.

LGS patients will have multiple daily attacks of various seizure types, with the most frequent seizures being drop seizures (37-39). Drop seizures result in a loss of muscle tone or stiffening of muscles, where people suddenly and unpredictably drop to the ground (24, 40). Drop seizures include generalised-tonic clonic (GTC), secondary GTC, tonic, atonic, and tonic-atonic seizures as described by the Epilepsy Study Consortium (ESC) (15, 18). These seizures are highly frequent (sometimes more than a hundred times per day), dangerous, and debilitating (15, 41). Drop seizures are physically demanding as they may result in falls, serious debilitating injury, subsequent pain, hospitalisation or even death (24, 42).

Nearly all patients with LGS are resistant to treatment with classic ASMs and a sustained reduction in seizure frequency is rarely achieved (32). Treatment-resistant epilepsy as seizures that do not respond successfully to two tolerated and appropriately chosen and used ASM regimens (as monotherapies or in combination) to achieve sustained freedom from seizures (43). Across six childhood epilepsy syndromes, patients with LGS had the highest seizure burden and experienced the least improvement (44). As an example, in the fenfluramine pivotal trial, patients experienced between 120 to 152 seizures per 28 days[1] at baseline (15).

Seizure clusters and convulsive status epilepticus[2] are common in LGS (24, 45, 46). Status epilepticus (convulsive or non-convulsive) constitutes an emergency and may result in severe consequences if not treated rapidly (45, 47). People who continuously have seizures are at greater risk of comorbidities (including serious brain injuries) or death, which is why preventing seizures is so important (48).

(ii) Severe developmental delays, cognitive impairments, and behavioural problems associated with treatment-refractory seizure activity.

From around 1 to 5 years of age, when most children achieve development milestones, LGS patients will experience a progressive worsening of their disease, with several seizures per day, sometimes leading to status epilepticus. Everyday experiences such as physical exertion, emotion, eating, bathing and flashing light may act as seizure triggers (41).

During this worsening phase, developmental delay also becomes evident, together with a spectrum of comorbidities, including ataxia, which affects balance, co-ordination, speech, and learning difficulties. The majority of LGS patients will typically experience cognitive regression at seizure onset, 90% of children being intellectually impaired, with a below-average intelligence quotient (IQ) (28). The degree of disability varies both between patients and over time in the same patient.

Cognitive impairment may be worse in cases of high seizure recurrence (49) and favourable cognitive outcomes may be more likely in patients with a later age of LGS onset (33). Early onset age and symptomatic aetiology have been shown to be risk predictors for intellectual deficiency (50). Intellectual disability will thus generally worsen over time, serious intellectual disability being present in 20-60% of patients at time of onset and rising to 75-95% at five years post-onset (21).

[1] Baseline median total seizure frequencies observed across the three arms of the trial.
[2] International League Against Epilepsy identifies generalised convulsive (tonic-clonic) status epilepticus as a seizure lasting longer than five minutes, with an increased risk of brain injury if the seizure continues for 30 minutes or longer.

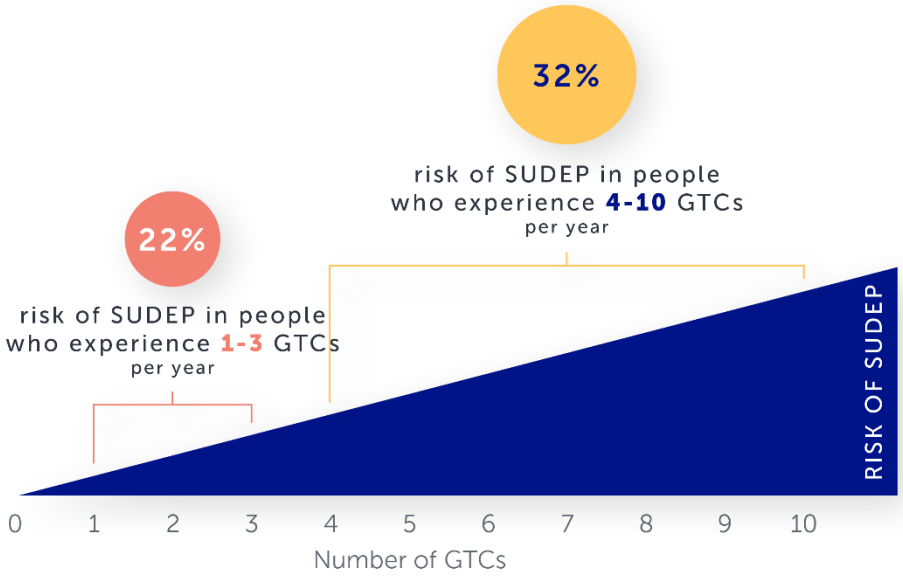
Along with cognitive problems, many patients with LGS develop behavioural disorders such as hyperactivity, anxiety, aggression, sleep disturbances and depression (51). Such disorders are present in approximately 50% of patients, making the condition more challenging for both patients and families (21, 24, 39, 52). It is uncertain if these problems differ from people with an intellectual disability alone; autism or autistic behaviour have also been reported, but only in a few cases of LGS (50).

(iii) Increased mortality risks which are worsened by seizure severity, frequency, and treatment resistance.

The risk of death is significantly elevated in patients with drug-resistant forms of epilepsy. All-cause mortality risk among children with LGS has been reported as 14 times greater than that of the general population (53). Median age of death for people with confirmed LGS was 26 (range 11 to 46) in a UK study (36). Approximately 5% of children with LGS will die during childhood (29) and one quarter of LGS patients die within 20 years of diagnosis (52).

LGS patients are at significant risk of SUDEP[3],which is highly correlated with the experience of uncontrolled and frequent GTC seizures (54, 55). 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 (55). As shown in Figure 3, the predominant risk factor for SUDEP is GTC seizures, with risk increasing from 22% to 32% according to the number of GTC seizures (55). This highlights the importance of controlling the numbers of seizures patients experience. Although rare, SUDEP is the cause of death for up to 5% of LGS patients, occurring at a higher rate compared with epilepsy patients overall (29, 52, 54, 56, 57).

Figure 3. Risk of SUDEP correlates with number of generalised tonic-clonic seizures (GTCs) experienced



Reference: Adapted from Sveinsson, O. et al. 2020 (55).
Abbreviations: GTC, Generalised Tonic Clonic; SUDEP, Sudden Unexpected Death in Epilepsy.

[3] SUDEP refers to deaths in people with epilepsy that are not from injury, drowning, or other known causes

B.1.3.2.3 Quality of life burden

The severity and frequency of seizure activity has a significant detrimental impact on patients' day-to-day life and family/caregiver burden (58, 59).

Drop seizures are accompanied by a high likelihood of accidental injury including concussions, jaw, limb, or tooth fractures (35, 60). Patients are often required to use protective equipment (e.g., wheelchair, helmet, faceguard) to minimise the physical effects of the seizures (24). Mobility is often severely impacted by frequent seizures, with 5% to 25% unable to walk even with support (18, 24, 61). One long-term prognosis study of adult patients with LGS (n=68) found that one quarter of LGS patients were non-ambulatory (61). Furthermore, approximately 60% were unable to complete independent daily living skills such as eating, bathing, toileting, and functional mobility (61). This can further impact their ability to perform activities of daily living and their quality of life (QoL) (58, 59).

The effects of LGS extend beyond the patient and have a profound impact on caregivers and family's daily QoL (28). Patients with LGS and their families may be affected by a perceived double stigma of mental illness and epilepsy (62). Hospital Anxiety and Depression Scale (HADS) scores in Gallop et al. (2010) suggested that some parents had substantial anxiety (62). Patients with LGS typically require round-the-clock care, requiring an average of 1.8 and up to 4 caregivers (40). Long-term outcomes for patients with LGS are typically very poor; the majority of patients will require home-care or institutionalisation (24). Patients' families have reported that their most significant concerns are fear of dying and the unpredictability of seizures, side effects and social isolation (62).

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 QoL, a high mortality risk and distress for patients, their caregivers, and families (62).

B.1.3.2.4 Economic burden

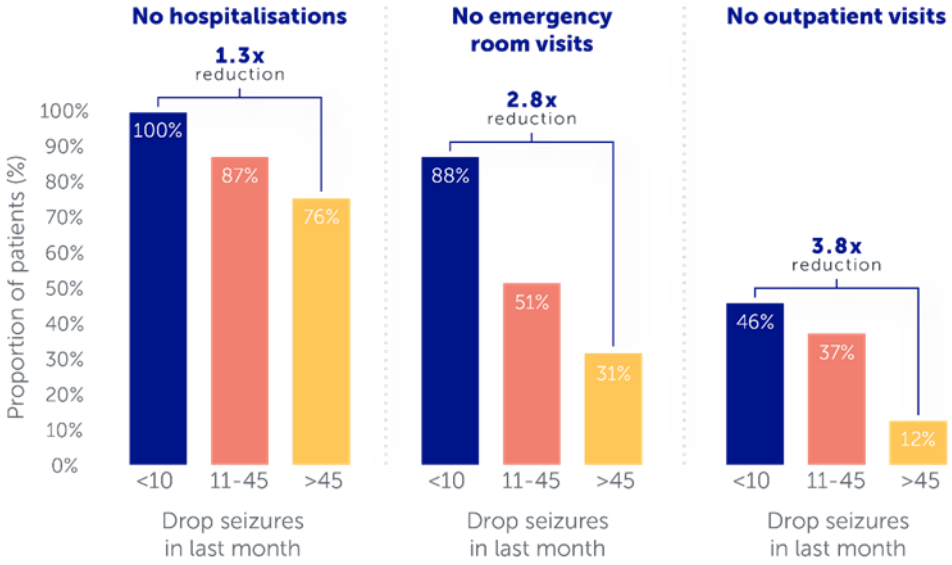
The annual cost of LGS is four times that of epilepsy in general (63). LGS is a rare disease that is burdensome to the National Health Service (NHS) healthcare and social system due to frequent seizures resulting in difficult patient management (24, 64). LGS is associated with high direct costs and healthcare resource utilisation (HCRU) compared to epilepsy or patients with other DEEs (36, 64-66). In the UK, HCRU of LGS patients is mainly driven by secondary care outpatient visits, inpatient admissions, and Accident and Emergency (A&E) visits (36).

Reducing drop seizure frequency (DSF) from baseline may be associated with a reduced need for unplanned and emergency hospitalisations. Patients with lower DSF were more likely to report no LGS-related hospitalisations, emergency room visits, or outpatient visits in a 12-month period compared with high drop-seizure rates in a real-world LGS study in France, Germany, Italy, Spain, and the UK (Figure 4):(67)

- 30-100% fewer hospitalisations
- 55-90% fewer A&E visits

- 26-40% fewer outpatient visits

Figure 4. Healthcare resource utilisation by number of drop seizures



Reference: Adapted from UCB Data on file Internal Adelphi survey results, 2023 (67)

The cost of social care in LGS patients is not well documented and is likely to be underestimated and underreported in cost of illness studies (33). Due to the extremely demanding nature of caring for a child with LGS, caregiver career opportunities can be negatively impacted, often resulting in reduced family income as well as financial concerns that contribute to emotional stress and anxiety (28).

B.1.3.3 LGS clinical care pathway

B.1.3.3.1 Treatment objectives

The heterogeneity in clinical presentation, and lack of clear aetiology explains challenges in both the diagnosis and treatment of LGS. As such, treatment remains mainly empirical with standard ASMs.

Whilst the aims of treatment in LGS may differ according to patient age and stage of disease, in many patients, the main aim is not necessarily to achieve seizure-freedom, but to reduce the frequency of the more disabling seizure types (i.e., drop seizures) (37). Indeed, seizure freedom appears to be unrealistic in some refractory epilepsies, especially LGS (16, 24, 68).

A key priority of seizure control is to avoid prolonged seizures and status epilepticus, given their morbidity and impact on developmental outcome (16, 69). Reducing seizure frequency and increasing seizure-free days is key to prevent debilitating cognitive symptoms and reduce mortality risks (29). Control of seizure activity should also greatly improve patients' and family/caregiver's QoL (58, 70).

Seizure burden is highly variable, and optimal control is a balance between a reduction in seizure severity and frequency whilst minimising treatment-related adverse events (24, 70, 71). The ultimate goal for treating LGS patients is to achieve seizure control in a safe manner whilst using

the fewest number of ASMs possible (68). ASMs are available; however, none have demonstrated complete control of seizures. That is why a combination of multiple ASMs are usually required, particularly in triple therapy (71).

B.1.3.3.2 Current clinical pathway of care in England

(i) Pharmacological therapies

A high overall medication burden is associated with numerous side effects that may exacerbate disease symptoms; therefore, patients require choice from a broad range of ASMs (both broad spectrum and precision drugs) to find a balance between efficacy, safety and/or tolerability.

Broad spectrum ASMs like sodium valproate and clobazam are commonly used in other epilepsies, while other ASMs have been specifically approved for treating LGS, i.e., topiramate, lamotrigine, rufinamide, and cannabidiol with clobazam (see Table 3). However, only cannabidiol with clobazam has been evaluated and recommended by NICE in 2019 (TA615) with the following conditions: only if the DSF is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment (40).

Table 3. Treatments with specific marketing for LGS

Treatment	Date of MA in LGS	Treatment type	LGS indication	NICE evaluation
Fenfluramine	5 July 2023 (MHRA)	Add-on	Treatment of seizures associated with LGS as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.	Ongoing
Cannabidiol (72)	19 Sept 2019 (EC) 25 July 2019 (CHMP)	Add-on in combination with clobazam	As adjunctive therapy of seizures associated with LGS, in conjunction with clobazam, for patients ≥2 years.	Recommended by NICE in November 2019 (TA615) (40)
Felbamate (18)	Early 1990 (Not licensed for use in the UK)	Add-on	If all other treatment options are unsuccessful for LGS, under the supervision of a neurologist with epilepsy expertise.	Not evaluated
Rufinamide (73)	16 Jan 2007	Add-on	Adjunctive therapy in the treatment of seizures associated with LGS in patients ≥1 years.	Not evaluated
Lamotrigine (74)	Early 1990s	Monotherapy or add-on	Adults and adolescents aged ≥13 years: Seizures associated with LGS. Lamotrigine is given as adjunctive therapy but may be the initial ASM to start with in LGS. Children and adolescents aged 2 to 12 years: Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with LGS.	Not evaluated
Topiramate (75)	1990s	Add-on	Adjunctive therapy in children aged ≥2 years, adolescents and adults with partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with LGS.	Not evaluated

Notes: Be aware that the following medications may exacerbate seizures in people with LGS and should not be used: carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenobarbital, pregabalin, tiagabine, vigabatrin (NICE guideline 217) (70).
Abbreviations: ASM, Antiseizure Medication; CHMP, Committee for Medicinal Products for Human Use; EC, European Commission; LGS, Lennox-Gastaut Syndrome; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; UK, United Kingdom.

Some ASMs may only be effective against certain seizure types while inducing or exacerbating others, as well as worsening associated comorbidities (76). NICE recommends sodium valproate as a first-line treatment option for LGS (see Figure 5). However, it should be noted that sodium valproate is contraindicated in women of childbearing age. If seizures are inadequately controlled, lamotrigine as an adjunctive treatment or monotherapy, is recommended as a second line. Further ASMs, including cannabidiol with clobazam, clobazam, rufinamide or topiramate are considered as third-line add-on treatment options if second-line treatment is unsuccessful. Finally, if other treatments prove ineffective, it is advisable to consider felbamate as an additional treatment option, under the guidance of a neurologist specialised in epilepsy despite felbamate not being approved for use in the United Kingdom (70). In UK clinical practice, the NICE treatment pathway, which involves a succession of 3 treatment lines, may not necessarily be observed in routine care by physicians. This is due to patients' heterogeneity and the lack of standardised practice. Treatment is highly individualised (34).

(ii) Non-pharmacological therapies

Non-pharmacological interventions (ketogenic diet, vagus nerve stimulation) and invasive surgery (e.g., corpus callosotomy) may also be additional treatment options for some patients and can be considered alongside medication (see Figure 5) (24).

(iii) Guidelines

The following treatment guidance and algorithms have been identified for the diagnosis and treatment of LGS:

- NICE guideline – Epilepsies in children, young people and adults [NG217] Published date: April 2022. Most recent guideline published in the UK (70).

- Expert Opinion on the Management of Lennox-Gastaut Syndrome: Treatment Algorithms and Practical Considerations, published 2017 (24). A treatment algorithm for LGS management in newly diagnosed patients was formulated by a panel of 5 European epileptologists, based on the available evidence from literature review and clinical experience.

(iv) Treatment approach

ASMs are the mainstay of treatment for LGS, despite characteristic refractory seizures (41). Treatment with multiple broad spectrum ASMs is likely to have been initiated before the diagnosis was established (34, 70), often because it is challenging to distinguish this epilepsy syndrome from others, particularly in the early stages of the presentation (18, 24, 77). For these reasons, the involvement of an adult or paediatric neurologist is current practice in treating people with LGS specific drugs.

Despite published guidelines, there is no existing standardised approach. Physicians' usual approach is to add and/or switch treatments to build overall efficacy for seizure reduction (78). The strategy for individualised antiseizure therapy is discussed with the person, their family and carers, according to their syndrome type, treatment goals and the preferences (70). Existing ASMs may

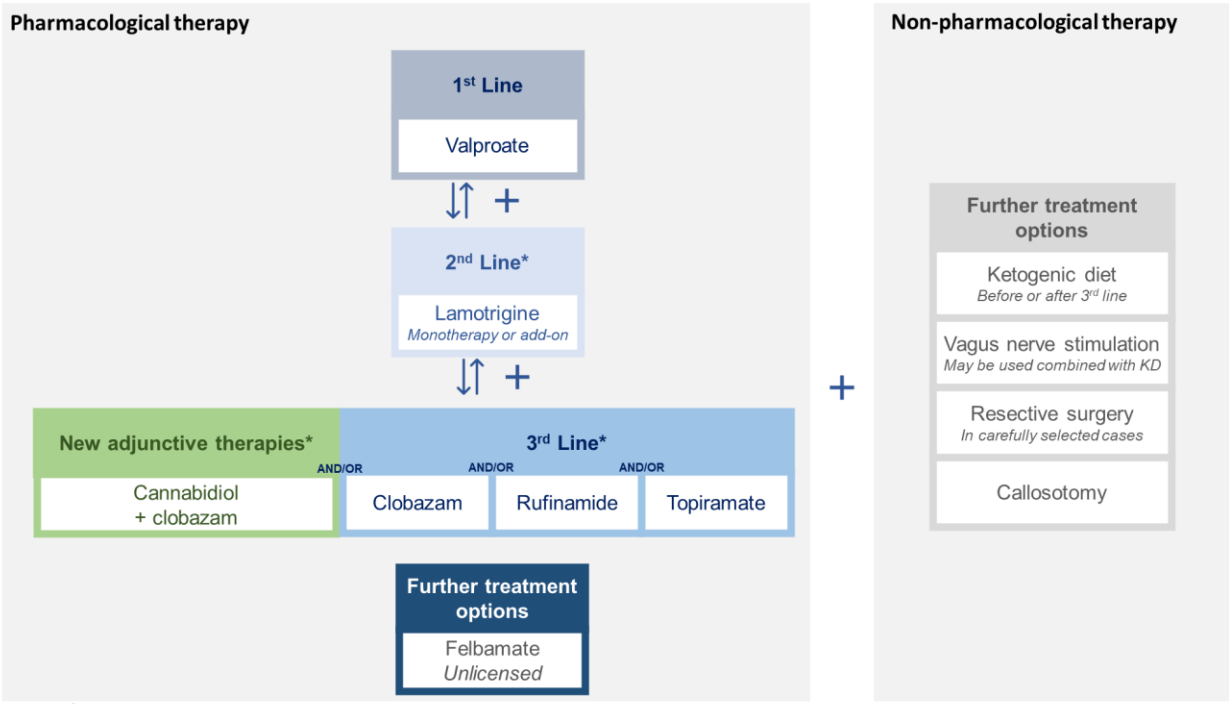
lose efficacy over time for a large proportion of patients ('honeymoon' effect/treatment waning) (14). It is thus common to recycle therapies from previous lines of treatment to try new combinations.

Treatment plans are regularly reassessed. As an example, NICE recommends that cannabidiol treatment be reassessed every 6 months and treatment be stopped in the absence of clinically meaningful benefit. This regular reassessment can be extrapolated to other ASMs as supported by UK clinical opinion (34). The patient, their family and carers, are made aware that they should be taking the least number of medicines as possible to be effective due to the side effects of being on numerous medications (70).

(v) Treatment algorithm

Based on the current treatment guidelines, a treatment algorithm for LGS management in newly diagnosed patients can be formulated as such as presented in Figure 5.

Figure 5. Current clinical management of LGS



Reference: Based on NICE guideline 217 (70) and Cross et al. 2017 (24).
Abbreviations : ASM, Antiseizure Medications; KD, Ketogenic Diet; LGS, Lennox-Gastaut Syndrome.

B.1.3.4 Remaining unmet need

LGS is chronically debilitating and life-threatening, yet despite multiple currently approved ASMs, the condition remains largely uncontrolled in most of its sufferers (36). Patients may try up to 28

different medicines, with a median of 7, and still suffer insufficient seizure control (15). Even if a patient is fortunate enough to find a treatment which provides an improvement, efficacy is usually not sustained in the long-term because of the evolving nature of the syndrome and the development of treatment tolerance (the 'honeymoon' effect)(24).

The current management of seizures is insufficient and suboptimal in patients with LGS. There is a high unmet need for additional treatment options with novel mechanisms of action for patients who have previously failed multiple ASMs. A lower seizure frequency prevents the continued debilitation of these patients, leading to improvements in QoL, and reductions in seizure related costs and HCRU. Ultimately, an individualised approach to LGS treatment is required (24). Treatment options with novel or multiple mechanisms of action may be particularly useful in the management of LGS (24).

The underlying causes and mechanisms of LGS remain obscure, making it difficult to optimise treatments for LGS (32, 79). Due to the complexity of the disorder, only a few randomised controlled trials (RCTs) have studied LGS, and many of the drugs that are more commonly used have little or no supporting evidence base from controlled trials (37, 70). There are few medications currently available to treat seizures in LGS and the long-term outlook is poor for most patients as many will experience refractory seizures (37, 70).

As a result, there remains a significant unmet need for supplementary ASMs that, when used in conjunction with standard therapy, can address the needs of patients whose seizures remain uncontrolled and improve their QoL, without significantly increasing medication burden (23).

B.1.3.5 Proposed positioning of fenfluramine within the current treatment pathway

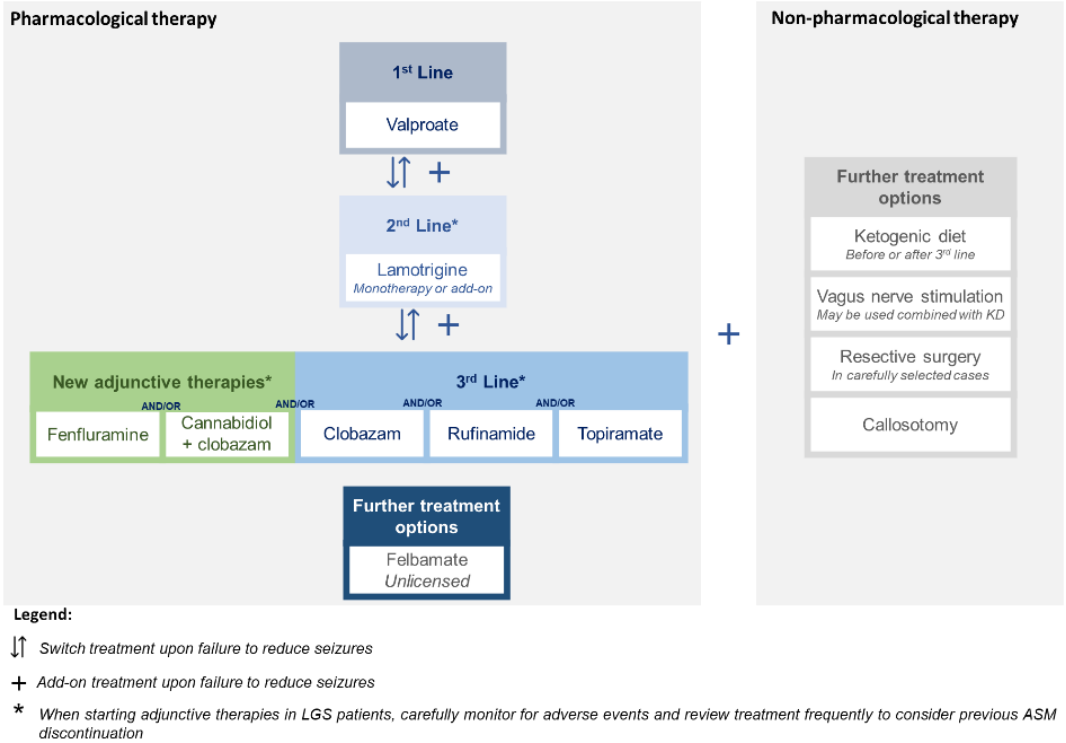
Fenfluramine is an additional treatment option with a dual mechanism, providing a novel treatment which may be particularly useful in patients who have previously failed multiple ASMs (1, 12). The proposed positioning of fenfluramine is informed by its Phase 3 pivotal study (Study 1601), product label, mechanism of action, and current treatment algorithms (1, 15).

Fenfluramine is indicated for the treatment of seizures associated with LGS as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older (1). In contrast to cannabidiol, fenfluramine is licensed for use both with or without concomitant clobazam.

In clinical practice, a lag in time exists between the first seizure and the confirmation of LGS, during which patients would usually try multiple standard ASMs. Fenfluramine is therefore anticipated to be used as a later-line adjunctive therapy following treatment failure with other standard ASMs, like the positioning of cannabidiol (Figure 6).

As traditional approaches have not provided adequate relief for all patients with LGS, there is a need to increase the number of treatment options available to patients and expert clinicians. Patients with LGS would benefit from fenfluramine's seizure reduction associated with a tolerable safety profile to allow a personalised approach. This can be tailored to the individual symptoms and responses of the patient during all stages of care, with regular assessment of treatment options that can prevent the overall burden of epilepsy from worsening (32).

Figure 6. Position of fenfluramine in the clinical management of LGS



Abbreviations: ASM, Antiseizure Medication; KD, Ketogenic Diet; LGS, Lennox-Gastaut Syndrome.

B.1.4 Equality considerations

The use of fenfluramine is unlikely to raise any equality issues. However, it is important to acknowledge the significant heterogeneity in clinical presentations of LGS, which presents challenges in diagnosis. As a result, many vulnerable patients may not receive optimal care or appropriate treatment to effectively control their seizures. Fenfluramine can be prescribed to all LGS patients, regardless of previous treatment failures, and can be combined with any additional treatment regimen. The lack of restrictions on prior treatments or specific concurrent medications allows for flexibility in using fenfluramine as an add-on to any ASM regimen taken by the patients. This prevents any potential disparities in treatment access for all patients, ensuring equal opportunities.

As is the case for other rare diseases, LGS patients face distinct and significant challenges that arise from the infrequency of their medical conditions, such as long diagnostic journeys, inadequate clinical management, and limited access to effective treatments. Finally, due to the low prevalence, there are limitations in the quality and availability of evidence, making the collection of data for LGS difficult.

B.2 Clinical effectiveness

Efficacy

- The robust and high-quality RCT data obtained from Study 1601 clearly demonstrated that significant and clinically meaningful reductions in drop seizure frequency (DSF) are achievable for most patients when fenfluramine is added to the most effective ASMs currently available.
- Fenfluramine significantly reduced the two most debilitating seizure types in LGS: drop seizures and GTC seizures. Treatment with fenfluramine led to a significant reduction of 19.9% in the median frequency of drop seizures from baseline compared to placebo (p=0.001). This reduction offered the potential of lowering the risk of seizure-related injuries in a highly refractory patient population. Additionally, fenfluramine resulted in a 45.7% reduction in the median frequency of GTC seizures from baseline vs placebo, offering the potential of reduced risk of SUDEP and seizure-related deaths.
- Fenfluramine also demonstrated improvements in non-seizure related benefits. Using the Clinical Global Impression-Improvement (CGI-I) scale, one quarter of fenfluramine-treated patients were much or very much improved as assessed by investigators within 14 weeks of treatment. Furthermore, significantly more children and young adults on fenfluramine showed clinically meaningful improvements in global executive functioning with specific improvements in the cognitive regulation Behaviour Rating Inventory of Executive Function 2 (BRIEF®2) index.
- Findings from an open-label extension (OLE) study provided compelling evidence that the significant reduction in DSF and the safety and tolerability observed with fenfluramine in Study 1601 are consistently maintained with long-term treatment over 12 months.

Safety

- The number of patients experiencing serious or severe treatment-emergent adverse events (TEAEs) was low. Decreased appetite was an anticipated side effect as fenfluramine was previously utilised as an appetite suppressant. To date, fenfluramine has not shown a significant impact on weight or growth. There have been no confirmed cases of valvular heart disease or pulmonary hypertension in the trials.

Network meta-analysis

- A network meta-analysis (NMA) compared fenfluramine's performance against cannabidiol and other ASMs. The NMA feasibility assessment excluded five treatments (lamotrigine, felbamate, soticlestat, clobazam and rufinamide). The resulting base case NMA compared fenfluramine, cannabidiol and placebo. The NMA showed that fenfluramine outranked cannabidiol across most clinical endpoints.

Value of fenfluramine

- There is a high unmet need for additional treatment options for LGS patients who have previously tried and failed multiple ASMs. Fenfluramine demonstrated efficacy in reducing drop (including GTC) and non-drop seizures from baseline in an RCT and OLE regardless of prior treatment failures. Fenfluramine is a clinically efficacious and well-tolerated medicine which substantially reduces seizure frequency, thereby potentially reducing the risk of SUDEP and associated mortality. Fenfluramine can be introduced in combination with any ASM and at any point within the current treatment pathway (unlike cannabidiol which is licensed to only be taken with clobazam).

B.2.1 Identification and selection of relevant studies

The clinical evidence included in this submission was identified with the help of a systematic literature review (SLR) conducted 5 October 2022 to identify all randomised controlled trials (RCTs) investigating the efficacy and safety evidence of fenfluramine and the other ASMs in LGS. Full details of the process and methods used to identify and select relevant studies is reported in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Fenfluramine's clinical effectiveness has been evaluated in a large global clinical trial programme of LGS patients, which included a pivotal Phase 3 RCT of fenfluramine (Study 1601) and its open label extension (OLE) study.

Details of the methodology and results of Study 1601 (NCT03355209) and interim results of its accompanying OLE study are available as full publications (12, 15). Additional details have been taken from the relevant Clinical Study Reports (80).

Both studies are summarised below in Table 4. A list of all secondary publications identified for Study 1601 is reported in Appendix D (81).

Table 4. Clinical effectiveness evidence

Study name	Study 1601 part 1, Knupp (2022) (15)	Study 1601 part 2 (OLE), Knupp (2023) (12)
Study title	A Two-Part Study of ZX008 in Children and Adults With Lennox-Gastaut Syndrome (LGS); Part 1: A Randomised, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults With LGS, Followed by Part 2: An Open-label Extension to Assess Long-Term Safety of ZX008 in Children and Adults With LGS.	
Trial registration	NCT03355209	
Study design	Phase 3 double-blind, placebo-controlled, multicentre, multinational RCT	Open-label extension study
Population	Children and adults, (n=263) aged 2 to 35 years, with ESC–confirmed LGS diagnosis who were using stable ASM regimens (≥1 and ≤4 concomitant ASMs) who met the following criteria: Onset of seizures at age 11 years or younger Multiple seizure types, including tonic and tonic or atonic seizures including countable motor seizures that result in drops Stable 4-week seizure baseline with 2 or more drop seizures per week of GTC, secondary GTC (SGTC) (i.e., focal to bilateral tonic-clonic seizures), tonic, atonic, or tonic or atonic seizure Abnormal cognitive development Medical history showing electroencephalogram evidence of abnormal background activity with slow spike-and-wave pattern (<2.5 Hz)	Patients with a confirmed LGS diagnosis who completed Study 1601 part 1 (aged 2–35 years at entry into the core study) (n=247)
Intervention(s)	Fenfluramine (0.2 or 0.7 mg/kg) in addition to SoC	
Comparator(s)	Placebo in addition to SoC	None
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes

Study name	Study 1601 part 1, Knupp (2022) (15)	Study 1601 part 2 (OLE), Knupp (2023) (12)
Rationale if study used in model	Pivotal phase 3 study in children and young adults with LGS treated with the investigational product. Provides individual patient-level data.	Extension of the pivotal phase 3 study in children and young adults with LGS treated with the investigational product. Used to provide longer-term data and support extrapolation assumptions beyond trial period.
Reported outcomes specified in the decision problem	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 effects of treatment Health-related quality of life (patients and carers)	Seizure frequency (overall and by seizure type) Response rate (overall and by seizure type) Proportion of people seizure-free** Adverse effects of treatment
All other reported outcomes	Proportion of patients who achieved improvement (minimally, much, or very much improved) on the CGI-I scale, investigator assessed. CGI-I rated by caregivers Change in frequency of all countable motor seizures (GTC, tonic, clonic, atonic, tonic or atonic, and clearly recognizable focal) Number of days free of drop seizures Standardised colour Doppler echocardiography to monitor cardiac valve structure/function and pulmonary arterial hypertension at screening, during treatment, and post-treatment	Proportion of patients who achieved improvement (minimally, much, or very much improved) on the CGI-I scale CGI-I rated by caregivers Treatment retention rates

** Definition of drop seizure: Seizures classified as GTC, SGTC, tonic, atonic, or tonic/atonic that are reviewed and confirmed as resulting in a drop for each subject by ESC based on the definition, "seizures involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface, or that could have led to a fall or injury depending on the subject's position at the time of the seizure." Synonymous with "seizures that result in drops," "seizures that result in drops (ESC-confirmed)," "drop seizures (ESC-confirmed)" and "ESC-confirmed drop seizures."*

***Proportion of people seizure-free was an outcome in fenfluramine trials, however, because the proportion of patients who are (drop) seizure-free was very low in the Phase 3 trials of fenfluramine and cannabidiol, this outcome was not considered in the model of this submission.*

Abbreviations: CGI-I, Clinical Global Impression-Improvement; ESC, Epilepsy Study Consortium; GTC, Generalised Tonic-Clonic; LGS, Lennox-Gastaut Syndrome; SGTC, Secondarily Generalised Tonic-Clonic, SoC, Standard of Care.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The methodology followed in Study 1601 and its OLE study is summarised below in Table 5.

Table 5. Summary of trial methodology

Study name	Study 1601 part 1, Knupp (2022) (15, 80, 82)	Study 1601 part 2 (OLE), Knupp (2023) (12, 80, 82)
Location	65 study sites: • 34 in North America (Canada, United States, Mexico); • 29 in Europe (Spain, Italy, Poland, France, Germany, Belgium, Netherlands, Denmark, Sweden); • 2 in Australia.	65 study sites: • 34 in North America (Canada, United States, Mexico); • 29 in Europe (Spain, Italy, Poland, France, Germany, Belgium, Netherlands, Denmark, Sweden); • 2 in Australia.
Trial design	Phase 3 double-blind, placebo-controlled, multicentre, multinational RCT (20-week trial duration)	Open-label extension study
Eligibility criteria for participants	Aged between 2 and 35 years, ESC–confirmed LGS diagnosis, using stable ASMs. Age of seizure onset: 11 years or younger, multiple seizure types (including tonic and tonic or atonic seizures), stable 4-week seizure baseline with 2 or more drop seizures per week, abnormal cognitive development, medical history showing EEG pattern of slow spike-and-wave complexes, (<2.5 Hz).	Patients with a confirmed LGS diagnosis who completed Study 1601 part 1 (aged 2–35 years at entry into the core study).
Settings and locations where data were collected	The main efficacy measures were based on seizures reported in the eDiary, an electronic, homebased handheld device (TrialMax TouchTM) provided to every subject. Additional scales and questionnaires were administered using a site-based electronic clinical outcome assessment tablet (TrialMax SlateTM, "Slate") provided to every clinical site. Clinic visits occurred at days 1, 15, 43 and 71; telephone assessment occurred at days 4, 8, 29, and 85. Final safety assessments occurred at days 99, 113 and 197.	The main efficacy measures were based on seizures reported in the eDiary, an electronic, homebased handheld device (TrialMax TouchTM) provided to every subject. Additional scales and questionnaires were administered using a site-based electronic clinical outcome assessment tablet (TrialMax SlateTM, "Slate") provided to every clinical site. Clinic visits occurred at days 1, 15, 30, 60, 90, 180 and 270; telephone assessment occurred at day 15. In some countries, a final safety assessment occurred up to 24 months after last dose.
Trial drugs (number in each group)	FFA 0.2 mg/kg (n=89), FFA 0.7 mg/kg/day (n=87), Placebo (n=87) FFA was administered orally twice daily as an oral solution of FFA hydrochloride containing 2.2 mg/mL FFA. Starting dose was 0.2	N= 247, no comparator group. A subject who completed Maintenance and was eligible for enrolment in the OLE study entered the Transition Period lasting 14 days between

Study name	Study 1601 part 1, Knupp (2022) (15, 80, 82)	Study 1601 part 2 (OLE), Knupp (2023) (12, 80, 82)
	mg/kg/day, titrated up to target dose over 2 weeks, followed by a 12-week maintenance period. The maximum dose of FFA was 26 mg per day. A subject who completed Maintenance and was not continuing into the OLE study entered the Taper Period, during which they tapered off study drug as shown in the table below in a blinded manner. At each taper step, the subject received product from a new bottle of study drug. A subject who withdrew during Maintenance entered Taper the day after withdrawal.	Visits 12 and 15, where patients were titrated to 0.2 mg/kg/day FFA and remained at this dose for 1 month regardless of their randomised treatment arm in the RCT. After Month 1, patients were flexibly titrated by effectiveness and tolerability, up to a maximum of 0.7 mg/kg/day.
Permitted and disallowed concomitant medication	Other ASMs permitted but had to be stable dose for 4 weeks before screening and during trial; Excluded if other use of cannabis evidenced by positive laboratory test, drugs that interact with central serotonin or current use of felbamate for <1yr.	Other ASMs permitted but had to be stable dose for 4 weeks before screening and during trial; Excluded if other use of cannabis evidenced by positive laboratory test, drugs that interact with central serotonin or current use of felbamate for <1yr.
Primary objective	To evaluate the effect of FFA 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 DSF between baseline and the combined Titration + Maintenance Periods	To assess the long-term safety and tolerability of FFA in children and adults with LGS regarding AEs, laboratory parameters, physical examination, neurological examination, Tanner Staging, cognition, vital signs, ECGs, ECHO, body weight, and body mass index
Primary outcomes	Percentage reduction in DSF/28 days[b]	N/A
Other outcomes used in the economic model or specified in the scope	• Percentage of patients with ≥25%, ≥50%, ≥75% and 100% reduction from baseline in DSF • Percentage reduction in total seizure[c] frequency from baseline; • Proportion of patients who achieved improvement (minimally, much, or very much improved) on the CG-I percentage reduction from baseline in frequency of seizures that typically results in drops (whether ESC confirmed or not), motor seizures (GTC, SGTC, TS, AS, Tonic aclonic (TA), CS, focal seizure (FS), and HCS), nonmotor seizures (absence seizures, myoclonic seizure (MS), focal seizures without clear observable motor signs, infantile spasms, and epileptic spasms) and individual seizures by type; • Parent or Caregiver Global Impression of Change; • Change from baseline in Quality of Childhood Epilepsy questionnaire score;	**Efficacy Endpoints** • Changes in seizure frequencies were compared to pre-randomisation baseline in the core study • Seizure subtype analysis assessed the median percentage reduction in GTC seizure, TS, AS, or TA in the subset of patients who experienced these seizure types at pre-randomisation baseline in the core study • ≥25%, ≥50%, and ≥75% seizure reduction responder levels • Proportion of patients achieving seizure freedom or near seizure freedom (defined as patients who had ≤1 seizure during the treatment period) • Median percentage increase in days free of drop seizures and median longest interval between drop seizures • CGI-I **Safety Endpoints:**

Study name	Study 1601 part 1, Knupp (2022) (15, 80, 82)	Study 1601 part 2 (OLE), Knupp (2023) (12, 80, 82)
	• Change from baseline in Vineland Adaptive Behaviour Scale score-II; • Incidence of status epilepticus episodes. • Incidence of rescue medication use • Incidence of hospitalisation to treat seizures	• Standardised two-dimensional colour Doppler ECHO assessed cardiac valve function/structure and any evidence of PAH every 3 months as described in a previous cardiovascular safety study and the core study • TEAEs were recorded during the treatment period
Pre-planned subgroups	None	None

a. Including GTC, secondary GTC (i.e., focal to bilateral tonic-clonic seizures), tonic, atonic, or tonic or atonic seizure
b. "ESC-confirmed"
c. All countable seizures (ie, motor and nonmotor)
Abbreviations: AEs, Adverse Events; AS, Atonic Seizure; ASMs, Antiseizure Medications; CS, Clonic Seizure; CGI-I, Clinical Global Impression-Improvement; CG-I, Clinical Global Impression-Improvement; DSF, drop seizures frequency, ECG, Electrocardiogram; ECHO, Echocardiogram; ESC, Epilepsy Study Consortium; FFA, fenfluramine; FS, Focal Seizure; GTC, Generalised Tonic-Clonic; HS, Hemoclonic seizure; LGS, Lennox-Gastaut Syndrome; kg, Kilogram; mg, Milligram; MS, Myoclonic Seizure; N/A, Not Applicable; PAH, Pulmonary arterial hypertension; RCT, Randomised Controlled Trial; TA, Tonic Aclonic; TEAEs, Treatment-Emergent Adverse Events; TS, Tonic Seizure.

B.2.3.1 Trial design

Study 1601 was a double-blind, randomised, placebo-controlled, multicentre trial conducted in patients aged 2 to 35 years with LGS, whose seizures were incompletely controlled with previous ASMs and those who experienced at least two drop seizures per week during the 4-week baseline (15).

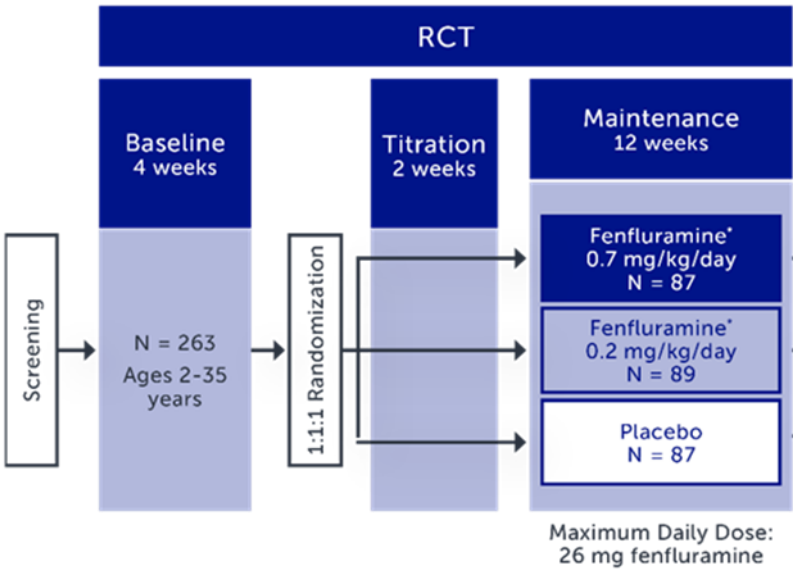
The intervention was fenfluramine in addition to SoC and the comparator was SoC without fenfluramine (i.e., SoC plus placebo). The RCT reported the percentage change in DSF from baseline as its primary endpoint (15).

Study 1601 included four distinct phases: a 4-week baseline period (Baseline), a 2-week titration Period (Titration), a 12-week maintenance phase (Maintenance), and a 2-week taper or transition Period (Taper/Transition). A subject who completed Maintenance and was not continuing into OLE study tapered off the study drug during the Taper Period (15).

Upon completion of baseline in Study 1601, patients who qualified for the OLE study entered the titration period and 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 placebo. Randomisation was stratified by weight (< 37.5 kg, ≥ 37.5 kg) to ensure balance across treatment arms (15). The objective of the OLE study was to evaluate the long-term safety and efficacy of fenfluramine in patients with LGS who participated in Study 1601 (12). During the OLE study, all patients were treated initially with fenfluramine 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study patients. After 1 month at a dose of 0.2 mg/kg/day, the investigator could adjust the dose for each subject based on effectiveness and tolerability. Effectiveness and safety/tolerability were assessed at months 1, 2, 3, 6, 9, and 12, with safety follow-up visits at 3 and 6 months after the last dose; in some countries, an additional follow-up occurred at 24 months after the last dose (12).

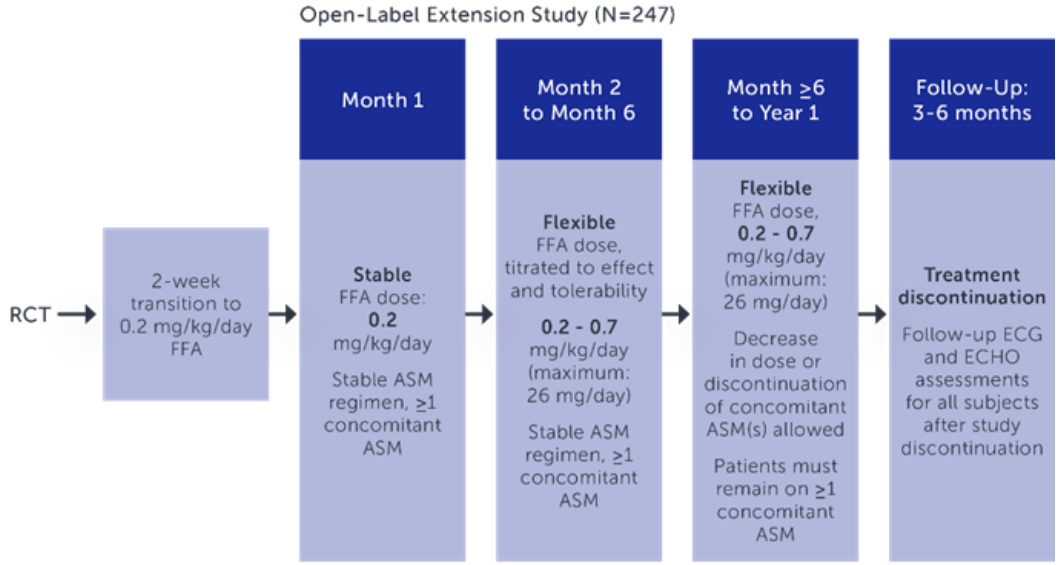
A summary of the trial design is shown in Figure 7 and Figure 8.

Figure 7. Study 1601 trial design



Reference: based on Knupp et al. 2022(15)
**Fenfluramine was administered orally twice daily as an oral solution of fenfluramine hydrochloride containing 2.2mg/mL fenfluramine.*
Abbreviations: kg, Kilogram; mg, Milligram; RCT, Randomised Controlled Trial.

Figure 8. OLE trial design



Reference: based on Knupp et al. 2023 (12)
Abbreviations: ASM, Antiseizure Medication; ECG, Electrocardiogram; ECHO, Echocardiogram; FFA, Fenfluramine; kg, Kilogram; mg, Milligram; RCT, Randomised Controlled Trial.

B.2.3.2 Eligibility criteria

Children and adults, aged 2 to 35 years, with ESC–confirmed LGS diagnosis who were using stable ASM regimens (≥1 and ≤4 concomitant ASMs) were eligible for enrolment if they met the following criteria: (i) onset of seizures at age 11 years or younger; (ii) multiple seizure types,

including tonic and tonic or atonic seizures; (iii) stable 4-week seizure baseline with 2 or more drop seizures per week of GTC, secondary GTC (i.e., focal to bilateral tonic-clonic seizures), tonic, atonic, tonic or atonic seizures; (iv) abnormal cognitive development; and (v) medical history showing EEG evidence of abnormal background activity with slow spike-and-wave pattern (<2.5 Hz) (15).

Key exclusion criteria were degenerative neurological disease; history of hemiclonic seizures (HCS) in the first year of life; only drop seizure clusters; previous or current exclusionary cardiovascular or cardiopulmonary abnormality that was detected on echocardiogram, electrocardiogram, or physical examination; and concomitant cannabidiol use (cannabidiol was not an approved medication anywhere in the world at the time of study enrolment). Race and ethnicity data were self-reported by patients or their caregivers. The race and ethnicity categories were Asian, Black or African American, White, other (American Indian or Alaskan Native and Native Hawaiian or Other Pacific Islander), and unknown (not reported or missing) (15).

B.2.3.3 Settings and locations where the data were collected

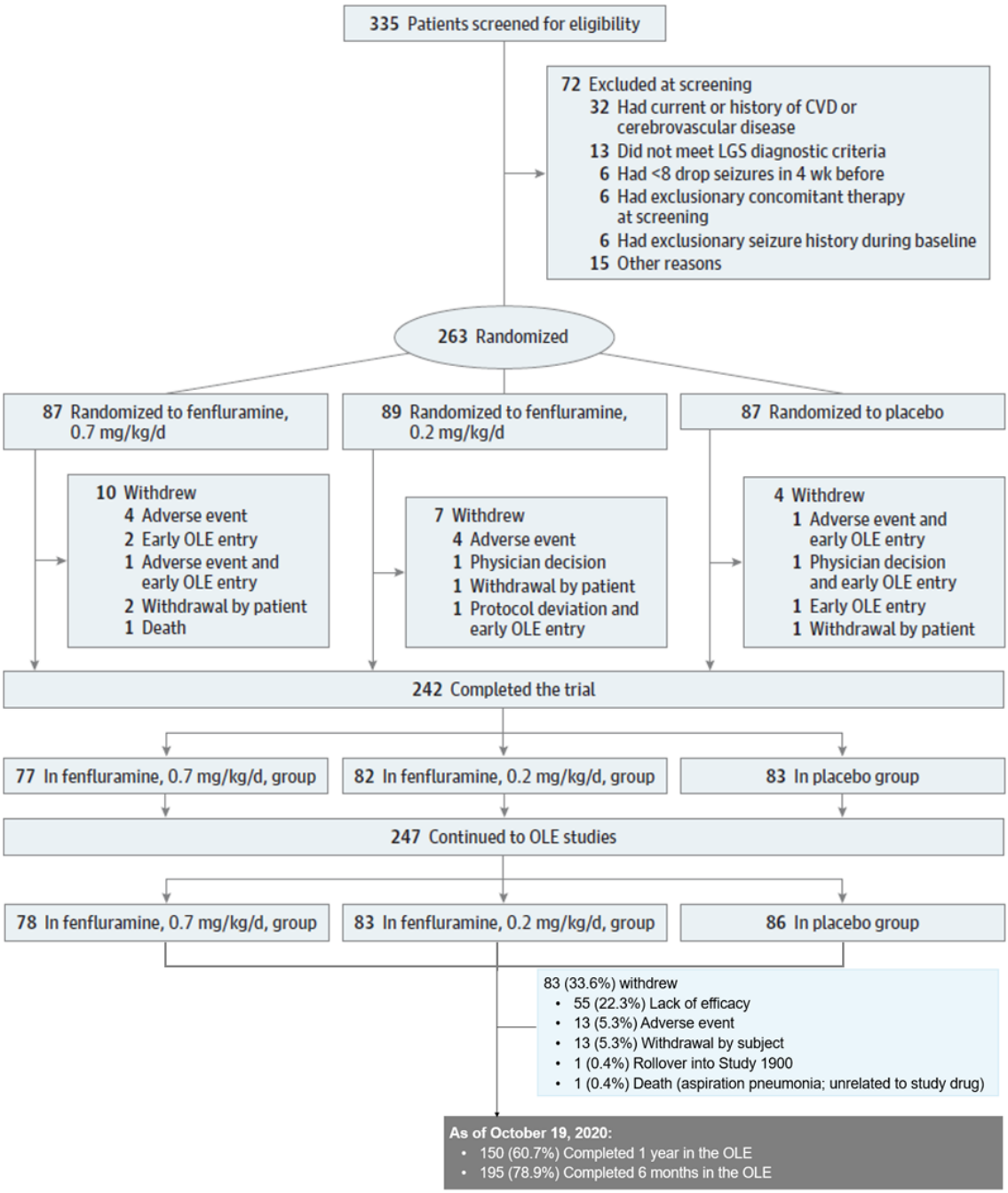
Patients were enrolled at 65 sites: 34 in North America (31 US, 2 Canada, 1 Mexico), 29 in Europe (1 Sweden, 1 Denmark, 3 Belgium, 6 Germany, 6 France, 4 Spain, 5 Italy, 1 Netherlands, 2 Poland), and 2 in Australia (15, 80).

B.2.3.4 Patient flow in the studies

In total, 263 eligible patients were randomised to the 0.7 mg/kg/day fenfluramine group (n=87), 0.2 mg/kg/day fenfluramine group (n=89), and placebo group (n=87). Among the randomised patients, 21 withdrew from the study early, with the most common reason (n=9) being AEs across all groups. A total of 242 patients completed the trial, and 247 entered the OLE study (Figure 9) (15).

The OLE study experienced delays in completion due to COVID-19 precautions that affected monitoring visits and posed scheduling challenges for in-person end-of-study visits. As a result, several participants who received the study drug were unable to attend their final in-person visit within the specified time frame of the protocol (365 ± 4 days) (12). To ensure appropriate transition of care and accommodate these circumstances, their treatment was extended until they could attend the visit and suitable arrangements for their continued care could be made. To evaluate the progress of the trial, an interim analysis of the OLE study was conducted using a snapshot of the clinical database collected on October 19th, 2020. This specific date was chosen to ensure that the analysis included a minimum of 365 ± 4 days of exposure in the OLE for almost all patients who remained in the trial (12). The effectiveness of the treatment, measured by the reduction in seizure frequency, was calculated at three-month intervals over time, starting from Month 1 until the end of the study (i.e., last treatment dose) within the modified intention-to-treat (mITT) population. In the OLE study, 83 (33.6%) patients withdrew; the most common reason for withdrawal was lack of efficacy (n=55, 22.3%). Patient count as of October 2020 is described in Figure 9.

Figure 9. Patient flow in Study 1601 and OLE Study



Reference: based on Knupp et al. 2022 and Knupp et al. 2023 (12, 15)
Abbreviations: kg, Kilogram; mg, Milligram; CVD, Cardiovascular disease; LGS, Lennox Gastaut syndrome; OLE, Open label extension.

B.2.3.5 Endpoints

In Study 1601, the primary endpoint of the study was the percentage change in confirmed drop seizures (including GTC, secondary GTC [focal to bilateral tonic-clonic], tonic, atonic, or tonic or atonic seizures) from baseline in the 0.7 mg/kg/day fenfluramine group compared to the placebo group (15).

Key secondary endpoints included evaluating the percentage change from baseline in DSF in the 0.2 mg/kg/day fenfluramine group, determining the responder rate of 50% or greater, and determining the proportion of patients who experienced improvement (ranging from minimal to much or very much improved) on the CGI-I scale. Additional secondary outcomes included evaluating the CGI-I ratings provided by caregivers, conducting subgroup analyses based on seizure type, assessing changes in the frequency of all countable motor seizures (such as GTC, tonic, clonic, atonic, tonic or atonic, and clearly recognisable focal seizures), and determining the number of drop seizure free days (15).

In the OLE study, the primary objective was to assess the long-term safety and tolerability of fenfluramine (i.e. AEs, laboratory parameters, physical examination, neurological examination, Tanner Staging, cognition, vital signs, electrocardiograms, echocardiograms, body weight, and body mass index). Effectiveness endpoints were also collected including: comparing changes in seizure frequencies to the pre-randomisation baseline in the core study, analysing the median percentage reduction in specific seizure subtypes for patients experiencing them at baseline, evaluating responder levels based on seizure reduction (≥25%, ≥50%, and ≥75%), determining the proportion of patients achieving seizure freedom or near seizure freedom (defined as having ≤1 seizure during treatment), measuring the median percentage increase in days free of drop seizures and the longest interval between drop seizures, and using the CGI-I scale to assess overall improvement (12).

B.2.3.6 Baseline patient characteristics

Study 1601

Patients had a median (range) age of 13 (2-35) years and consisted of 146 male (56%) and 117 female (44%) individuals (15). Median (range) number of ASMs used previously was 7 (1-20). At baseline, 233 of 263 patients (89%) were using 2 to 4 concomitant ASMs (median [range] number, 3 [1-5]). Of these ASMs, the 5 most common were valproate (147 [56%]), clobazam (119 [45%]), lamotrigine (88 [33%]), levetiracetam (60 [23%]), and rufinamide (53 [20%]). At baseline, the median (range) DSF for all patients was 77 (2-2,943) per 28 days. The median (range) DSF was higher in the 0.7 mg/kg/day and 0.2 mg/kg/day fenfluramine groups compared to the placebo group (83 [7-1,803] and 85 [4-2,943] vs 53 [2-1,761] per 28 days respectively) (15). Further details of the patient characteristics are reported in Table 6 and Appendix D.

Table 6. Baseline characteristics of patients included in Study 1601

Baseline characteristics	Placebo	FFA 0.2 mg/kg/day	FFA 0.7 mg/kg/day
Number randomised	87	89	87
Age, mean (SD), y	14 (8) Range 2-35	13 (8) Range 3-35	13 (7) Range 2-35
Sex (%)	46 (53) male	46 (52) male	54 (62) male
Ethnicity*			
Asian	2 (2)	3 (3)	4 (5)
Black or African American	4 (5)	5 (6)	3 (3)
White	71 (82)	67 (75)	70 (80)
Other	0	1 (1)	0
Unknown, not reported	10 (11)	13 (15)	10 (11)
Motor seizure frequency per 28 days: median (interquartile range [IQR])	68 (14-1,761)	106 (4-2,943)	111 (10-1,897)
Total (motor and non-motor) seizure frequency per 28 days: median (IQR)	120 (14-1,761)	138 (14-2,967)	152 (10-5,472)
DSF per 28 days: median (IQR)	53 (2-1,761)	85 (4-2,943)	83 (7-1,803)
Number or previous ASM use Mean (SD) Median (Range)	7 (4) 6 (1-19)	7 (4) 7 (1-18)	8 (4) 7 (1-20)
Concurrent ASM use Total Mean (SD) Total Median (Range)	3(1) 3 (1-4)	3 (1) 3 (1-5)	3 (1) 3 (1-4)
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)

** Self-reported by patients or their caregivers.*
Reference: Knupp et al. 2022 (15)
Abbreviations: ASM, Antiseizure Medication; DSF, Drop Seizure Frequency; FFA, Fenfluramine; kg, Kilogram; mg, Milligram; SD, Standard Deviation; IQR, Interquartile Range.

OLE study

The mean (standard deviation (SD)) age of patients in the OLE study was 14 (8) years, with 168 (68.0%) of patients being <18 years of age. A total of 79 (32.0%) patients were ≥18 to 36 years. Approximately 55% of patients were male. During the OLE study, a subject was required to remain on ≥1 concomitant ASM throughout the study. Most (98.4%) patients were receiving between 1 and 5 concomitant ASMs. The most commonly used (≥ 25% of patients) ASMs were valproate (all forms), clobazam, and lamotrigine. Most patients received a mean daily dose of fenfluramine between 0.3 and 0.5 mg/kg/day (12). Further details of the patient characteristics are reported in Table 7.

Table 7. Baseline characteristics of patients included in OLE study

Baseline characteristic	FFA dose 0.2–0.7 mg/kg/day (maximum: 26 mg/day)
Number of patients	247*
Mean age at entry, years (SD)	14 (8)
Age group, years, n (%) 2–<6 6–<12 12–<18 18–36	 28 (11.3) 69 (27.9) 71 (28.7) 79 (32.0)
Sex (%)	136 (55.1) male
Race and ethnicity White Black or African American Asian Other, unknown, or multiple Not reported†	 199 (80.6) 12 (4.9) 8 (3.2) 8 (3.2) 20 (8.1)
DSF per 28 days determined during the core study: Median (IQR)	75 (4, 2943)
Number or previous ASM use: Median (range)	7 (1–20)
Concomitant medications, median (range) Valproate, all forms, n (%) Clobazam, n (%) Lamotrigine, n (%) Levetiracetam, n (%) Rufinamide, n (%) Cannabidiol, n (%)	3 (1–7) 149 (60.3) 112 (45.3) 87 (35.2) 57 (23.1) 52 (21.1) 12 (4.9)
Duration of exposure by age group at entry into core study, days, median (IQR) Paediatric: 2–<18 years (n=174) Adult: 18–36 years (n=73)	 364 (191–368) 364 (210–373)
Mean daily dose of fenfluramine (mg/kg/day), n (%) Up to 0.2 >0.2 to <0.3 0.3 to 0.5 >0.5 to 0.7	 6 (2.4) 67 (27.1) 113 (45.7) 60 (24.3)

**A total of 247 patients had enrolled in the OLE as of October 19, 2020 (interim cut-off date) and had at least 1 dose of study drug and 1 month of diary data in the OLE.*
†Privacy laws in some regions/countries preclude disclosure of certain personal information.
Reference: Knupp et al. 2023 (12)
Abbreviations: ASM, Antiseizure Medication; DSF, Drop Seizure Frequency; FFA, Fenfluramine; kg, Kilogram; mg, Milligram; SD, Standard Deviation; IQR, Interquartile Range.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The study groups in Study 1601 were determined by treatment received, with no additional planned subgroup analyses (15, 80). The analysis sets used are defined as followed (15, 80):

- Randomised population (n=263): All patients randomised to receive study treatment. This is the intention-to-treat (ITT) population.
- mITT population (n=263): All randomised patients who received at least one dose of fenfluramine or placebo and for whom at least one week of diary data was available.
- Per protocol (PP) population (n=209): All randomised patients who received at least one dose of fenfluramine or placebo, completed at least 4 weeks of the Maintenance Period, and had no important protocol deviations that would have a significant impact on clinical outcome.
- Safety (SAF) population (n=263): All randomised patients who received at least one dose of fenfluramine or placebo.

B.2.4.1 Efficacy

Efficacy parameters were summarised by descriptive statistics. Two-sided statistical significance testing (α=0.05) comparing each active treatment group with placebo were performed for the primary and secondary endpoints as described in the sections below, unless otherwise noted. A serial gatekeeping strategy was developed to control the type 1 error rate for pairwise comparisons between active-treatment and placebo groups among the primary and key secondary efficacy parameters, as follows (80):

Step 1: The primary efficacy endpoint of percent change from baseline in DSF in titration and maintenance (T+M) periods was formally tested first between the fenfluramine 0.7 mg/kg/day and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 2.

Step 2: The key secondary efficacy endpoint, the proportion of patients who achieve a ≥50% reduction from Baseline in T+M Periods, was compared between the fenfluramine 0.7 mg/kg/day and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 3.

Step 3: The key secondary endpoint, the proportion of patients who achieve improvement (minimally, much, or very much improved) in the CGI-I as assessed by the Principal Investigator, was compared between fenfluramine 0.7 mg/kg/day and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 4.

Step 4: The key secondary endpoint, percent change from baseline in DSF in T+M periods, was formally tested between the fenfluramine 0.2 mg/kg and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 5.

Step 5: The key secondary efficacy endpoint, the proportion of patients who achieve a ≥50% reduction from baseline in DSF, was compared between the fenfluramine 0.2 mg/kg and placebo

groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 6.

Step 6: The key secondary endpoint, the proportion of patients who achieve improvement (minimally, much, or very much improved) in the CGI-I as assessed by Principal Investigator, was compared between the fenfluramine 0.2 mg/kg and placebo groups using a significance level of α=0.05 (2-sided).

The percent change from Baseline in DSF was assessed using a nonparametric, rank analysis of covariance (ANCOVA) with treatment group and weight group (<37.5 kg, ≥37.5 kg) as factors; rank DSF per 28 days during Baseline as a covariate; and rank percentage change from Baseline in DSF per 28 days during T+M as the response variable. The primary analysis compared the fenfluramine 0.7 mg/kg/day treatment group versus the placebo group at the α=0.05 level of significance. The difference between the fenfluramine 0.7 mg/kg/day treatment group and the placebo group in percentage change in DSF and its 95% Confidence Interval (CI) were estimated using the Hodges-Lehmann (HL) method.

Number of drop seizure–free days and countable motor seizure–free days per 28 days, using the baseline as the covariate, was done with a similar nonparametric ANCOVA model as the primary endpoint analysis.

Percentage of patients with at least a 50% reduction from baseline in DSF and additional response analyses were analysed using a logistic regression model that incorporated the same factors as the ANCOVA used in the primary analysis.

The CGI-I data comparison between each active-treatment group and the placebo group was conducted by the Cochran-Mantel-Haenszel (CMH) test stratified by weight group.

The longest drop seizure–free interval was analysed using nonparametric methods; summary statistics included median, mean, minimum, maximum, the 25th and 75th percentiles, and 95% Cis on the difference in medians between groups (HL estimator). The Wilcoxon rank sum test was used to test for differences between each active treatment group and placebo.

The Quality-of-Life in Childhood Epilepsy (QOLCE) was collected at Visits 3 and 12. 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 patients. Each treatment group was compared pairwise with the others using pairwise Wilcoxon tests. QOLCE domain data were listed by subject.

B.2.4.2 Safety

All safety analyses were performed for the Safety Population. Results were reported by treatment group and for the combined fenfluramine groups. The Safety Population was defined as all randomised patients who received at least 1 dose of study drug. The statistical approach is summarised in Table 8.

Table 8. Statistical methodology used

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
The null hypothesis for the primary efficacy endpoint in the double-blind phase was that mean decrease in DSF would be equal when adding fenfluramine at 0.7 mg/kg/day to current therapy placebo to current therapy.	Analyses of the primary and all secondary efficacy endpoints were performed on the mITT* population. And repeated on the PP Population**. Percentage change from baseline in DSF in Titration + Maintenance Periods was assessed using a nonparametric, rank analysis of covariance (ANCOVA) at the α=0.05 level of significance. The difference between fenfluramine and placebo in percentage change in DSF and its 95% CI were estimated using the HL method. Proportion of fenfluramine patients who achieved a response was compared versus placebo using a logistic regression model. CGI-I was compared versus the placebo group using the Cochran-Mantel-Haenszel test stratified by weight group. Control of statistical analyses for multiplicity using a gatekeeping approach, where primary and key secondary endpoints were arranged in a hierarchy and tested sequentially.	Sample size assumption: 63 patients per group would identify 30% reduction in DSF with 90% power at 2-tailed significance level of 5% Assuming a 20% withdrawal rate prior to the start of Maintenance yielded a requirement for an additional 16 patients per group for a total of 79 patients per treatment group. Similar calculations for the fenfluramine 0.2 mg/kg/day group led to a total required sample size of 237. The required number of patients randomised was estimated to be approximately 250 due to the long Baseline, during which additional patients could already be enrolled by the time the randomisation target was met. The variability expected in the trial was estimated from a Phase 3 trial of clobazam in patients with LGS (Ng 2011(83)), leading to an assumption that the SD would be 50%.	No imputation for missing data for primary analysis. Sensitivity analyses used 2 different methods for imputation of missing data due to subject drop out: worst value substituted for dropouts and a differential imputation method for dropouts.

** The Modified Intent-to-Treat (mITT) Population was defined as all randomised patients who received at least 1 dose of FFA or placebo and for whom at least 1 week of diary data were available. Patients were analysed according to the treatment group to which they were randomised.*
*** The Per Protocol (PP) Population was defined as all randomised patients who received at least 1 dose of study drug; who completed at least 4 weeks of diary data in Maintenance; who had no major protocol deviations that would have had a significant impact on clinical outcome in Study 1601; and who met the inclusion criterion for baseline drop seizure count.*
Abbreviations: ANCOVA, Analysis of Covariance; CI, Confidence Interval; CGI-I, Clinical Global Impression-Improvement; DSF, Drop Seizure Frequency
HL, Hodges-Lehmann; kg, Kilogram; mg, Milligram; mITT, Modified Intent-to-Treat; PP, Per-Protocol; SD, Standard Deviation.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A risk-of-bias analysis was conducted for all studies identified in the SLR, using the Cochrane Risk of Bias Assessment (RoB) Tool 2.0. The tool assesses quality across five domains: randomisation process; deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported result. Table 9 contains a summary of the quality assessment for Study 1601 and demonstrates this study was completed to the highest standards possible in the context of this rare disease, with an overall low risk of bias.

Table 9. Summary of quality assessment of Study 1601

Study name	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Judgement
Knupp, 2022 (15) Study 1601 (NCT03355209) **FFA vs. placebo**	Low	Low	Low	Low	Low	**Low**

Abbreviations: FFA, Fenfluramine.

B.2.6 Clinical effectiveness results of the relevant studies

Summary of clinical efficacy

- Comprehensive efficacy data in support of fenfluramine are available from one robust, phase 3 RCT (Study 1601; NCT03355209) and its subsequent open label extension (OLE) study providing efficacy data for up to 1 year of treatment.
- Study 1601 met its primary endpoint:
    - Fenfluramine 0.7 mg/kg/day significantly reduced drop seizure frequency (DSF; estimated median difference vs placebo: -19.9% (p = 0.001)).
    - Add-on fenfluramine was effective in reducing GTC seizures, with 45.7% and 58.2% reductions from baseline observed in the 0.7 and 0.2 mg/kg/day fenfluramine groups, respectively, compared with a worsening of -3.7% in the placebo group.
    - Fenfluramine was generally well tolerated in patients with LGS, with no observations of valvular heart disease (VHD) or pulmonary arterial hypertension (PAH).
    - Children and young adults with LGS treated with fenfluramine were more likely to show clinically meaningful improvement in executive functioning, measured by BRIEF®2, than those receiving placebo.
- Fenfluramine also showed directional improvements in patient and caregiver quality of life (QoL). Using the CGI-I rating, carers Parents/caregivers (61.3%) and investigators (48.8%) independently rated significantly more patients on fenfluramine 0.7 mg/kg/day to be “very much improved”, ”much improved” or “minimally improved” compared with patients receiving placebo (37.0% and 33.8%, respectively) at the end of their treatment period.
- In the OLE study, patients with LGS experienced sustained (39.4 at Month 3 – 51.8% at Month 12) clinically meaningful reductions in DSF during treatment with fenfluramine for up to 1 year. In addition, the median percentage reduction in all seizures not associated with a drop was -66.9% after 1 year.
- Collectively, these data clearly demonstrate the significant reductions in drop and non-drop seizure frequency in high proportions of LGS patients when fenfluramine is added to ASMs currently available.
- Fenfluramine was generally well tolerated with no observations of VHD or PAH during the OLE. Consistent results support the use of fenfluramine across the add-on therapy pathway.

B.2.6.1 Double blind RCT – Study 1601

Study 1601 met the primary endpoint in reducing DSF by -26.5% in patients treated with fenfluramine 0.7 mg/kg/day over 14 weeks. This was a significant 3.5-fold reduction compared with placebo, which showed a reduction of -7.6% (Figure 10); the estimated median difference was -19.9 percentage points, p=0.001). Results of the primary, key secondary and selected efficacy endpoints are summarised in Table 10. Results of selected secondary efficacy endpoints relating to patients and caregiver health status ratings and QoL are summarised in Table 11.

Table 10. Primary, key secondary and selected additional endpoints from Study 1601

Efficacy Endpoints	Placebo (n=87)	FFA 0.2 mg/kg/day (n=89)	FFA 0.7 mg/kg/day (n=89)
Primary endpoint			
Median percentage change from BL in DSF during T+M *Fenfluramine 0.7mg/kg/day arm*	-7.59%	-	-26.49%
p-value for comparison with placebo		0.0939	0.0013
Median difference between the groups – HL estimator		-19.9 (95% CI: -31.02, -8.74)	
Key secondary endpoints			
Median percentage change from BL in DSF during T+M *Fenfluramine 0.2 mg/kg/day arm*	-7.59%	-14.16%	-
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
Median difference between the groups – HL estimator		-10.5 (95% CI: -24.99, 3.99).	
Selected additional endpoints			
≥25% reduction in DSF: T+M and maintenance only, logistic regression, (mITT Population)	31%	47.2%	51.7%
Odds ratio		1.91 (95% CI: 1.02, 3.57)	2.39 (1.28, 4.49)
p-value for comparison with placebo		0.0417	0.0065
≥50% reduction in DSF: T+M and maintenance only, (mITT Population)	10.3%	28.1%	25.3%
p-value for comparison with placebo		0.0051	0.0150
≥75% reduction in DSF: T+M and maintenance only, logistic regression, (mITT Population)	4.6%	10.1%	8%
Odds ratio		2.68 (95% CI: 0.78, 9.21)	1.97 (95% CI: 0.55, 7.09)
p-value for comparison with placebo		0.1174	0.2971
≥100% reduction in DSF (seizure-free): T+M and maintenance only, logistic regression, (mITT Population)	1.1%	1.1%	0%
Odds ratio		1.84 (95% CI: 0.06, 58.39)	N/A
p-value for comparison with placebo		0.7303	N/A
Median percentage decrease in GTC seizure during T+M	-3.7%	58.2%	45.7%
p-value for comparison with placebo		0.0001	0.0005
Median number of drop seizure-free days per 28 Days: T+M, logistic regression, (mITT Population), least square mean (standard error (SE))	84.84 (6.075)	83.51 (6.640)	104.15 (6.423)
Difference from placebo		-1.33 (95%CI; -19.00, 16.35)	19.31 (95% CI; 1.97, 36.65)
p-value for comparison with placebo		0.8824	0.0293
Number and percentage of patients with ≥1 incidence of SE using the composite definition during T+M	47.1%	50.6%	51.7%
p-value for comparison with placebo		0.6546	0.6493

Efficacy Endpoints	Placebo (n=87)	FFA 0.2 mg/kg/day (n=89)	FFA 0.7 mg/kg/day (n=89)
Percentage of patients with at least one rescue medication used during maintenance period of Study 1601	32.2%	27.3%	38.4%
p-value for comparison with placebo		0.5112	0.4288
Percentage of randomised patients who had hospital visits during the study to treat seizures	8.0%	6.7%	5.7%

Reference: Knupp et al. 2022 (15), UCB Study 1601 CSR (80)
Abbreviations: BL, Baseline Period; CI, Confidence Interval, DSF, Drop Seizure Frequency; FFA, Fenfluramine; HL, Hodges Lehmann; kg, Kilogram; mg, Milligram; mITT, Modified Intent-to-Treat; N/A, Not Applicable; SE, Standard Error; T+M, Titration and Maintenance.

Table 11. Additional secondary and exploratory endpoints relating to condition ratings and quality of life in Study 1601

Patient/caregiver reported outcomes and quality-of-life endpoints	Placebo (n=87)	FFA 0.2 mg/kg/day (n=89)	FFA 0.7 mg/kg/day (n=89)
Patient condition rating and quality of life			
Percentage of patients with improvement [a] on CGI-I, Investigator rating at Visit 12	33.8%	44.7%	48.8%
p-value for comparison with placebo		0.1565	0.0567
Percentage of patients with improvement [a] on CGI-I, Parent/caregiver rating at Visit 12	37.0%	43.5%	61.3%
p-value for comparison with placebo		0.3960	0.0023
Percentage of patients with clinically meaningful improvement [b] on CGI-I, Investigator rating at Visit 12	6.3%	20.0%	26.3%
p-value for comparison with placebo		0.0100	0.0007
Percentage of patients with clinically meaningful improvement [b] on CGI-I, Parent/caregiver rating at Visit 12	4.9%	27.1%	33.8%
p-value for comparison with placebo		0.0100	0.0100
QOLCE – overall quality of life Mean change from baseline at visit 12 (SD)	[redacted]	[redacted]	[redacted]
p-value for comparison with placebo		[redacted]	[redacted]
Caregiver condition rating and quality of life			
HADS – total score Mean change from baseline at visit 12 (SD)	[redacted]	[redacted]	[redacted]
p-value for comparison with placebo		[redacted]	[redacted]
Zarit caregiver inventory index – total score Mean change from baseline at visit 12 (SD)	[redacted]	[redacted]	[redacted]
p-value for comparison with placebo		[redacted]	[redacted]

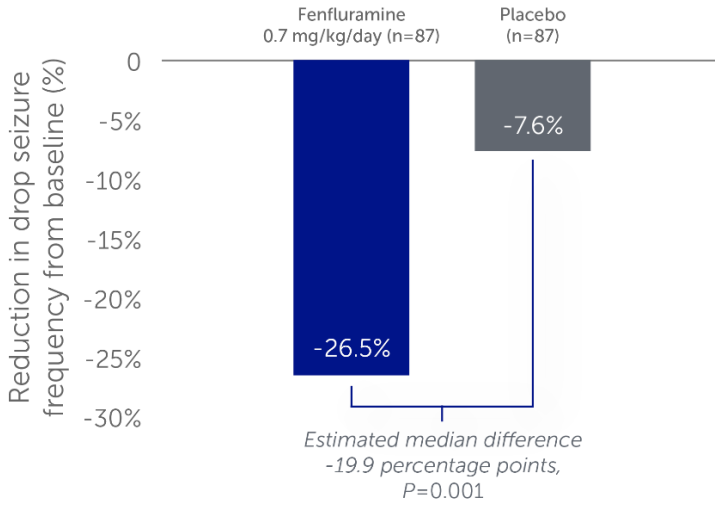
a. Improvement=minimally, much, or very much improved
b. Clinically meaningful improvement=much improved or very much improved
Reference: UCB Study 1601 CSR (80)
Abbreviations: CGI-I, Clinical Global Impression of Improvement, FFA, Fenfluramine; HADS, Hospital Anxiety and Depression Scale; kg, Kilogram; mg, Milligram; QOLCE, Quality-of-life of Childhood and Epilepsy; SD, Standard Deviation.

B.2.6.1.1 Primary endpoint: Percent change from baseline in drop seizure frequency in T+M versus placebo in the fenfluramine 0.7 mg/kg/day arm

The primary endpoint of Study 1601 was expressed as the percentage change from baseline in DSF per 28 days during T+M for the fenfluramine 0.7 mg/kg/day group compared with the placebo group.

Based on this primary endpoint, a statistically significant benefit for fenfluramine 0.7 mg/kg/day was demonstrated. Median percentage reduction was -26.5% for the intervention group compared with -7.6% in the placebo one. The HL estimate of the median difference in percentage change from baseline in DSF between these two groups was -19.9 percentage points (95% CI: -31.02, -8.74) (p=0.0013) (Figure 10). Furthermore, fenfluramine showed sustained reduction in median percentage of DSF over time (Figure 11).

Figure 10. Reduction in median percentage of drop seizure frequency in the titration (2-weeks) and maintenance period (12-weeks) – Study 1601



Reference: adapted from Knupp, et al. 2022. (15).
Abbreviations: kg, Kilogram; mg, Milligram.

Figure 11. Median percentage Change in Drop Seizure Frequency (mITT Population) over time

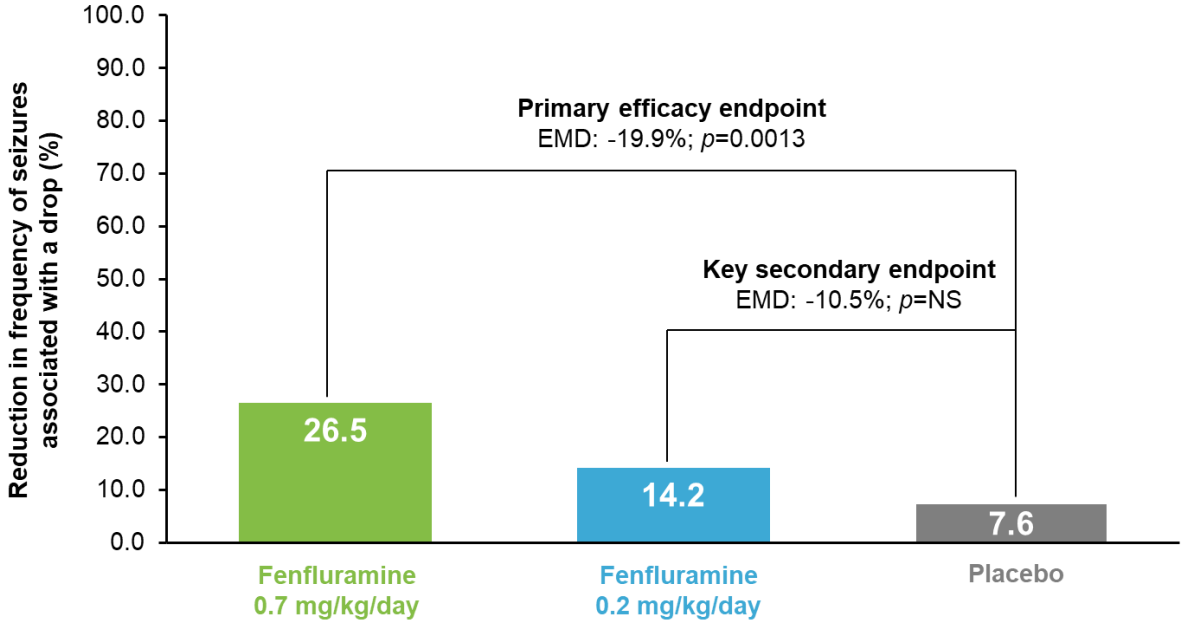
Reference: extracted from the clinical study report of Study 1601 (80).
Note: descriptive statistics are calculated from all seizure data available up to the indicated time point.
Doses of ZX008 are expressed as the fenfluramine hydrochloride salt. The 0.2, 0.5, and 0.8 mg/kg/day doses are equivalent to 0.2, 0.4, and 0.7 mg/kg/day (rounded).
Abbreviations: kg, Kilogram; mg, Milligram;

B.2.6.1.2 Key secondary endpoint: Percent change from baseline in drop seizure frequency in T+M versus placebo in the fenfluramine 0.2 mg/kg/day arm

As a key secondary endpoint (the fourth endpoint in the testing hierarchy), the change from baseline in DSF during T+M for the fenfluramine 0.2 mg/kg/day group was also compared with the placebo group using the same nonparametric ANCOVA model as for the primary endpoint. The difference between fenfluramine 0.2 mg/kg/day and placebo was not significant (p=0.0939). The median percentage reduction from baseline for the fenfluramine 0.2 mg/kg/day group was 14.2%, compared with 7.6% in the placebo group. The HL estimate of the median difference between the fenfluramine 0.2 mg/kg/day and placebo groups was -10.5 percentage points (95% CI: -24.99, 3.99).

Figure 12 illustrates the results of the Study 1601 for the primary and key secondary endpoints above mentioned.

Figure 12. Primary and key secondary efficacy endpoint – Study 1601



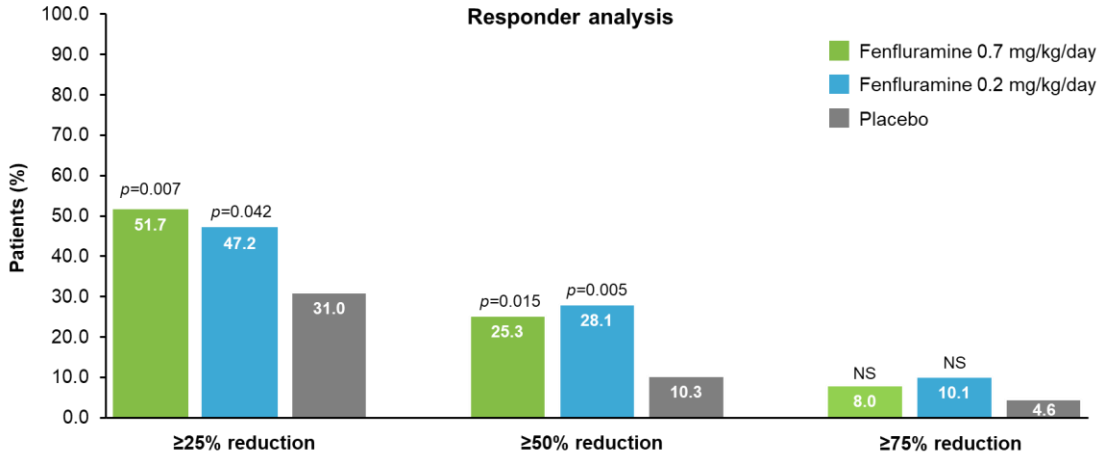
Reference: adapted from Knupp, et al. 2022. (15).
Abbreviations: EMD, Estimated Median Difference (Hodges-Lehmann estimate), NS, Not Significant.

B.2.6.1.3 Key secondary endpoints: Proportion of patients achieving ≥25%, ≥50% or ≥75% reduction in drop seizure frequency

Separate percentages of patients with a ≥50% reduction from baseline in DSF (50% responder rate) during T+M in the two fenfluramine arms compared with the placebo group, were key secondary endpoints. Patients in the fenfluramine 0.7 mg/kg/day group (25.3%) and fenfluramine 0.2 mg/kg/day group (28.1%) had a ≥50% statistically significant reduction from baseline in DSF during T+M vs the placebo group (10.3%) (p=0.0150).

Similar to the key secondary endpoint that evaluated the 50% responder rate during T+M, the percentages of patients with ≥25% and ≥75% reductions from baseline in DSF during T+M were compared between the fenfluramine groups and the placebo group using a logistic regression model. The percentage of patients with a ≥25% reduction was statistically significant in both the fenfluramine 0.7 mg/kg/day group (51.7%) (p=0.0065) and fenfluramine 0.2 mg/kg/day group (47.2%) (p=0.0417) compared with the placebo group. Statistical significance was not reached at the ≥75% reduction level for the fenfluramine 0.7 or 0.2 mg/kg/day groups compared with the placebo group (8.0%, 10.1% and 4.6% respectively) (p=0.2971 and p=0.1174, respectively) (Figure 13), however percentages changes were numerically higher.

Figure 13. Proportion of patients achieving ≥25%, ≥50% and ≥75% reductions from baseline in drop seizure frequency during the T+M period

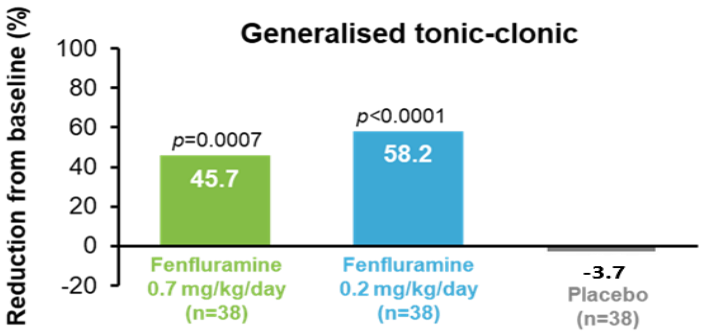


Reference: based on Knupp et al. 2020 (84)
Abbreviations: kg, Kilogram; mg, Milligram; NS, Not Significant; T+M, Titration and Maintenance.

B.2.6.1.4 GTC seizures

Changes from baseline during T+M in the frequency of GTC seizures per 28 days also were evaluated for the mITT population. The greatest median percentage decrease in the fenfluramine 0.7 mg/kg/day group relative to the placebo group was seen for GTC (45.7% decrease vs 3.7% increase, respectively; p=0.0005). Similar results were observed for the fenfluramine 0.2 mg/kg/day group for the change in GTC seizure frequency (58.2% decrease; p=0.0001) (Figure 14).

Figure 14. Percentage reduction from baseline of GTC seizures in Study 1601



Reference: based on Knupp et al. 2022 (15)
Abbreviations: kg, Kilogram; mg, Milligram.

B.2.6.1.5 Proportion of patients seizure-free T+M and Maintenance only

Few patients achieving seizure-freedom were reported. Seizure freedom was achieved by 1 of 89 patients (1%) in the fenfluramine 0.2 mg/kg/day group, 1 of 87 patients (1%) in the placebo group, and 0 of the 87 patients in the 0.7mg/kg/day group. Near seizure freedom (defined as ≤1 observed seizure), was reported in 1 of 87 patients (1%) in the 0.7-mg/kg/d fenfluramine group, 2 of 89

patients (2%) in the 0.2-mg/kg/day fenfluramine group, and 1 of 87 patients (1%) in the placebo group.

B.2.6.1.6 Number of drop seizure-free days per 28 days

Fenfluramine 0.7 mg/kg/day had a statistically significant positive effect on the number of drop seizure–free days versus placebo (p=0.0293). The median percentage increases were respectively 38.9% (median absolute change: 1.4 days, range: -10.4 to 20.3), compared with 13.8% (median absolute change: 0.6 days, range: -11.3 to 14.7). The comparison between the fenfluramine 0.2 mg/kg/day and placebo groups was not statistically significant (p=0.8824).

B.2.6.1.7 Incidence of status epilepticus on rescue medication use and hospitalisation

Status epilepticus is a condition in which a seizure lasts longer than 5 minutes or when seizures occur close together and the patient does not recover between episodes (85). It is an emergency condition that leads to use of rescue medication and emergency hospitalisation.

Seizures that evolved into status epilepticus were recorded by type and duration (>10 minutes). Status epilepticus lasting for <30 minutes was considered an AE, unless 1 of the other serious adverse events (SAE) criteria (e.g., hospitalisation) was met. Two patients in the fenfluramine 0.7 mg/kg/day group (each of whom had 1 episode) and 1 subject in the placebo group (who had 2 episodes) had AEs of status epilepticus during T+M.

The number and percentage of patients with ≥1 incidence of status epilepticus using the composite definition during T+M was similar between the treatment groups: 41 (47.1%), 45 (50.6%), and 45 (51.7%) in the placebo, 0.2 mg/kg/day, and 0.7 mg/kg/day groups, respectively; p=0.6493 for the comparison of fenfluramine 0.7 mg/kg/day versus placebo and p=0.6546 for the comparison of fenfluramine 0.2 mg/kg/day versus placebo.

The mean (SD) number of episodes of status epilepticus per 28 days during T+M was 3.4 (10.2), 6.6 (22.6), and 4.6 (12.1) in the placebo, fenfluramine 0.2 mg/kg/day, and fenfluramine 0.7 mg/kg/day groups, respectively. Based on a nonparametric ANCOVA analysis, no difference between the treatment groups was observed (p=0.5402 for fenfluramine 0.7 mg/kg/day versus placebo, p=0.7136 for fenfluramine 0.2 mg/kg/day versus placebo).

The comparison between each of the fenfluramine groups and the placebo group in patients who used rescue medication during T+M was not significant (p=0.5142 for fenfluramine 0.2 mg/kg/day and p=0.5282 for fenfluramine 0.7 mg/kg/day).

The numbers and percentage of randomised patients who had hospital visits during the study to treat seizures in the fenfluramine 0.2 and 0.7 mg/kg/day groups (6 [6.7%] and 5 [5.7%], respectively) were similar to the number and percentage in the placebo group (7 [8.0%]).

B.2.6.2 Patient reported outcomes and Quality of Life

B.2.6.2.1 Clinical Global Impression of Change – Improvement (CGI-I) rating

Parents/caregivers and study investigators independently rated how patients' symptoms had improved or worsened relative to baseline using the CGI-I scale. This provides an overall evaluation of a patient's response to treatment taking into consideration efficacy, safety, and tolerability.

In Study 1601, significantly more patients receiving fenfluramine 0.7 mg/kg/day were rated as “Very much”, “Much improved” or “Minimally improved” by parents/caregivers (61.3%) and investigators (48.8%) compared with patients receiving placebo at the end of their treatment period (37% and 33.8%, p=0.0023 and p=0.0567 respectively). The lack of statistical significance between fenfluramine 0.7 mg/kg/day and placebo on the investigator-rated CGI-I scale stemmed primarily from a large percentage of patients in the placebo group who were rated as minimally improved. In contrast, the percentage of patients rated on the CGI-I by the Investigator as having met a more stringent threshold of improvement (much improved or very much improved, indicating a clinically meaningful improvement) at Visit 12 (end of study/early termination) was highly statistically significant in favour of patients receiving fenfluramine 0.7 mg/kg/day compared with patients receiving placebo (26.3% versus 6.3%, respectively; p=0.0007). This result indicates that the reduction in DSF in the fenfluramine 0.7 mg/kg/day group was associated with clinically meaningful improvements in clinical status as reflected by the CGI-I score (Table 11) (15).

B.2.6.2.2 Quality of Life in Childhood Epilepsy Scale (QOLCE) Paediatric QoL inventory

The Quality of Life in Childhood Epilepsy Scale (QOLCE) is an epilepsy-specific instrument to assess how epilepsy affects day-to-day functioning of children in various areas, including physical activities, wellbeing, cognition, social activities, behaviour, and general health. The results for the QOLCE in the fenfluramine treatment groups did not show significant differences in the overall score between treatment groups (Table 11).

B.2.6.2.3 Caregiver quality of life, anxiety and depression

Caregiver levels of anxiety and depression were also assessed in Study 1601 using the Hospital Anxiety and Depression Scale (HADS) and Zarit Caregiver Burden Inventory, respectively. Regarding the HADS, levels of anxiety for the parent/caregiver were near the high end of the normal range (0 to 7) at baseline in each treatment group. However, the changes from baseline in total scores for anxiety and depression were not significantly different between the fenfluramine groups and the placebo group, indicating that total emotional distress in parents/caregivers did not notably change in any of the treatment groups during the study. Similarly, no notable differences between each of the fenfluramine treatment groups and placebo group in change from baseline were observed in Index Scores or any of the Zarit Caregiver Burden Inventory categories at any visit (Table 11) (80).

B.2.6.3 Open label extension study

The OLE study was a flexible-dose extension for patients who completed Study 1601. In contrast to the part 1 fixed dosing, the OLE had an initial dose of 0.2 mg/kg/day added to their initial regimen. After month 1, the study allowed the investigator to adjust the dose for each subject in 0.7 mg/kg/day maximum increments (0.4 mg/kg/day for patients taking concomitant stiripentol) based on effectiveness and tolerability. The maximum daily dose was capped at a total dose of 26 mg/day (or 17 mg/ day for patients taking concomitant stiripentol) (80).

Effectiveness and safety/tolerability were assessed at months 1, 2, and 3, and thereafter at 3-month intervals (see Table 12). Aligned with Study 1601, one of the effectiveness endpoints was the change from baseline in DSF per 28 days during the OLE treatment period. Similarly, other endpoints included proportion of patients who achieved an improvement from baseline including

≥25%, ≥50%, ≥75% reduction, and “near seizure freedom” (i.e., ≤1 seizure) from baseline in frequency, improvement in CGI-I rating and number of seizure-free days.

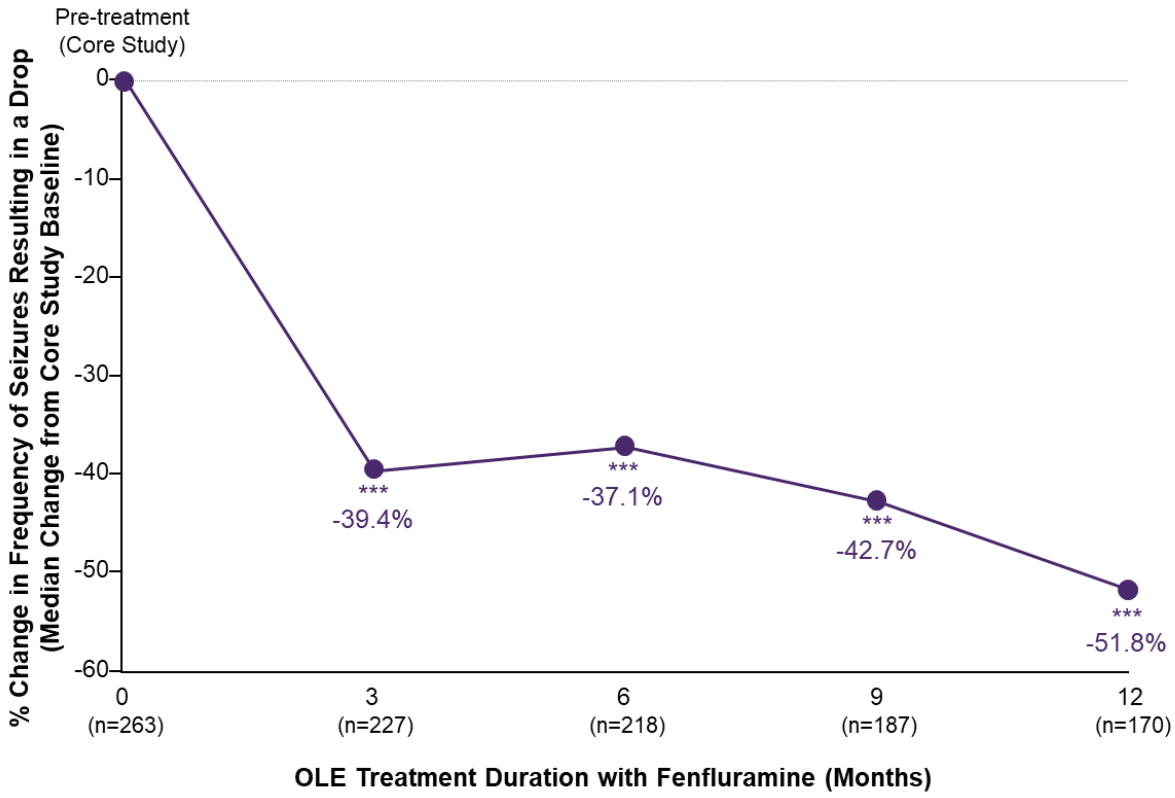
Table 12. Key effectiveness endpoint: Change from Baseline in DSF per 28 days during the OLE Treatment Period Responder analysis (mITT)

Timepoint	mITT (n=241)
Frequency of Seizures Resulting in drops (ESC Confirmed) per 28 days, mean (SD)	
Baseline, Study 1601	188.70 (361.677)
Median % change from baseline in DSF per 28 days (p-value*)	
Study 1601, transition period	-23.10 (NR)
Open-Label Extension (OLE) study, month 1	-4.18 (p<0.0001)
OLE study, month 3	-39.42 (p<0.0001)
OLE study, month 4-6	-37.12 (p<0.0001)
OLE study, month 7-9	-42.69 (p<0.0001)
OLE study, month 10-12	-51.77 (p<0.0001)
OLE study, month 13-15	-50.53 (p<0.0001)

Reference: UCB Study 1601 CSR (80), Knupp et al. 2023 (12)
aThe mean daily dose is calculated over the complete treatment duration in the OLE study, using the sum of doses in mg/kg on each day and dividing by the duration of treatment in the OLE study
**P-value is from a Wilcoxon signed-rank test that the median % change from baseline is significantly different from 0.*
Abbreviations: DSF, Drop Seizure Frequency; ESC, Epilepsy Study Consortium; OLE, Open-Label Extension; kg, Kilogram; mg, Milligram; mITT, Modified Intention-To-Treat; NR, Not Reported; SD, Standard Deviation.

Fenfluramine significantly reduced the median DSF which was maintained throughout the first 12 months of the OLE. At Year 1 of the OLE, the median percentage reduction in DSF was -51.8% (p<0.0001) (Figure 15). Over the entire OLE, the median change in DSF was -28.6% (n=241, p<0.0001).

Figure 15. Median percentage change from baseline in drop seizure frequency



Reference: reproduced from Knupp et al.2021 (86).
****P<0.0001 by Wilcoxon signed rank test. Decreasing n over time is due in part to staggered study entry; 150 patients (60.7%) completed 12 months of treatment. Months 6, 9, and 12 represent median frequency for the previous 3 months vs RCT baseline.*
Abbreviations: OLE, Open-Label Extension.

B.2.6.3.1 Proportion of patients seizure-free

Notably, 3 (1.2%) patients were near drop seizure-free (0 or 1 seizures observed) during the entire OLE Treatment Period, and the number of patients who were near drop seizure-free increased to 7 (2.9%) when assessed during Month 2 to End of Study (EOS).

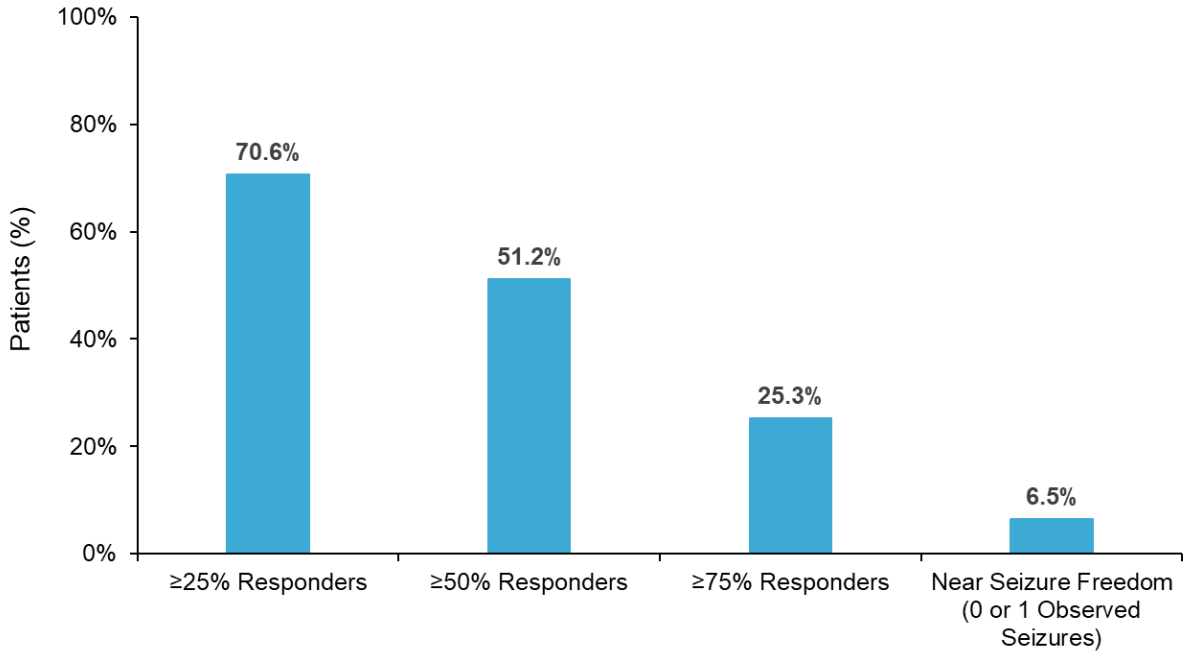
B.2.6.3.2 Seizure-free days

Statistically significant percentage change from baseline in the number of drop seizure-free days per 28 days was observed for the OLE mITT population during the OLE Treatment Period (Day 1 to EOS) ($p<0.0001$). During Baseline (Study 1601), the median number of drop seizure-free days per 28 days for the overall study population was 4.0 days (range 0 to 26.0). The median percentage increase in the number of drop seizure-free days was 44.6%, with a median absolute change of 2.03 days (range: -23.0 to 27.8 days). Similar results were observed for Month 2 to EOS ($p<0.0001$); the median percentage increase in the number of drop seizure-free days was 48.7%, with a median absolute change of 2.0 days (range: -23.0 to 27.9 days).

B.2.6.3.3 Responder analysis

The responder analysis for typical drop seizures yielded similar results: 51.2% of patients responded with a clinically meaningful (≥50%) reduction, and 25.3% of patients demonstrated profound (≥75%) reduction in DSF for the overall OLE Treatment Period. 6.5% patients were near seizure-free (0 or 1 seizures observed) for typical drops during the entire OLE treatment period (Figure 16).

Figure 16. Responder rates for drop seizures after 1 year of fenfluramine treatment



Reference: based on Knupp et al. 2021 (86)
Note: Represents previous 3 months vs RCT baseline.
Abbreviations: RCT, Randomised Controlled Trial.

B.2.6.3.4 Additional endpoints

A total of [redacted] patients received ≥1 administration of rescue medication during the OLE treatment period, with a mean (SD) number of days of rescue medication use per 28 days approximately [redacted] than during the 4-week baseline: [redacted] days; p=0.1289 (80).

In addition, nearly [redacted] and caregivers [redacted] rated their patients as having clinically meaningful improvement on the CGI-I, i.e., “Much Improved” or “Very Much Improved” (80).

Results of the quality-of-life questionnaires (QOLCE, Zarit Caregiver Burden Inventory, HADS) were not yet available (12, 15).

Overall, these data therefore confirm the sustained efficacy of fenfluramine in the longer term and suggest an increasingly positive impact on patient QoL with sustained fenfluramine treatment and seizure control.

B.2.7 Subgroup analysis

No subgroup analyses were conducted.

B.2.8 Meta-analysis

No meta-analysis was undertaken for fenfluramine.

B.2.9 Indirect and mixed treatment comparisons

ITC need and methodology

- There are no direct comparative data between fenfluramine and cannabidiol (with clobazam). Whilst the placebo-controlled trials of fenfluramine demonstrate the efficacy and safety of its use in LGS, this does not inform the comparative clinical and cost-effectiveness of fenfluramine in patients in need of add-on therapy.
- A network meta-analysis (NMA) was therefore performed to provide the relevant comparative data for fenfluramine as an add-on therapy option alongside existing add-on therapies.
- Nine studies with seven ASMs (fenfluramine, cannabidiol, clobazam, lamotrigine, topiramate, rufinamide, felbamate) reported efficacy and/or safety outcomes at 10-20 weeks. The final trial network was confined to fenfluramine (0.7 mg/kg), cannabidiol (10 mg/kg), cannabidiol (20 mg/kg) and placebo based on the feasibility assessment.

Results

- **Fenfluramine (0.7 mg/kg) was ranked first among the four treatments for all the efficacy outcomes (i.e., median percent reduction in frequency of GTC seizure, ≥25%, and ≥50% reduction in DSF) except for the ≥75% reduction in DSF where it ranked third. The risk ratios (with 95% credible intervals) versus placebo for the ≥50% reduction in DSF were [redacted] for fenfluramine (0.7 mg/kg), cannabidiol (with clobazam) 10 mg/kg and 20 mg/kg, respectively.**
- **Fenfluramine (0.7mg/kg) showed a better safety profile compared to cannabidiol (20mg/kg), which had the highest probability of discontinuation due to AEs versus placebo.**

Outcome

- Whilst producing a robust NMA for fenfluramine and other NICE-recommended add-on therapies in totality is not feasible, the inclusion of cannabidiol (with clobazam) is highly relevant to the decision problem. Cannabidiol (with clobazam) was accepted by NICE as a recommended option for treating LGS in 2019. Given the need for treatments with new action mechanism in LGS, specialists confirmed fenfluramine would be positioned as a credible alternative to cannabidiol (with clobazam).
- **As the NMA provides robust evidence of the clinical efficacy of fenfluramine against cannabidiol (with clobazam) in similar patient populations, and confirms that fenfluramine is superior for the majority of the efficacy and safety outcomes, it is anticipated that fenfluramine would be used as an alternative add-on therapy to cannabidiol (with clobazam).**
- A primary clinical and economic comparison against cannabidiol (with clobazam) is therefore the most appropriate approach to determine the clinical and cost-effectiveness of fenfluramine in the existing add-on therapy pathway.

Fenfluramine is indicated for treatment of seizures associated with LGS as an add-on therapy to other ASMs for patients aged 2 years and older. It is anticipated to be used as a third-line adjunctive treatment option following treatment failure with first- and second-line ASMs, similar to the positioning of the previously approved cannabidiol (40). The treatment pathway is outlined in section B.1.3.3. In the absence of direct head-to-head comparisons between fenfluramine and comparator ASMs, including cannabidiol in the LGS population, indirect comparisons were required to assess the comparative efficacy of each treatment indicated for LGS.

NMAs were conducted to develop a comprehensive assessment of the efficacy and safety of fenfluramine among patients with LGS compared with cannabidiol and other ASMs identified through an SLR detailed in Appendix D.

B.2.9.1 Identification of relevant studies

The SLR was conducted in accordance with Preferred Reporting Items for Systematic Reviews And Meta-Analyses (PRISMA) guidelines to identify relevant clinical efficacy data of fenfluramine and key ASMs recommended in existing NICE guidance for LGS (70, 87). To ensure all the relevant evidence was gathered, a bibliographic search of all existing NMAs, meta-analyses, regulatory documents, Health Technology Assessment (HTA) submissions, and clinical guidelines was undertaken. Studies or data identified in the search that met the inclusion Population, Intervention, Comparison, Outcomes and Study type (PICOS) criteria were added to the complete list of clinical studies in the SLR and then subsequently assessed for use in this NMA analysis.

Key ASMs recommended in NICE clinical guideline [NG217] include cannabidiol, sodium valproate, lamotrigine, rufinamide, topiramate, felbamate, clobazam, and levetiracetam (70). The database searches were conducted in MEDLINE and Embase using the Ovid platform for literature on October 5th, 2022, with an update performed on June 7th, 2023, to align with NICE requirements. The search yielded 38 publications reporting on 16 unique studies in LGS. Out of these 16 trials, studies satisfying the following criteria were included in the NMA feasibility assessment: RCT study design, reporting at least one of the outcomes of interest within a treatment period of 10-20 weeks, and targeting currently licensed interventions. If a trial had multiple publications, only the primary publication that contained the main trial analyses was included. If a post-hoc analysis reported additional outcomes of interest not reported in the primary publication, these outcomes were included in the NMA analysis only if the baseline characteristics of the populations in both publications were comparable.

Based on the above criteria, only 10 trials were selected for the NMA feasibility assessment, with 5 of the 16 trials excluded because the results did not report the outcomes of interest for the comparison with sufficient granularity or within the suitable timeframe of assessment (10 to 20 weeks). Finally, one article was excluded because it studied soticlestat, which is still in clinical trials and is not yet approved by the European Medicines Agency (EMA) leaving the review with a total of nine studies (Table 13).

Table 13. Summary of the trials used to carry out the indirect or mixed treatment comparison

Trial Name	Author, Year	FFA 0.2 mg/kg	FFA 0.7 mg/kg	CBD 10 mg/kg	CBD 20 mg/kg	RUF 45 mg/kg	FEL 45 mg/kg	LAM 100-400mg	CLB 0.25 mg/kg	CLB 0.50 mg/kg	CLB 1.0 mg/kg	TOP 6mg/kg	Placebo
Study 1601	Knupp, 2022 (15)	Yes	Yes										Yes
GWPCARE3	Devinsky, 2018 (88)			Yes	Yes								Yes
GWPCARE4	Thiele, 2018 (89)				Yes								Yes
E2080-J081-304	Ohtsuka, 2014 (90)					Yes							Yes
-	Ritter, 1993 (91)						Yes						Yes
-	Jensen, 1994 (92)						Yes						Yes
-	Motte, 1997 (93)							Yes					Yes
OV-1012	Ng, 2011 (83)								Yes	Yes	Yes		
-	Sachdeo, 1999 (94)											Yes	Yes
Study 022	Glauser, 2008 (95)					Yes							Yes

Abbreviations: CLB, Clobazam; CBD, Cannabidiol; FEL, Felbamate; FFA, Fenfluramine; LAM, Lamotrigine; kg, Kilogram; mg, Milligram; TOP, Topiramate; RUF, Rufinamide.

B.2.9.2 NMA feasibility assessment

Inconsistency may arise from variations in the design of studies or from divergent direct and indirect estimates of effect sizes obtained from the literature. To address these issues, NMA models rely on three crucial assumptions: transitivity, homogeneity, and consistency (96). The primary NMA assumption of transitivity was assessed by reviewing the inclusion/exclusion criteria and baseline patient characteristics of each trial. It was not feasible to assess the homogeneity assumption for each individual treatment because all treatments were reported by no more than two trials. It was also not possible to evaluate inconsistency because there was no closed loop in the networks, i.e., there was no intervention pair that had direct and indirect evidence available simultaneously. Quality assessment of all selected NMA trials was done using the Cochrane Risk of Bias Assessment (RoB) Tool 2.0 for all the selected NMA publications and is available in Appendix D.1.1.3.

B.2.9.2.1 Comparison of study designs and characteristics

Overall, the 10 included trials were similar with respect to trial design and inclusion/exclusion criteria of participants. The patient sample size varied from 59 patients in Ohtsuka et al. 2014 (97) to 263 for Knupp et al. 2022 (15). The feasibility assessment identified several key considerations including, criteria with respect to concomitant ASMs, baseline concomitant ASM usage, and treatment characteristics i.e., the specific durations of titration and maintenance phases in each trial (See Appendix D.1.1.4.6 for full details of feasibility assessment).

Regarding concomitant ASMs, most studies had pre-specified inclusion/exclusion criteria for the number of concomitant ASMs that patients took. These were overlapping requirements for concomitant ASMs and are fully outlined in Appendix D.1.1.4.6. Baseline concomitant ASM usage differed across included trials, likely because these trials were published over the last three decades. Four of the 10 studies did not report the specific concomitant ASMs used, and six studies reported different types of ASMs. The proportion of patients taking specific concomitant ASMs in each study is detailed in Appendix D.1.1.4.7. While concomitant ASM usage may be an important factor for the treatment of LGS, further assessment and/or adjustment for the number of concomitant ASMs was not possible due to the limited availability of data.

For treatment characteristics, all trials selected for the NMA feasibility assessment had a total treatment duration between 10 and 20 weeks, which included titration and maintenance periods. Notable differences were reported across a minority of studies for duration of titration and maintenance phases. Most RCTs included a two-week titration period followed by an 8- to 12-week maintenance period, with the exception of a study on lamotrigine by Motte et al. 1997, with a longer titration phase (6 weeks) (93).

Finally, efficacy and safety outcomes of interest were median percent reduction in frequency of GTC seizures, response rates of ≥25%, ≥50%, and ≥75% reduction in DSF, and discontinuation due to AEs. Included trials mainly reported outcomes in terms of the clinically meaningful ≥50% response rate as it was the most used as a primary trial endpoint, due to its higher clinical usefulness. Although the definitions of drop seizures varied significantly between studies, in most cases drop seizures were defined as atonic or tonic seizures that led or could lead to falls. Details of availability of efficacy and safety outcomes in each trial are available in Appendix D.1.1.4.7. Table 14 provides a summary of included studies design and characteristics.

Table 14. Summary of study designs and characteristics

Study/trial name	Study design	Sample size	Population*	Intervention(s) and comparator(s)	Treatment duration	ASM-related inclusion/ exclusion criteria	Outcome(s) reported	
							Efficacy	Safety
Knupp, 2022 (15) Secondary publications (80, 81, 98) Study1601 (NCT03355209)	Phase 3, double-blind, placebo-controlled RCT	263	Mixed	Fenfluramine (0.2 or 0.7 mg/kg) vs. placebo	14 weeks Titration: 2 weeks Maintenance: 12 weeks	✗	✓ **	✓
Devinsky, 2018 (88) Secondary publications (72, 99-101)} GWPCARE3 (NCT02224560)	Phase 3, double-blind, placebo-controlled RCT	225	Mixed	Cannabidiol (10 or 20 mg/kg) vs. placebo	14 weeks Titration: 2 weeks Maintenance: 12 weeks	**Inclusion:** Patients taking between 1–4 ASMs	✓	✓
Thiele, 2018 (89) Secondary publications (72, 99-102) GWPCARE4 (NCT02224690)	Phase 3, double-blind, placebo-controlled RCT	171	Mixed	Cannabidiol (20 mg/kg) vs. placebo	14 weeks Titration: 2 weeks Maintenance: 12 weeks	Inclusion: Patients taking 1–4 ASMs	✓	✓
Ohtsuka, 2014 (90) Secondary publications (97) E2080-J081-304 (NCT01146951)	Double-blind, placebo-controlled RCT	59	Mixed	Rufinamide (1000 to 3200 mg) vs. placebo	12 weeks Titration: 2 weeks Maintenance: 10 weeks	✗	✓	✓ †
Ritter, 1993 (91)	Placebo-controlled RCT	73	Mixed	Felbamate (45 mg/kg) vs. placebo	10 weeks Titration: 2 weeks Maintenance: 8 weeks	**Inclusion:** Patients taking no more than 2 ASMs	✓	✓
Motte, 1997 (93)	Double-blind, placebo-controlled RCT	169	Mixed	Lamotrigine (100 to 400 mg) vs. placebo	16 weeks Titration: 6 weeks Maintenance: 10 weeks	**Exclusion:** Patients receiving more than 3 ASMs	✓	✓

Study/trial name	Study design	Sample size	Population*	Intervention(s) and comparator(s)	Treatment duration	ASM-related inclusion/ exclusion criteria	Outcome(s) reported	
							Efficacy	Safety
Ng, 2011 (83) **Secondary publications(103, 104)** **OV-1012 (NCT00518713)**	Phase 3, double-blind, dose comparison RCT	238	Mixed	Clobazam (0.25 or 0.50 mg/kg) vs. placebo	15 weeks Titration: 3 weeks Maintenance: 12 weeks	✗	✓	✓
Sachedo, 1999 (94)	Double-blind, placebo-controlled RCT	98	Mixed	Topiramate (6 mg/kg) vs. placebo	11 weeks Titration: 3 weeks Maintenance: 8 weeks	**Inclusion:** Patients being maintained on 1–2 standard ASMs	✓	✓
Glauser, 2008 (95) **Secondary publications (105, 106)** **Study 022**	Phase 3, double-blind, placebo-controlled RCT	139	Mixed	Rufinamide (45 mg/kg) vs. placebo	12 weeks Titration: 2 weeks Maintenance: 10 weeks	**Inclusion:** Patients having a fixed-dose regimen of 1–3 concomitant ASMs **Exclusion:** Patients receiving more than 3 ASMs	✓ **	✓ **
Jensen, 1994 (92)	Placebo-controlled RCT	73	NR	Felbamate (45 mg/kg) vs. placebo	10 weeks Titration: 2 weeks Maintenance: 8 weeks	✗	✓	✗

**Mixed denotes paediatric and adult, additional information on the study population (i.e., inclusion/exclusion criteria) is provided in Appendix D.*
***Subgroup data extracted*
†Long-term data extracted
Note: green highlighted availability of evidence and red represents data not available.
Abbreviations: kg, Kilogram; mg, Milligram; NR, Not Reported; RCT, Randomised Controlled Trial

B.2.9.2.2 Comparison of patient baseline characteristics

The baseline characteristics of patients enrolled in all trials included in the NMA were analysed and plotted to assess the variations across studies. The Grubbs' test was used to identify outliers (107). The Grubbs' test, or the extreme studentised deviant (ESD) method, is based on a test statistic (Z) that corresponds to a p-value that represents the likelihood of detecting a data point as an outlier, assuming the underlying data are normally distributed.

The characteristics assessed included age, sex, ethnicity, median seizure frequency, median number of previous ASM, DSF at baseline and the number of concurrent ASMs. Age, sex, and ethnicity were the most reported patient characteristics across studies. In terms of patients' age, all studies included both paediatric and adult patients. They all reported mean age except for one felbamate trial (92). The mean age value reported across studies was 13 years old, ranging from 9.6 to 16 years. The mean age was randomly distributed around the overall mean of the studies. Age was unlikely to cause a major violation of the transitivity assumption. All studies reported on sex by providing the proportion of male patients except for 1 felbamate trial. The mean value reported across studies was 60%, ranging from 50% to 73%. Sex was randomly distributed around the overall mean of the studies. Sex was also unlikely to cause a major violation of the transitivity assumption. Finally, with respect to ethnicity, studies provided the proportion of white patients which was randomly distributed around the mean of 83%, with values ranging from 56% to 94%. The clobazam trial had the lowest proportion of white patients.

Seven studies reported median seizure frequency. The mean value was 313, ranging from 68 to 1,617 seizures. The felbamate trial (91) had a very high baseline number of seizures compared to the other trials, which was considered an outlier. Since baseline seizure frequency (all seizures) may have a major impact on treatment outcomes, the felbamate trial was excluded from the NMA. There were 5 studies that reported DSF at baseline. The mean value across studies was 78.5 per month, ranging from 46.4 to 98.3 drop seizures.

Only the fenfluramine, cannabidiol, and felbamate trials (15, 89, 91) reported the median number of previous ASMs. The restricted availability of data for the number of previous ASMs limited any further assessment of this characteristic. Finally, only the fenfluramine and cannabidiol trials (15, 88, 89) reported median concurrent ASM information, each with a median of 3 ASMs. Although concomitant ASMs may have been an important factor for treatment outcomes, the existing data for the number of concomitant ASMs did not allow for adjustment in the NMA.

The baseline characteristics of patients of included trials are presented in Table 15.

Table 15. Patient baseline characteristics

Author, year (study name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF#
Knupp, 2022(15) Study 1601 NCT03355209	Fenfluramine (0.2 mg/kg) (n = 87)	13 (3–35) [paediatrics + adults]	46 (52.0)	75%	42.4 (20.9)	7	3	106	85
	Fenfluramine (0.7 mg/kg) (n = 89)	13 (2–35) [paediatrics + adults]	54 (62.0)	80%	42.2 (21.4)	8	3	111	83
	Placebo (n = 87)	13 (2–35) [paediatrics + adults]	46 (53.0)	82%	43.9 (20.7)	7	3	68	53
Devinsky, 2018(88) GWPCARE3 NCT02224560	Cannabidiol (10 mg/kg) (n = 73)	15.4* (9.5) [paediatrics + adults]	40 (55.0)	84.9%	44.3 (26.2)	6	3	165	86.9
	Cannabidiol (20 mg/kg) (n = 77)	16* (10.8) [paediatrics + adults]	45 (59.0)	88.2%	41 (20.6)	6	3	174.3	85.5
	Placebo (n = 76)	15.3* (9.3) [paediatrics + adults]	44 (58.0)	90.8%	45.7 (23.2)	6	3	180.6	80.3
Thiele, 2018(89) GWPCARE4 NCT02224690	Cannabidiol (20 mg/kg) (n = 86)	14.2 (NR) [paediatrics + adults]	45 (52.0)	87%	41.6 (21.5)	6	3	144.6	71.4
	Placebo (n = 85)	13.3 (NR) [paediatrics + adults]	43 (51.0)	93%	39.6 (23)	6	3	176.7	74.7
Ohtsuka, 2014(90) E2080-J081-304	Rufinamide (1000–3200 mg) (n = 28)	16.0* (7.1) [paediatrics + adults]	17 (60.7)	✗	39.0 kg (19.5)	✗	✗	253.0	✗

Author, year (study name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF[#]
NCT01146951	Placebo (n = 30)	13.9* (6.1) [paediatrics + adults]	19 (63.3)	X	40.9 kg (18.0)	X	X	296.7	X
Ritter, 1993(91)	Felbamate (45 mg/kg) (n = 37)	12* (SD: NR) [paediatrics + adults]	27	X	37 kg (SD: NR)	8	≥2[†]	1,617**	X
	Placebo (n = 36)	14* (SD: NR) [paediatrics + adults]	24	X	40 kg (SD: NR)	**8**	≥2[†]	716**	X
Motte, 1997(93)	Lamotrigine (100–400 mg) (n = 79)	9.6* (5.2) [paediatrics + adults]	54 (68.0)	94%	32.5 kg (18.1)	X	≤3[†]	X	14.5[#¤]
	Placebo (n = 90)	10.9* (5.9) [paediatrics + adults]	45 (50.0)	**93%**	34.3 kg (19.7)	X	**≤3[†]**	X	11.6[#¤]
Ng, 2011(83) OV-1012 NCT00518713	Clobazam (0.25 mg/kg) (n = 58)	10.9* (7.2) [paediatrics + adults]	36 (62.1)	56.9%	33.6 kg (22.6)	X	X	X	40.9[#¤]
	Clobazam (0.50 mg/kg) (n = 62)	14.1* (10.4) [paediatrics + adults]	36 (58.1)	56.5%	35.1 kg (20.3)	X	X	X	23.5[#¤]
	Clobazam (1.0 mg/kg) (n = 59)	11.7* (8.5) [paediatrics + adults]	34 (57.6)	62.7%	34.7 kg (22.1)	X	X	X	28.9[#¤]
	Placebo (n = 59)	13.0* (9.2) [paediatrics + adults]	38 (64.4)	71.2%	36.5 kg (22.2)	X	X	X	35.5[#¤]

Author, year (study name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF[#]
Sachedo, 1999(94)	Topiramate (6 mg/kg) (n = 48)	11.2* (SD: NR) [paediatrics + adults]	28	✗	36.7 kg (19.0)	✗	✗	267	90
	Placebo (n = 50)	11.2* (SD: NR) [paediatrics + adults]	25	✗	31.6 kg (17.8)	✗	✗	244	98
Glauser, 2008(95) Study 022	Rufinamide (45 mg/kg) (n = 74)	13 (4.0–35.0) [paediatrics + adults]	46 (62.2)	83.8%	35.9 kg (15.5–138.5)	✗	1-3[†]	290	92
	Placebo (n = 64)	10.5 (4.0–37.0) [paediatrics + adults]	40 (62.5)	82.8%	33.5 kg (16.2–86.0)	✗	1-3[†]	205	92.5
Jensen, 1994(92)	Felbamate (45 mg/kg)	✗	✗	✗	✗	✗	✗	✗	✗
	Placebo	✗	✗	✗	✗	✗	✗	✗	✗

**Mean value*
*** Reported as average seizure frequency. Timepoint unclear.*
[†]Reported as study inclusion criteria. Median value at baseline not reported.
[#] All baseline values are 28-day median frequencies, except values from Motte et al; 1997 and Ng et al. 2011 which report weekly values
Abbreviations: ASM, Anti-seizure Medication; DSF, Drop Seizure Frequency; GTC, Generalised Tonic-Clonic; kg, Kilogram; mg, Milligram; SD, Standard Deviation.

B.2.9.2.3 Feasibility assessment conclusion

Overall, the 10 included trials were similar in trial design and patient selection criteria, with age and sex distributed relatively close to the overall mean. One felbamate trial was excluded due to high baseline seizure frequency (all seizures) which may have had a major impact on treatment outcomes in the NMA analysis (92). A clobazam trial was identified as having high risk of bias mainly due to the high drop-out rate in this trial (83). However, it is unlikely that this would materially impact the comparability of this trial in the NMA, and the trial was not excluded from the analyses. This has resulted in a total of 9 trials included in the analysis. Among the ASM trials assessed, only the fenfluramine trial and 2 cannabidiol trials reported all key patient characteristics: baseline seizure frequency, number of prior ASMs used, and number of concomitant ASM use (Table 16). Additionally, these 3 trials had low risk of bias, and reported ≥25/50/75% response rate of DSF required for the health economic modelling. As a result, a base case with a network including only fenfluramine (FFA), cannabidiol (CBD), and placebo (PBO) (FFA-PBO-CBD) was analysed. The broader network was deemed inappropriate for comparison as most outcomes of interest were not available in the other included trials included.

ITT populations (consisted of patients on different concomitant medications) from the fenfluramine and cannabidiol trials were used in the base case. The base case analyses were based on outcome data from T+M period for the ITT population in each trial, unless a specific outcome was only reported in a non-ITT population.

Table 16. Summary of feasibility assessment

Author, Year	Interventions	Risk of bias^	Transitivity assessment*			Reported 25/50/75% response rate†	NMA base case
			Baseline seizure frequency	Number of prior ASMs used	Number of concomitant ASM use		
Knupp, 2022	Fenfluramine (0.7 mg/kg) Placebo	Low	✓	✓	✓	✓	●
Devinsky, 2018	Cannabidiol (10 mg/kg) Cannabidiol (20 mg/kg) Placebo	Low	✓	✓	✓	✓	●
Thiele, 2018	Cannabidiol (20 mg/kg) Placebo	Low	✓	✓	✓	✓	●
Ohtsuka, 2014	Rufinamide (45mg/kg) Placebo	Some concern	✓	NR	NR	✓	
Ritter, 1993	Felbamate (45mg/kg) Placebo	Some concern	✓	✓	NR	NR	
Motte, 1997	Lamotrigine (100-400mg) Placebo	Some concern	NR	NR	NR	NR	
Ng, 2011	Clobazam (0.25 mg/kg) Clobazam (0.50mg/kg) Clobazam (1.0mg/kg) Placebo	High	NR	NR	NR	✓	
Sachedo, 1999	Topiramate (6mg/kg) Placebo	Low	✓	NR	NR	NR	
Glauser, 2008	Rufinamide (45mg/kg) Placebo	Low	✓	NR	NR	NR	
Jensen, 1994	Felbamate (45mg/kg) Placebo	Low	NR	NR	NR	NR	Excluded due to high baseline seizure frequency

**This table reflects the data availability for the NMA feasibility assessment*
^Risk of bias was assessed using Cochrane assessment tool 2.0
†25/50/75% response rate of drop seizure was required in the health economics modelling
Abbreviations: kg, Kilogram; mg, Milligram; NMA, Network Meta-Analysis, NR, Not Reported.

B.2.9.3 Methods of the NMA

B.2.9.3.1 Trial data used in the base case (selected endpoints)

In the fenfluramine trial, Study 1601, the primary outcomes were captured through the 14-week treatment period (2-week titration and 12-week maintenance period). Since trials for many other ASMs have used different lengths of treatment duration, outcomes captured between 10- and 20-week timepoints were considered in this NMA. Selected outcomes of interest from the NMA are listed in Table 17 below.

Table 17. Selected outcomes of interest from the network meta-analysis

NMA outcome
Median percent reduction in frequency of GTC seizures
≥25% reduction in drop seizure frequency
≥50% reduction in drop seizure frequency
≥75% reduction in drop seizure frequency
Discontinuation due to AEs

Abbreviations: AEs, Adverse Events; GTC, Generalised Tonic-Clonic; NMA, Network Meta-Analysis.

(i) Statistical methods

NMAs were conducted using the Bayesian framework on each of the continuous or binary outcomes of interest (108, 109). NMA produces estimates of the relative effects between any pair of treatments in the network, and also allows estimation of the ranking and hierarchy of interventions (110). The ITT population of the selected trials was used unless a specific outcome was only reported in a non-ITT population.

Continuous outcomes

Continuous outcomes were analysed using contrasted outcome measures with the associated confidence intervals (CI), e.g., estimated median differences from placebo were calculated using the Hodges-Lehmann estimate (15). Identity link was used to estimate the mean difference (MD) between treatments.

For trials with more than two arms, the SE of the placebo arm was required as this determined the covariance of the differences. If interquartile range (IQR) was reported instead of SE, SD was first estimated using the IQR using the formula provided in the Cochrane Handbook:

$$SD \approx \frac{q3 - q1}{1.35}$$

where q3 is the third quartile and q1 is the first quartile from the interquartile range (111). SE was calculated using the SD and the sample size. If neither SE nor SE derived from IQR were available, the average SD of the placebo arms from other trials was used to impute the SE.

Binary outcomes

Binary outcomes were analysed using arm-level data consisting of the total number of patients and number of patients with events. If the number of patients with events was zero for one or more arms in a trial, no data adjustment or imputation was considered to correct the zero values, and the NMA with that trial included was considered infeasible. Log-binomial model was used to estimate the risk ratio (RR) between treatments.

RR represents the probability of having an event in 1 treatment group versus the probability of having an event in the comparator group. An RR greater than 1 indicates a higher probability of having events in the treatment group compared to the comparator group, while an RR of less than 1 indicates a lower probability in the treatment group. RR was used over odds ratio (OR) as it provides statistics that are easier to interpret and can be directly implemented in health economic models.

Fixed effects and random effects models

For each outcome and each scenario analysed, both fixed effects and random effects models were performed (Table 18). Placebo was used as the reference treatment in the analysis. The fixed effects models were presented as a base case to accommodate the small number of studies and simple networks. The random effects models were reported as supplementary results in the appendix section D1.3. In most analyses conducted in this study, fixed-effects models had better model fit (lower or similar deviance information criterion (DIC)) than random-effect models. Additionally, fixed-effects models had estimates that were closer to the trial results, compared with random-effects models, which may have inflated uncertainty.

Table 18. NMA models for continuous and binary outcomes

Outcome type	Likelihood	Link	Model	Effect measure
Continuous	Normal	Identity	Fixed effects	Mean difference
			Random effects	Mean difference
Binary	Binomial	log	Fixed effects	Risk ratio
			Random effects	Risk ratio

All analyses were performed using R version 4.2.2 within the R Studio environment (112). The “gemtc” package (version 1.0-1) was used to conduct the NMA using Bayesian methods, with 50,000 burn-in iterations, 100,000 actual iterations, and a thinning factor of 10 (113). Model convergence was assessed using trace plots and Gelman-Rubin-Brooks plots of the potential scale reduction factor with a minimum cut-off below 1.05 by the final iteration.

(ii) Covariate adjustment

In the analysis of RCTs, adjustments for baseline covariates can lead to a significant rise in power when the covariates are highly predictive (114). Hernández et al. found that increases in power of greater than 20% are possible and this has been demonstrated with actual datasets in simulation studies (115) and confirmed through an RCT in Turner el. 2012(116). Other benefits of adjustment include protection against coincidental imbalances in important baseline covariates (117), and

keeping correct type I error rates when the covariates have been used in the randomisation process (118).

There are several techniques available to adjust baseline characteristics in a trial, however, not all of them are possible. The most relevant technique to use in this analysis is meta-regression. However, meta-regression requires a sufficiently large number of trials for each regimen assessed, which, in the case of this analysis, was not possible due to the limited number of studies available for each regimen. Therefore, no covariate adjustment was used in this analysis.

B.2.9.4 Results of the NMA of fenfluramine versus cannabidiol

B.2.9.4.1 Trial networks

The rationale to select the relevant trial networks to derive comparative data of fenfluramine versus cannabidiol is detailed below. There were two key constraints to address. First, ensuring that these comparative results versus cannabidiol were matching the cannabidiol EMA label, which requires patients to receive clobazam concomitantly. Second, securing results for all the clinical outcomes of interest. These outcomes could then be used to populate the submission's health economic analyses.

In the UK, cannabidiol's approved indication is for treating LGS patients in conjunction with clobazam (CBD w CLB) (72). However, the base case clinical trial ITT patient population included a broader treatment scope with patients not systematically receiving clobazam with cannabidiol. Providing that subgroup analyses were reported for the CBD w CLB patients as part of the EMA dataset, this specific patient population was preferred to derive comparative data. An additional constraint was that these EMA data did not include safety data nor the ≥25% reduction in DSF, which is needed for the economic analysis. To address this gap, a second NMA analysis was performed on CBD w CLB data, based on additional key comparative CBD w CLB data published by the German HTA body (Federal Joint Committee of Germany - *Gemeinsamer Bundesausschuss* (GBA)). Unlike the EMA ITT dataset, these GBA documents contain some more CBD w CLB subgroup data on ≥ 25 / 50 / 75% reduction of convulsive seizures. Since definition of drop seizure vary, convulsive seizures were considered similar to drop seizures in this data set. Finally, since neither the median reduction in frequency of GTC seizures nor the discontinuation due to AEs were available using GBA CBD w CLB data, the ITT dataset was used by default for these two outcomes. A summary of the clinical outcomes available as well as the selected trial network for the analysis are summarised in Table 19 and Table 20, respectively.

Table 19. Summary of the efficacy and safety outcomes available

NMA outcome	FFA-PBO-CBD (ITT)	CBD w CLB (EMA)	CBD w CLB (GBA)
Median percent reduction in frequency of GTC seizures	Yes	No	No
≥25% reduction in drop seizure frequency	Yes	No	Yes
≥50% reduction in drop seizure frequency	Yes	Yes	Yes
≥75% reduction in drop seizure frequency	Yes	Yes	Yes
Discontinuation due to adverse events	Yes	No	No

Notes: Shaded cells denote outcomes selected for base case NMA analysis.
Abbreviations: CBD w CLB, Cannabidiol with Clobazam; EMA, European Medicine Agency; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); GTC, Generalised Tonic-Clonic; ITT, Intention-to-Treat; NMA, Network Meta-Analysis.

Table 20. Network meta-analysis selected outcomes with their corresponding trial network

NMA outcome	Corresponding trial network
Median percent reduction in frequency of GTC seizures	ITT data: FFA-PBO-CBD
≥25% reduction in drop seizure frequency	GBA data: (FFA-PBO-CBD w CLB (GBA))
≥50% reduction in drop seizure frequency	GBA data: (FFA-PBO-CBD w CLB (GBA))
≥75% reduction in drop seizure frequency	GBA data: (FFA-PBO-CBD w CLB (GBA))
Discontinuation due to adverse events	ITT data: FFA-PBO-CBD

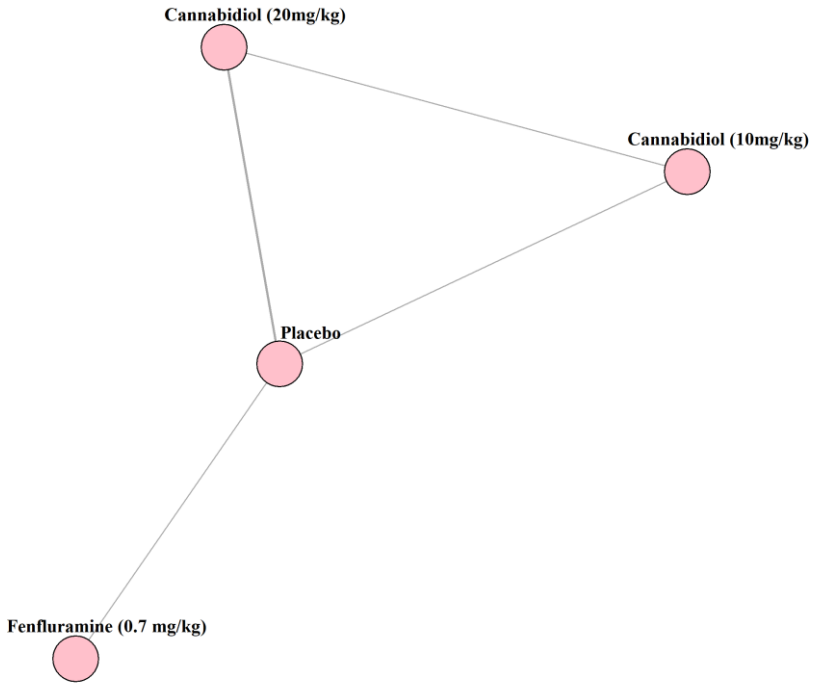
Abbreviations FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; CBD w CLB, Cannabidiol with Clobazam; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); GTC, Generalised Tonic-Clonic; ITT, Intention-to-Treat.

B.2.9.4.2 Fenfluramine versus cannabidiol: selected efficacy and safety outcomes results

(i) Median percent reductions in frequency of GTC seizures (FFA-PBO-CBD)

The network of evidence for median percent reductions in frequency of GTC seizures is shown in Figure 17. A total of 3 studies with 4 unique treatments and 290 patients were included in the analysis. The relative effect estimates showed that fenfluramine (0.7 mg/kg), cannabidiol (10 mg/kg), and cannabidiol (20 mg/kg) were significantly superior versus placebo (Figure 18). Using surface under the cumulative ranking curve (SUCRA), fenfluramine (0.7 mg/kg) was ranked first among the four treatments (Table 21).

Figure 17. Network diagram for median percent reductions in frequency of GTC seizures (FFA-PBO-CBD)



Abbreviations: kg, Kilogram; mg, Milligram.

Figure 18. Forest plot for median percent reductions in frequency of GTC seizures, fixed effects (FFA-PBO-CBD)

Abbreviations: CrI, Credible Interval; GTC, Generalised Tonic-Clonic; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; MD, Mean Difference.
Note: All credible intervals are overlapping

Table 21. Mean difference, probability of being the best, and SUCRA for median percent reductions in frequency of GTC seizures, fixed effects (FFA-PBO-CBD)

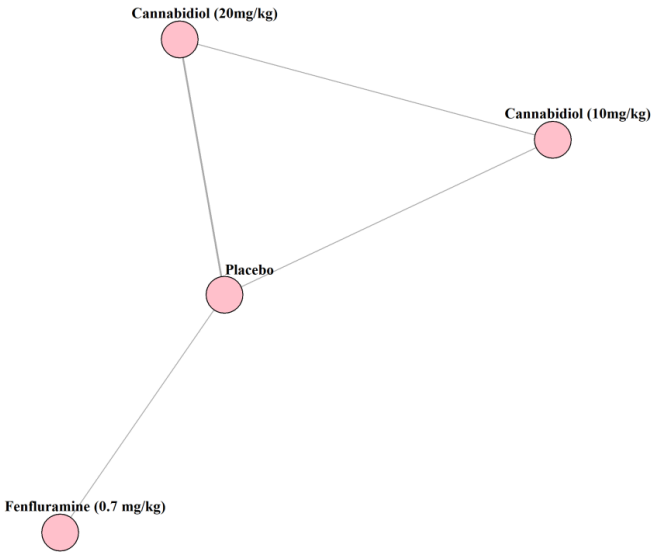
Treatment	Mean difference with 95% CrI – (vs Placebo)	Probability of being the best	SUCRA
Fenfluramine (0.7 mg/kg)	[redacted]	[redacted]	[redacted]
Cannabidiol (10 mg/kg)	[redacted]	[redacted]	[redacted]
Cannabidiol (20 mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	Reference	[redacted]	[redacted]

Abbreviations: CrI, Credible Interval; GTC, Generalised Tonic-Clonic; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; kg, Kilogram; mg, Milligram; SUCRA, Surface Under the Cumulative Ranking.
Note: All credible intervals are overlapping

(ii) ≥25%, ≥50% and ≥75% reduction in DSF (FFA-PBO-CBD w CLB (GBA))

The network of evidence for ≥25%, ≥50% and ≥75% reduction in DSF is shown in Figure 19. A total of 3 studies with 4 unique treatments and 368 patients were included in the analysis. The relative effect estimates showed that fenfluramine (0.7 mg/kg), cannabidiol (10 mg/kg), and cannabidiol (20 mg/kg) were significantly superior versus placebo except for the ≥75% reduction in DSF where solely cannabidiol (20 mg/kg) was significantly superior versus placebo (Figure 20, Figure 21, Figure 22). Using SUCRA, fenfluramine (0.7 mg/kg) was ranked first among the four treatments except for the ≥75% reduction in DSF where it was ranked third (Table 22).

Figure 19. Network diagram for ≥25%, ≥50% and ≥75% reduction in DSF (FFA-PBO-CBD w CLB (GBA))



Abbreviations: kg, Kilogram; mg, Milligram.

Figure 20. Forest plot for ≥25% reduction in drop seizure frequency, fixed effects (FFA-PBO-CBD w CLB (GBA))

Abbreviations: CrI, Credible Interval; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; CBD w CLB, Cannabidiol with Clobazam; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); kg, Kilogram; mg, Milligram; RR, Risk Ratio.
Note: All credible intervals are overlapping.

Figure 21. Forest plot for ≥50% reduction in DSF, fixed effects (FFA-PBO-CBD w CLB (GBA))

Abbreviations: CrI, Credible Interval; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; CBD w CLB, Cannabidiol with Clobazam; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); kg, Kilogram; mg, Milligram; RR, Risk Ratio.
Note: All credible intervals are overlapping.

Figure 22. Forest plot for ≥75% reduction in DSF, fixed effects (FFA-PBO-CBD w CLB (GBA))

Abbreviations: CrI, Credible Interval; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; CBD w CLB, Cannabidiol with Clobazam; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); RR, Risk Ratio.
Note: All credible intervals are overlapping.

Table 22. Risk ratios, probability of being the best, and SUCRA for ≥25%, 50% and 75% reduction in DSF, fixed effects FFA-PBO-CBD w CLB (GBA))

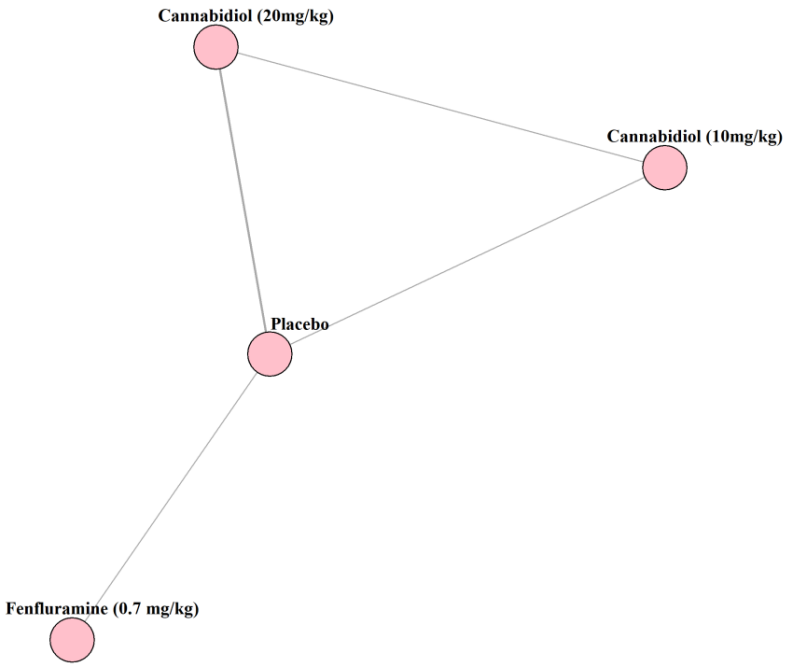
Treatment	Risk ratio with 95% CrI – (vs Placebo)	Probability of being the best	SUCRA
FFA-PBO-CBD w CLB (GBA)			
≥ 25% reduction in DSF			
Fenfluramine (0.7mg/kg)	[redacted]	[redacted]	[redacted]
CBD w CLB (10mg/kg)	[redacted]	[redacted]	[redacted]
CBD w CLB (20mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	-	[redacted]	[redacted]
≥ 50% reduction in DSF			
Fenfluramine (0.7mg/kg)	[redacted]	[redacted]	[redacted]
CBD w CLB (10mg/kg)	[redacted]	[redacted]	[redacted]
CBD w CLB (20mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	-	[redacted]	[redacted]
≥ 75% reduction in DSF			
Fenfluramine (0.7mg/kg)	[redacted]	[redacted]	[redacted]
CBD w CLB (10mg/kg)	[redacted]	[redacted]	[redacted]
CBD w CLB (20mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	-	[redacted]	[redacted]

Abbreviations: CrI, Credible Interval; DSF, Drop Seizure Frequency; FFA-PBO-CBD, fenfluramine-Placebo-Cannabidiol; CBD w CLB, Cannabidiol with Clobazam; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); kg, Kilogram; mg, Milligram; RR, Risk Ratio; SUCRA, Surface Under the Cumulative Ranking. Note: All credible intervals are overlapping.

(iii) Discontinuation due to AEs (FFA-PBO-CBD)

The network of evidence for discontinuation due to AEs is shown in Figure 23. A total of 3 studies with 4 unique treatments and 570 patients were included in the analysis. The relative effect estimates showed that cannabidiol (20 mg/kg) had significantly higher probability of discontinuation due to AEs versus placebo (Figure 24). Using SUCRA, cannabidiol (20 mg/kg) was ranked last among the four treatments (Table 23).

Figure 23. Network diagram for discontinuation due to AEs (FFA-PBO-CBD)



Abbreviations: kg, Kilogram; mg, Milligram

Figure 24. Forest plot for discontinuation due to AEs, fixed effects (FFA-PBO-CBD)

Abbreviations: AEs, Adverse Events; CrI, Credible Interval; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; kg, Kilogram; mg, Milligram; RR, Risk Ratio.
Note: All credible intervals are overlapping.

Table 23. Risk ratios, probability of being the best, and SUCRA for discontinuation due to AEs, fixed effects (FFA-PBO-CBD)

Treatment	Risk ratio with 95% CrI – (vs Placebo)	Probability of being the best	SUCRA
Fenfluramine (0.7 mg/kg)	[redacted]	[redacted]	[redacted]
Cannabidiol (10 mg/kg)	[redacted]	[redacted]	[redacted]
Cannabidiol (20 mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	Reference	[redacted]	[redacted]

Abbreviations: AEs, Adverse Events; CrI, Credible Interval; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; kg, Kilogram; mg, Milligram; SUCRA, Surface Under the Cumulative Ranking.
Note: All credible intervals are overlapping.

(iv) Results summary

As cannabidiol is the main comparator to fenfluramine, a summary of the ITT scenario results is shown in Table 24. The effect measures of the fixed effects model are presented for the key outcomes used in the economic analysis. In the base case analysis, the assessed efficacy outcomes favoured fenfluramine (0.7 mg/kg) significantly compared to placebo.

Table 24. Summary of ITT scenario results

Outcome	Effect measure	Preferred direction	Fenfluramine (0.7 mg/kg)	Cannabidiol (10 mg/kg)	Cannabidiol (20 mg/kg)
			vs Placebo		
Median percent reductions in frequency of GTC seizure	MD				
Discontinuation due to AE	RR				

Abbreviations: AE, Adverse Event; ITT, Intention-to-Treat; GTC, Generalised Tonic-Clonic; MD, Mean Difference; kg, Kilogram; mg, Milligram; RR, Risk Ratio; ↘, the lower the better; ↗, the higher the better.
Note: All credible intervals are overlapping

In the GBA data analysis, the assessed efficacy outcomes favoured fenfluramine (0.7 mg/kg) significantly compared to placebo, with the exception of "≥ 75% reduction in DSF" in which the result numerically favoured cannabidiol 20mg/kg with clobazam (Table 25).

Table 25. Summary of results for (FFA-PBO-CBD w CLB (GBA)) network

Outcome	Effect measure	Preferred direction	Fenfluramine (0.7 mg/kg)	CBD w CLB (10 mg/kg)	CBD w CLB (20 mg/kg)
			vs Placebo		
≥ 25% reduction in drop seizure frequency	RR				
≥ 50% reduction in drop seizure frequency	RR				
≥ 75% reduction in drop seizure frequency	RR				

Abbreviations: RR, Risk Ratio; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; CBD w CLB, Cannabidiol with Clobazam; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); kg, Kilogram; mg, Milligram; ↘, the lower the better; ↗, the higher the better.
Note: All credible intervals are overlapping

This analysis was compared to the existing NMA analyses for the treatment of LGS. Four recently published NMAs were identified, Zhang et al. 2022, Devi et al. 2022, and Damavandi et al. 2023, and Talwar et al. 2023 (119-122). Although they provided some external validation for the networks, none were fit for the purpose of comparing fenfluramine with its comparators. Zhang et al. 2022 and Devi et al. 2022 did not include fenfluramine in the analyses and used a frequentist approach. Zhang et al. 2022 did not assess the transitivity assumption, pooled different dosages for the same treatment, and only reported ≥50% reduction in drop seizures as the efficacy outcome. Devi et al. 2022 did not assess the baseline drop seizure / total seizure frequency of the included studies and did not analyse percent reduction in drop seizures as a continuous outcome. Damavandi et al. 2023 only summarised evidence for fenfluramine and did not compare it to the other ASMs, while Talwar et al. 2023 only synthesised the efficacy and safety evidence of cannabidiol. Therefore, these four NMAs were not fit for the purpose of comparing fenfluramine to its comparators and the subsequent cost-effectiveness analysis but provided some external validation for the networks.

B.2.9.5 Conclusions of the NMA

This NMA provided a comprehensive assessment of the efficacy and safety of fenfluramine for the treatment of patients with LGS. Fenfluramine (0.7 mg/kg) outranked cannabidiol (10 and 20 mg/kg) in three of the four efficacy outcomes and consistently resulted in higher probability of reaching the clinically meaningful ≥50% reduction in DSF (including GTC or convulsive seizures) compared with other ASMs, although results were not statistically significant. Moreover, fenfluramine (0.7 mg/kg) showed a better safety profile with less probability of discontinuation due to AEs compared to cannabidiol (20mg/kg).

However, the NMA results should be interpreted with caution due to network limitations. Most important limitations are differences in placebo responses across trials, which might be attributed to unmeasured/unreported effect modifiers, and statistical non-significance of numerical differences between ASMs (see section B2.9.6).

Both the fenfluramine and cannabidiol trials reported outcome data for a maintenance period only of 12 weeks. Without the titration period, the results from the maintenance alone may have differed slightly from the titration + maintenance results in both trials. Therefore, a sensitivity analyses was performed to assess the outcomes with maintenance only data. Full details are provided in appendix section D.1.4.

This NMA is novel, being the first to include fenfluramine as a comparator. Further research, increasing the availability of more studies per regimen, could improve the precision of the NMA estimates and allow for adjustments of important effect modifiers.

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

This NMA is the first to include fenfluramine in the comparison of ASMs for LGS under a Bayesian NMA framework. Systematic criteria were developed to select the best comparative data for this rare disease. An extensive feasibility assessment was performed that evaluated differences in the distribution of study and patient characteristics across trials, and based on these findings, nine RCTs were included but the NMA focused on fenfluramine-cannabidiol-placebo network as the broader network was deemed inappropriate for comparison in the feasibility assessment.

Despite conducting the feasibility assessment and applying robust methodologies, the current analyses had several inherent limitations. First, variation existed in placebo response across studies. It could not be determined if these differences were due to imbalances in prognostic variables or treatment effect modifiers, and the latter of which must be balanced across trials. The differences in placebo response could have been due to several reasons. The fenfluramine and cannabidiol trials were published in the past five years, while the lamotrigine and topiramate trials date to the late 1990s. Not only has the treatment landscape for LGS evolved during this span, but differences are likely in study populations, previous ASMs, and concomitant ASMs. For example, 27% of patients in the fenfluramine trial had previous cannabidiol use, while fenfluramine had not yet received regulatory approval when the two cannabidiol trials were conducted. In another example, in both the fenfluramine and cannabidiol trials, clobazam was used by approximately 40% of the patients as a concomitant medication, while clobazam was not available for LGS treatment at the time of the lamotrigine trial and topiramate trial. Additionally, the median number of previous

ASMs and concomitant ASMs were only reported by few trials; therefore, it was not possible to adjust for these characteristics. The base case analysis used those trials that reported previous and concomitant ASM use, where the numbers were similar.

Although the included studies seemed sufficiently comparable based on the patient characteristics reported, there was still likely to be some confounding. This NMA did not control for effect modifiers, since there were few studies and data for baseline characteristics were sparse. Not adjusting for important factors may bias the results, as relative treatment effects may vary by population. More advanced statistical techniques (e.g., matched-adjusted indirect comparison or simulated trial comparisons) may help reduce uncertainty, but they would limit the comparison to one at a time. The most relevant technique to adjust for baseline characteristics is meta-regression which requires a sufficiently large number of trials for each regimen assessed; the limited number of studies in the current analysis precluded the use of meta-regression. Therefore, no covariate adjustment was used in this analysis. Among the treatments analysed, there were relatively few included trials comparing the same treatments (mostly one trial per treatment), which meant that networks were sparse for some less well-reported outcomes. Most outcomes of interest were available in the fenfluramine and cannabidiol trials, but many were not available in the other trials included; data for the maintenance period only were limited to fenfluramine and cannabidiol. This limited the comparison of fenfluramine with the non-cannabidiol ASMs.

In the analysis of ≥25%/≥50%/≥75% reduction in DSF, a log-binomial model was used. Instead, a multinomial model could be used that considers the three response rate cut-offs at the same time and generates the absolute risk of each treatment. However, the multinomial model assumes that treatment effect is the same regardless of the cut-off; this assumption can be checked informally by examining the relative treatment effects at different cut-offs in each trial and to see if they are approximately the same (123). The RR of fenfluramine (0.7 mg/kg) vs placebo across the three cut-offs indicated that this assumption might be violated (Table 22).

A small difference was observed between the cannabidiol trial population and the CBD w CLB subpopulation. Compared with the ITT population of the cannabidiol trials, the number of previous ASMs was marginally lower in the cannabidiol plus clobazam post-hoc subpopulation. As a potential marker of refractory disease, a difference in number of previous ASMs may possibly further support that the subgroup receiving concomitant clobazam achieved slightly improved outcomes of seizure frequency and response rate relative to the ITT population from these trials.

Finally, the CBD w CLB subgroup from the cannabidiol trials was used because the EMA recommends cannabidiol use in conjunction with clobazam. However, the comparison of these subgroup data with the ITT population of the fenfluramine trial was limited by the potential break of randomisation of cannabidiol trials and the possible existence of unbalanced effect modifiers (e.g., previous ASMs usage and concomitant usage), which may result in biased findings.

B.2.10 Adverse reactions

During clinical development in LGS, fenfluramine showed a good safety and tolerability profile. Sustained retention rates in the use of fenfluramine during the OLE study supported the evidence that fenfluramine is a generally well tolerated ASM. No case of valvular heart disease nor pulmonary arterial hypertension was reported at any point. More details about adverse events from Study 1601 are reported in Appendix F.

B.2.10.1 Adverse reactions in Study 1601

B.2.10.1.1 Most common treatment-emergent adverse events (≥10%) in Study 1601

In Study 1601 (Table 26), most patients (212 of 263 [81%]) experienced a TEAE (78 of 87 patients [90%] in the 0.7-mg/kg/day fenfluramine group; 69 of 89 [78%] in the 0.2-mg/kg/day fenfluramine group; 65 of 87 [75%] in the placebo group).

The most common TEAEs included decreased appetite (59 of 263 [22%]), somnolence (33 of 263 [13%]), and fatigue (33 of 263 [13%]). More patients in the fenfluramine treatment groups than in the placebo group experienced decreased appetite (31 of 87 [36%] in the 0.7-mg/kg/day fenfluramine group; 18 of 89 [20%] in the 0.2-mg/kg/day fenfluramine group; 10 of 87 [11%] in the placebo group).

Table 26. Most common treatment-emergent adverse events (Study 1601)

	Fenfluramine 0.7 mg/kg/day (n=87)	**Fenfluramine** 0.2 mg/kg/day (n=89)	**Placebo** (n=87)	**Overall** (N=263)
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)
Diarrhoea, n (%)	11 (13)	10 (11)	4 (5)	25 (10)
Pyrexia, n (%)	7 (8)	9 (10)	10 (11)	26 (10)
Fatigue, n (%)	16 (18)	8 (9)	9 (10)	33 (13)
Vomiting, n (%)	7 (8)	12 (13)	5 (6)	24 (9)

Reference: Knupp et al. 2022 (15)
Abbreviations: kg, Kilogram; mg, Milligram; TEAE, Treatment Emergent Adverse Events.

B.2.10.1.2 Serious Adverse Events and treatment discontinuation in Study 1601

In Study 1601 (Table 27), more patients in the 0.7-mg/kg/day fenfluramine group (10 of 87 [11%]) compared with the 0.2-mg/kg/day fenfluramine group (4 of 89 [4%]) and the placebo group (4 of 87 [5%]) experienced 1 or more serious TEAE (15). One SUDEP was reported which was unrelated to fenfluramine use. No cases of valvular heart disease or pulmonary arterial hypertension were observed at any time during the trial (15). One patient (fenfluramine 0.7 mg/kg/day) had an end of study echocardiography read as mild aortic regurgitation, but subsequent diagnostic transoesophageal echocardiography revealed absent aortic regurgitation and a normal aortic valve (15).

The most frequent TEAEs leading to study withdrawal were seizure (3 patients in the 0.2-mg/kg/day fenfluramine group) and somnolence (3 patients in the 0.7-mg/kg/day fenfluramine group) (15).

Table 27. Serious TEAEs and treatment discontinuation (Study 1601)

Category	Fenfluramine 0.7 mg/kg/day (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Placebo (n=87)	Overall (N=263)
Patients with ≥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)

Reference: Knupp et al. 2022 (15)
Abbreviations: kg, Kilogram; mg, Milligram; TEAE, Treatment Emergent Adverse Events; AE, Adverse Event

B.2.10.2 Adverse reactions in OLE study

B.2.10.2.1 Most common treatment-emergent adverse events in OLE study

In the OLE study (Table 28), the majority of patients (203 of 247 [82.2%]) experienced a TEAE, most of which were mild or moderate in severity (188 of 247 [76.1%]). The most common TEAEs were decreased appetite (40 of 247 [16.2%]) and fatigue (33 of 247 [13.4%]) (12).

Table 28. Most common treatment-emergent adverse events OLE study

Category	N = 247
Any TEAE, n (%)	203 (82.2)
Decreased appetite, n (%)	40 (16.2)
Fatigue, n (%)	33 (13.4)
Nasopharyngitis, n (%)	31 (12.6)
Seizure, n (%)	27 (10.9)

Reference: Knupp et al. 2023 (12)
Abbreviations: TEAE, Treatment Emergent Adverse Events; SAE, Serious Adverse Events

B.2.10.2.2 Serious adverse events and treatment discontinuation

In the OLE study, forty of 247 patients (16.2%) experienced a serious TEAE, including nine patients (3.6%) with changes in seizure presentation, eight patients (3.2%) with status epilepticus, and five patients (2.0%) with pneumonia (12).

Twelve patients (4.9%) experienced a TEAE that led to study discontinuation, most commonly fatigue or change in seizure presentation (n=3, 1.2% each) and 94% of patients chose to continue receiving fenfluramine treatment (12). One patient died due to aspiration pneumonia, which was considered unrelated to fenfluramine.

Echocardiography revealed that no patient had developed valvular heart disease (VHD) or pulmonary arterial hypertension (PAH) by the interim analysis cut-off date (12):

- 2 patients in the LGS programme demonstrated instances of mild aortic regurgitation (AR) without the presence of VHD.
- Neither subject exhibited valvular morphological (or structural) changes, nor did findings progress to a higher grade of regurgitation.
- One of these patients had 2 diagnostic transoesophageal echocardiograms (a method with higher resolution than standard transthoracic ECHO); both patients demonstrated absent AR and normal valve structure.
- Both patients were examined by cardiologists, who concluded no VHD in either patient.
- Rates of mild AR observed in the study (2 of 247 [0.8%]) are consistent with those seen in the screening period prior to treatment with fenfluramine (3 of 335 [0.9%]).
- Both patients continue to be treated with fenfluramine without development of VHD.

B.2.10.3 Adverse events of special interest

Fenfluramine was previously marketed at significantly higher doses of 60-120mg/day as an appetite suppressant for the treatment of obesity but was withdrawn from the market over 20 years ago due to its reported association with valvular heart disease. Based on its known adverse event profile and mode of action, the incidence of adverse events of special interest (AESI) listed in Table 29 were identified for collection in the protocols of Study 1601 and OLE study interim analysis. Occurrence of lethargy, status epilepticus, and weight loss were generally of low prevalence. Decreased appetite was highest in fenfluramine 0.7mg/kg/day.

Table 29. Adverse events of special interest in Study 1601

Adverse event of special interest	Fenfluramine 0.7 mg/kg/day (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Placebo (n=87)
Somnolence, n (%)	15 (17.2)	9 (10.1)	9 (10.3)
Weight loss, n (%)	7 (8.0)	2 (2.2)	2 (2.3)
Decreased appetite, n (%)	31 (35.6)	18 (20.2)	10 (11.5)
Status epilepticus, n (%)	3 (3)	0 (0)	1 (1)
Lethargy, n (%)	5 (5.7)	2 (2.2)	2 (2.3)

Reference: Knupp et al. 2022 (15)
Abbreviations: kg, Kilogram; mg, Milligram; n, number of patients; TEAE, Treatment-emergent adverse event.

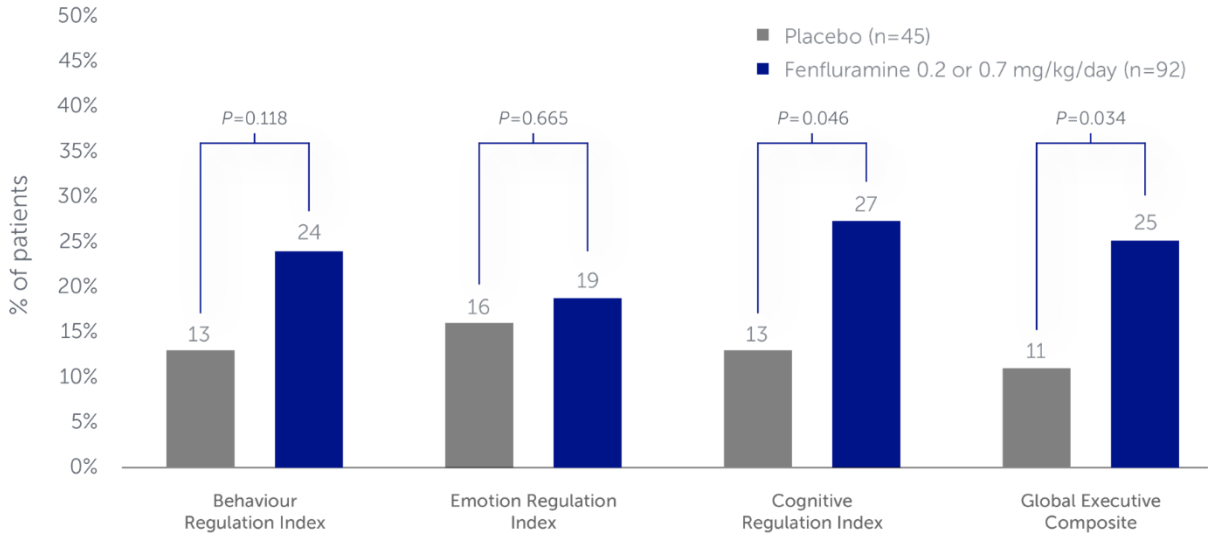
In the OLE study (12), weight changes from baseline ranged from weight loss of 22.4% to weight gain of 34.4%. Overall, body weight gain ≥7% of OLE baseline was reported at any visit for 32.4% of patients and body weight decrease ≥7% was reported for 17.0% of patients.

B.2.10.4 Other observations related to the cognition and executive function

Treatment with fenfluramine was not associated with clinically meaningful worsening in cognitive regulation index and global executive composite (Reliable Change Index (RCI) ≥80%) in any of the

BRIEF®2 indexes/composite T-scores compared to placebo (p>0.05). Indeed, in pooled analysis, including both 0.2 mg and 0.7 mg/kg dosing, significantly more children and young adults on fenfluramine showed clinically meaningful improvement in global executive functioning with specific improvement in the cognitive regulation index (124) (p<0.05; RCI ≥95% certainty) (Figure 25): Approximately twice as many children and young adults showed clinically meaningful improvement after fenfluramine than after placebo in the cognitive regulation index (27% vs. 13%) and global executive composite (25% vs. 11%).

Figure 25. Clinically meaningful improvement (RCI ≥95% certainty) in BRIEF®2 indexes/composite (pooled analysis including 0.2 and 0.7 mg/kg dose of fenfluramine)



Notes: Based on Bishop et al.2021 (124); p-values are active versus placebo; calculated by Somers' D. Highlighted p-values show statistical significance.
Abbreviations: BRI, Behavior Regulation Index; BRIEF®2, Behavior Rating Inventory of Executive Function®, Second Edition; CRI, Cognitive Regulation Index; ERI, Emotion Regulation Index; GEC, Global Executive Composite; kg, Kilogram; mg, Milligram; RCI, Reliable Change Index.

B.2.10.5 Confirmation of safety and tolerance observations from the Dravet syndrome (DS) safety data

As reported in fenfluramine SmPC (1), findings from Study 1601 (15) are consistent with the observed safety and tolerance outcomes in the DS indication. The most reported adverse reactions in DS were decreased appetite (44.2%), diarrhoea (30.8%), pyrexia (25.6%), fatigue (25.6%), upper respiratory tract infection (20.5%), lethargy (17.5%), somnolence (15.4%), and bronchitis (11.6%).

Long-term safety data is available from various studies, including the OLE study conducted in DS, which provided a 3-year follow-up (125). Retrospective and prospective observational studies have also contributed data with up to 5 years of follow-up (126, 127), while a prospective study provided follow-up data for up to 27 years (128). The collective findings from these studies indicate little uncertainty regarding the long-term safety of fenfluramine. Notably, there have been no clinically significant cases of cardiovascular or cardiopulmonary events observed in these studies. Furthermore, in the commercial setting, the requirement of routine echo monitoring and pharmacovigilance reporting has not identified any significant cases thus far.

B.2.11 Ongoing studies

The completion of the OLE study is expected for Q1 2025 (82).

B.2.12 Interpretation of clinical effectiveness and safety evidence

LGS is a rare, severe, highly complex DEE which begins in childhood and continues into adulthood. It causes significant developmental delay or loss of developmental skills, leading to substantial social difficulties and costs (37). The aim of current treatment is to reduce the impact of seizures on developmental comorbidities, and subsequently improve patient and caregiver's abilities to perform daily living activities and their quality of life (32).

Despite multiple currently approved ASMs, the condition remains largely uncontrolled in most patients. A high unmet need exists for additional treatment options with novel mechanisms of action and proven seizure control for LGS patients who have previously failed multiple ASMs.

B.2.12.1 Summary of clinical evidence base

The clinical efficacy and safety of fenfluramine as an add-on therapy to standard of care ASMs in LGS has been established through a robust clinical development programme. This includes a high-quality phase 3 RCT providing efficacy and safety data through 14 weeks of treatment exposure in children and young adults (Study 1601 [n=263] (15, 80)), and an OLE study providing long-term efficacy and safety data in 247 children and young adults with treatment periods up to 1 year (OLE study (12, 80)).

B.2.12.1.1 Efficacy and safety in phase 3 RCT and OLE study

Fenfluramine at its recommended maintenance dose of 0.7mg/kg/day provided substantial, significant reductions in mean DSF: -19.9 percentage points over placebo when added to standard of care ASMs (Study 1601) based on the HL estimate of the median difference in percentage (15). Fenfluramine demonstrated a meaningful treatment effect as add-on therapy in patients who were extensively pre-treated and are refractory/intolerant to multiple ASMs. Significantly more patients on fenfluramine than placebo achieved a clinically meaningful reduction in DSF of at least 50% in the RCTs: one quarter of patients (25%) achieved a ≥50% reduction in DSF with fenfluramine 0.7 mg/kg/day at Week 14 compared with 10% with placebo (p=0.02) (15). Furthermore, numerically more patients achieved a ≥75% reduction in DSF with fenfluramine 0.7 mg/kg/day at Week 14 compared with placebo (8% vs. 5% respectively). By one year, 1 in 2 patients had achieved ≥50% reduction in DSF (51%). and one quarter of patients experienced a ≥75% reduction in DSF (25%) (12).

Patients who experienced GTCs at baseline had a 45.7% reduction in GTC seizure frequency with fenfluramine over 14 weeks (15). Patients treated with placebo experienced an increase of 3.7%. This was significant compared with the placebo group (Estimated median difference -50.3 percentage points (95% CI: −76.7 to −23.8 percentage points; p<0.001).

Regarding the overall clinical condition of patients (as measured by the CGI-I), data from Study 1601 indicated that one quarter of fenfluramine-treated patients were much or very much improved as assessed by investigators with 14 weeks of treatment. Proportions increased through one year with 21 out of 80 patients rated by site investigators as very much or much improved, compared

with 5 out of 80 patients with placebo at Week 14. The proportion increased to 38% through 1 year of treatment as shown in the OLE trial (12, 15).

Fenfluramine was generally safe and well tolerated. The most commonly reported side effects of fenfluramine in clinical trials for both children and adults with LGS were decreased appetite, fatigue, somnolence, vomiting, and diarrhoea. These side effects were more frequently observed in patients taking fenfluramine compared to those on a placebo. Some patients also experienced weight loss, which was related to the dosage of fenfluramine. However, most patients regained weight over time while continuing the fenfluramine treatment. The trial did not report any cases of valvular heart disease or pulmonary arterial hypertension at any point. These data therefore support the initiation and use of fenfluramine across all age groups, and at any point across the current add-on therapy pathway.

B.2.12.1.2 Comparative evidence versus NICE-recommended add-on therapies

Current NICE-recommended add-on therapies at third-line include clobazam, rufinamide, topiramate and cannabidiol. Cannabidiol was the latest to be approved, which based on its licensed indication should be taken with clobazam. However, only cannabidiol has been formally appraised by NICE, and was recommended for use without any comparative data beyond placebo. Therefore, an SLR was conducted to analyse all currently available clinical evidence of LGS treatments and assess the comparative value of fenfluramine. The SLR identified 35 studies, reporting on 16 unique studies in LGS. 10 clinical trials, representing eight interventions were selected for inclusion in the NMA feasibility assessment. The NMA feasibility assessment excluded five treatments (lamotrigine, felbamate, soticlestat, clobazam and rufinamide). The resulting base case network meta-analysis compared fenfluramine, cannabidiol (10 mg/kg and 20 mg/kg) and placebo. The NMA indicated that fenfluramine outranked cannabidiol in three of the four clinical efficacy outcomes and showed a superior safety profile versus cannabidiol safety endpoints.

B.2.12.2 Generalisability and relevance of the clinical evidence base

The clinical evidence base for fenfluramine is generalisable to UK clinical practice and is therefore the appropriate and relevant dataset to use to address the decision problem.

B.2.12.2.1 Patient population

The phase 3 RCT enrolled LGS patients from North America and Europe aged 2-35 years, with a mean age of approximately 13.7 years (weighted average across trial arms) (15). The populations were stratified by weight to ensure balance across treatment arms, with a target of at least 25% in each weight group.

Safety population patients at baseline had a history of multiple prior ASMs and received a mean average of 7.1 prior standard of care ASMs (Study 1601). 36.5% of the patients reported receiving 3 concomitant ASMs (80).

The LGS patients enrolled in the phase 3 RCTs and the long-term observational studies are assumed to be reflective of the UK clinical practice. There is no evidence to suggest that the outcomes observed in the RCT population would differ from fenfluramine treatment initiation in practice.

B.2.12.2.2 Intervention

The phase 3 RCT evaluated fenfluramine as an add-on to standard of care ASMs at the dose and dosing schedule aligned with its anticipated license. The dose in the RCTs reflected the anticipated use in practice.

B.2.12.2.3 Comparators

The phase 3 RCT compared fenfluramine against placebo as an add-on therapy to SoC regimens (15). At the time of trial design and initiation, cannabidiol was not a licensed product in LGS in any jurisdiction. Consequently, there are no comparative RCT data to enable a direct comparison between fenfluramine and cannabidiol.

In order to generate comparative effectiveness data for fenfluramine, ITCs were explored. Sufficient data were available to enable a robust ITC for fenfluramine vs cannabidiol (see section B.2.9). Cannabidiol is a relevant comparator in the decision problem, and it is appropriate to use the ITC of fenfluramine vs cannabidiol as the primary evidence of comparative effectiveness on the use of fenfluramine in the current add-on treatment pathway.

B.2.12.2.4 Outcomes

The primary and secondary efficacy endpoints for the phase 3 RCT (Study 1601) appropriately focus on key seizure endpoints that drive patient morbidity and mortality, including percentage change from baseline in DSF, responder analyses based on clinically meaningful reductions in DSF and longest convulsive seizure-free intervals and seizure-free days. Evaluations of non-convulsive seizure reductions, patient health status and patient and carer quality of life were also pre-specified, as were safety endpoints (15). These are all outcomes that matter to patients and carers, several are used in clinical practice to assess patient response to treatment, and most are listed as outcomes in the scope of this appraisal (129). The outcomes assessed are therefore highly relevant to clinical practice and to the decision problem in this appraisal.

B.3 Cost-effectiveness

Cost-utility analysis of fenfluramine

- A semi-Markov model was developed to determine the cost-effectiveness of fenfluramine as an add-on therapy in LGS patients. The simulated population and relevant inputs are reflective of the LGS population in the UK as validated by clinical experts.
- A primary base case comparison has been conducted on fenfluramine plus SoC versus cannabidiol (with clobazam) plus SoC as this is the most appropriate comparison to determine the cost-effectiveness of fenfluramine in the existing treatment pathway.
- Secondary analyses of fenfluramine plus SoC versus SoC alone was provided for completeness and transparency.

Model features

- The percentage of reduction in drop seizures is the main outcome measure of efficacy within the model. Four health states 0 to 3 represent no-response (state 0: <25% decrease), low response (state 1: 25% to <50% decrease), medium response (state 2: 50% to <75% decrease), and best response (state 3: >75% decrease), with each cycle lasting 3 months. Efficacy endpoint using fenfluramine Study 1601 and its open-label extension study supported the transition probabilities estimates for each 3-month cycle. The four health states are also used to determine the impact of add-on therapy on costs, resource use, mortality and HRQoL.
- The relative treatment effect of fenfluramine and cannabidiol (with clobazam) are derived from a robust ITC that was validated by UK clinical opinion. LGS-specific data inputs for patients and carers are incorporated appropriately and in line with the NICE reference case, and UK-specific healthcare resource use data is derived from a detailed UK Pathway study.

Base case results and sensitivity analysis

- Using the most robust data sources possible and conservative assumptions, the incremental cost-effectiveness ratio (ICER) for fenfluramine + SoC compared to cannabidiol (with clobazam) + SoC was estimated to be [redacted] per quality-adjusted life year (QALY) gained and therefore above the current decision-making threshold.
- In a secondary analysis, that could reflect patients for whom cannabidiol is not a desirable option or is not tolerated, the ICER for fenfluramine + SoC compared to SoC alone was [redacted] per QALY gained.
- Fenfluramine meets the criteria for a severity weight of x1.7. The estimated absolute QALY shortfall was 22.97 and the proportional QALY shortfall was 0.98, with both values satisfying the x1.7 threshold. With the modifier applied, the resulting base case ICER vs cannabidiol (with clobazam) reduced from [redacted] to [redacted], which is below the £20,000/QALY threshold.
- Deterministic and probabilistic sensitivity analyses demonstrated that the results of the base case analysis were robust to parameter uncertainty. The mean probabilistic ICER of fenfluramine compared to cannabidiol with (clobazam) was [redacted] per QALY gained, which was lower than the deterministic base case ICER of [redacted], due to the cap applied on the dose per day for fenfluramine (no cap is applied for cannabidiol) while varying the patient weights in the simulations.
- The probability of the ICER being below the £30,000/QALY threshold was [redacted] However, when the severity modifier of x1.7 is applied on QALYs, the probability of the ICER being

below £30,000/QALY is [redacted] These results would suggest that fenfluramine would represent a cost-effective intervention for LGS patients.

- Extensive scenario analyses further demonstrate that under plausible alternative assumptions, fenfluramine remained cost-effective at the x1.7 severity modifier level, with most ICERs falling below the cost per QALY threshold of £30,000.

Conclusion

- LGS, a rare and severe disease, has limited effective and well-tolerated treatment options available for patients. Fenfluramine offers a cost-efficient alternative as an add-on therapy to the currently NICE-recommended options. Fenfluramine qualifies for a severity modifier of x1.7 and should therefore be recommended within its full licensed indication as a clinically significant and cost-effective add-on therapy option for LGS patients.

B.3.1 Published cost-effectiveness studies

B.3.1.1 Identification of the studies

A SLR was conducted to identify economic evaluations from published literature on LGS. Searches were initially conducted on 05 October 2022, with an update performed on 07 June 2023 to align with NICE requirements. Full search strategies, inclusion and exclusion criteria and the PRISMA flow diagrams are provided in Appendix G.

To identify relevant literature, database searches were conducted in data sources listed in Table 30. The proceedings of the relevant conferences from January 2020 to December 2022 were hand-searched for any editions not yet indexed in Embase. The bibliographies of systematic reviews identified through the database searches were cross-referenced against both the results of the search strategies and screening processes as a quality-assurance step.

Table 30. Summary of information sources

Source	Description of sources
Electronic databases	• MEDLINE and MEDLINE In-process (via Ovid) • Evidence-based medicine (EBM) Reviews: Cochrane Central Register of Controlled Trials (via Ovid) • EBM Reviews: HTAs (via Ovid) • EBM Reviews: Cochrane Database of Systematic Reviews (via Ovid)
Topic-specific electronic databases	• EconLit (via Ovid) • National Health Service Economic Evaluation Database * (via Ovid) • Cost-effectiveness analysis (CEA) registry (https://research.tufts-nemc.org/cear/Deult.aspx)
Conferences	All conferences indexed via Embase in the last 3 years (January 2020–June 2023)
Other sources	• Hand search of the bibliography list of relevant SLRs/meta-analyses identified by the database searches (January 2020– June 2023) • Hand search of the proceedings of the last two editions of congresses not (yet) indexed via Embase (American Epilepsy Society, The Professional Society for Health Economics and Outcomes Research, International League Against Epilepsy, European Epilepsy Congress, American Academy of Neurology and European Paediatric Neurology Society) • International HTA Database (INAHTA) (database.inahta.org)*
HTAs	HTAs will be reviewed for recent appraisals in LGS (and similar indications e.g., DS and developmental and epileptic encephalopathy) to cross-check literature and information against the proposed SLRs. Agencies, such as: • United Kingdom: National Institute of 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 • United States: Institute for Clinical and Economic Review • France: Haute Autorité de santé • Wales: All Wales Therapeutics and Toxicology Centre

*Notes: * This database was discontinued in 2015 and only the archived version is available.*
*** The INAHTA HTA database was searched using the search interface on https://database.inahta.org/.*
Abbreviations: CEA , Cost-Effectiveness Analysis; DS, Dravet Syndrome; EBM, Evidence-Based Medicine; HCRU, Healthcare Resource Use; HRQoL, Health-Related Quality of Life; HTA, Health Technology Assessment; LGS, Lennox Gastaut Syndrome; SLR, Systematic Literature Review.

B.3.1.2 Description of the identified studies

In total, nine publications reporting on eight unique economic evaluations were included for data extraction. Among these, three are CEA and four Cost-utility analyses (CUA) and one budget-impact analysis (BIA) (Table 31). Details of the SLR methods are detailed in Appendix G.

Overall, most cost-effectiveness evaluations were designed from the payer perspective of either the UK (n=3) or the US (n=3). Treatment-wise, rufinamide, topiramate and lamotrigine were the most evaluated interventions (with three models each). Most of the analyses capped the time horizons between three months to 15 years. Patient outcomes were conceptualised through Markov models in three studies, a decision tree in one study, and a patient-level simulation in another. Two studies did not specify model design. Across most of the economic evaluations, the LGS population was broadly defined as patients with LGS; only one evaluation reported on paediatric patients and one evaluation specified a mixed paediatric and adult population. Table 31 presents an overview of the characteristics of identified studies.

Table 31. Summary of study characteristics – economic evaluations

Author, year	Population	Country and perspective	Currency and cost year	Intervention and comparator(s)	Type of analysis	Type of economic evaluation	Time horizon
UK studies							
Verdian, 2010 (130)	Paediatric patients with LGS	UK - Payer (UK NHS)	GBP 2006-2007	Rufinamide (Intervention) Topiramate (Comparator) Lamotrigine (Comparator)	CUA	Markov	3 years
Benedict, 2010 (131)	Mixed patients with LGS (adults and paediatrics)	UK - Payer (UK NHS)	GBP 2006	Rufinamide + Soc (Intervention) Topiramate + SoC (Comparator) Lamotrigine + SoC (Comparator) SoC alone (Comparator)	CEA	Patient-level simulation	3 years
NICE, 2019 (TA615) (40)	Patients with LGS	UK - Payer (UK NHS)	GBP*	Cannabidiol + SoC (Intervention) SoC (Comparator)	CUA	Markov	15 years
Non-UK studies							
Majoie, 2001 (132)	Patients with LGS	Netherlands - Societal	Euro*	Vagus Nerve Stimulation (VNS) (Intervention) No VNS (preoperative) (Comparator)	CEA	Not specified	NR
Clements, 2013 (133)	Patients with LGS Patients with LGS	US - Payer	USD 2013	Clobazam (Intervention) Rufinamide (Comparator) Topiramate (Comparator) Lamotrigine (Comparator)	CUA	Not specified	3 months and 2 years
Neuberger, 2020 (134)	Patients with LGS	US - Payer	USD 2013	Cannabidiol (Intervention) SoC (Comparator)	CUA	Markov	Lifetime
Abel, 2021 (135)	Patients with LGS	US - Healthcare	USD 2020	Corpus callosotomy (Intervention) VNS (Comparator)	CEA	Decision tree	1 year
Skornicki, 2014(136)	Patients with LGS	US - Payer	USD*	Clobazam, rufinamide, topiramate, lamotrigine	BIA	Budget Impact model	2 years

** Cost year not reported.*
Abbreviations: BIA, Budget Impact Analysis, CEA, Cost-Effectiveness Analysis; CUA, Cost-Utility Analysis; GBP, British Pound; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SoC, Standard of Care; UK, United Kingdom; US, United States; USD, United States Dollar; VNS, Vagus Nerve Stimulation.

B.3.1.3 Summary of published cost-effectiveness results

The sections below summarise the key cost-effectiveness outcomes for the treatments assessed in the SLR studies (clobazam, cannabidiol, rufinamide, topiramate, lamotrigine, VNS, corpus callosotomy). Compared to the other interventions, cannabidiol reported the highest ICER ($451,800/QALY [discounted]) vs SoC.

Clobazam

Clements *et al.* 2013 aimed to estimate the short- and long-term cost-effectiveness of clobazam as adjunctive therapy for LGS from a payer perspective (133). The study used three-month and two-year time horizons. Clobazam was compared to three other ASMs: rufinamide, topiramate and lamotrigine. Over the three-month time horizon, the costs per patient ranged from $30,147 to $35,378 with QALYs ranging from 0.119 to 0.129. In the two-year model, clobazam was only compared to rufinamide. The costs per patient were $177,068 and $265,814, respectively. The estimated QALYs were 1.127 for clobazam and 0.986 for rufinamide. The study concluded that clobazam was more effective and less expensive than the comparators in both cases (i.e., clobazam dominated the comparators).

Cannabidiol

A US study, Neuberger *et al.* 2020, estimated the cost-effectiveness of cannabidiol add-on therapy compared with SoC for patients diagnosed with LGS using a Markov model with a lifetime horizon and a willingness-to-pay (WTP) threshold of $150,000 per QALY (134). The base-case ICER of adding cannabidiol to usual care was $451,800/QALY (discounted) and $445,400/QALY (undiscounted). Cannabidiol was not a cost-effective add-on treatment option at commonly used cost-effectiveness thresholds as none of the base-case, sensitivity or scenario analyses resulted in an ICER below $150,000/QALY.

The NICE technology appraisal document evaluated cannabidiol (NICE TA615) in addition to current clinical management (CCM) compared to CCM alone (40). The incremental cost was £48,907 and incremental benefit 1.58. The ICER for cannabidiol + SoC was reported as £30,970 and exceeded the WTP threshold of £30,000. A secondary analysis was conducted for a subpopulation of patients on clobazam. For this subgroup, the incremental cost was £52,519 with an incremental QALY of 1.79. The ICER for cannabidiol + SoC in this subgroup was reported as £29,280.

Rufinamide, topiramate, lamotrigine

A first UK study, Benedict *et al.* 2010, reported on the cost-effectiveness of rufinamide + SoC compared with topiramate + SoC, lamotrigine + SoC, and SoC alone from a payer (i.e., UK NHS) perspective using a patient-level simulation with a three-year time horizon (131). The total mean costs for all seizures ranged from £37,064 (lamotrigine + SoC) to £38,828 (rufinamide + SoC) and the total mean seizure reduction ranged from 22.1% (SoC only) to 27% (rufinamide + SoC). Compared to lamotrigine, rufinamide cost an additional £2,151 per 1% increase in successfully treated patients (defined as a >50% reduction in the seizure frequency). Both topiramate and standard therapy alone were dominated by lamotrigine. With regards to drop attacks only,

topiramate had the lowest overall costs and was therefore chosen as the comparator. Rufinamide resulted in an additional cost of £62 per 1% increase in successfully treated patients, while lamotrigine and standard therapy only were dominated. Using a WTP of £250 for a 1% increase in the number of successfully treated LGS patients in terms of drop attacks, rufinamide had an >80% probability of being cost-effective versus topiramate.

A second UK-based cost-utility study, Verdian *et al.* 2010, reported that over a three-year time horizon, the base-case analysis showed that rufinamide resulted in a higher cost than topiramate and lamotrigine but was more effective (130). The incremental cost per QALY gained with rufinamide therapy vs. topiramate or lamotrigine, was £20,530 and £154,831, respectively.. Overall, rufinamide was cost-effective in the UK relative to topiramate as adjunctive therapy in LGS and although, when compared with lamotrigine, the ICER of rufinamide exceeded the accepted UK thresholds (i.e., £20,000 and £30,000), there were higher levels of uncertainty around these estimates.

A summary of results for all included economic evaluation studies are provided in Appendix G.

B.3.2 Economic analysis

As confirmed by the SLR presented in Section B.3.1., no cost-effectiveness studies appraising fenfluramine for the treatment of seizures associated with LGS were published prior to this submission. Therefore, a de novo cost-effectiveness analysis was required.

B.3.2.1 Patient population

The target patient population for the cost-effectiveness analysis comprises patients with LGS aged 2 years or older and in whom the condition is inadequately controlled by the established SoC in the UK. This is in line with the EMA MA (1) and MHRA licensed indication for fenfluramine (1) for the treatment of seizures associated with LGS as an add-on therapy to other anti-epileptic medicines for patients two years of age and older.

The cost-effectiveness model followed paediatric and adult patients (patients aged 2 years and older) diagnosed with LGS. Patient characteristics were obtained from the fenfluramine trial, Study 1601 (15); the baseline model population had a mean starting age of 13.7 years, of which 55% were male and a median of 70.5 drop-seizures (15).

The target population is also consistent with the final scope published by NICE for the health technology appraisal of fenfluramine in LGS (129).

B.3.2.2 Model structure

A semi-Markov model was developed in Microsoft Excel® to represent the natural history of the disease, clinical pathway, and clinical outcomes reported for people with LGS (Figure 26). The semi-Markov cohort model structure was preferred to account for the treatment approach for LGS, and the resistant nature of seizures, i.e., application of time-dependent efficacy, and stopping rule in case of low response for a set duration. Unlike in a traditional Markov chain, time spent in health state 0 is not memoryless and alters the likelihood of transitioning to discontinuation state due to

the stopping rule. Previous LGS economic models have generally been based on similar Markovian approach (see Section B3.1). This approach was further corroborated by UK clinical opinion (34).

The model used the drop-seizure frequency as the main efficacy driver (40), which is a primary endpoint in Study 1601 and aligned with NICE clinical guideline NG217. Health states were defined as four mutually exclusive and clinically established categories of percent change in drop seizure frequency since baseline as shown in Table 32. Health states 0 to 3 represent the following: no-response (state 0: <25% decrease), low response (state 1: 25% to <50% decrease), medium response (state 2: 50% to <75% decrease), and best response (state 3: >75% decrease) (Figure 26). Moreover, the model included two additional states: one for discontinued patients and an absorbing state of death. Discontinuation could occur at titration and at any cycle after that throughout the time horizon due to AE, lack of efficacy and stopping rule.

The model cohort would receive either fenfluramine and standard of care (FFA + SoC), cannabidiol with clobazam and standard of care (CBD w CLB + SoC) or SoC alone which included a basket of ASM.

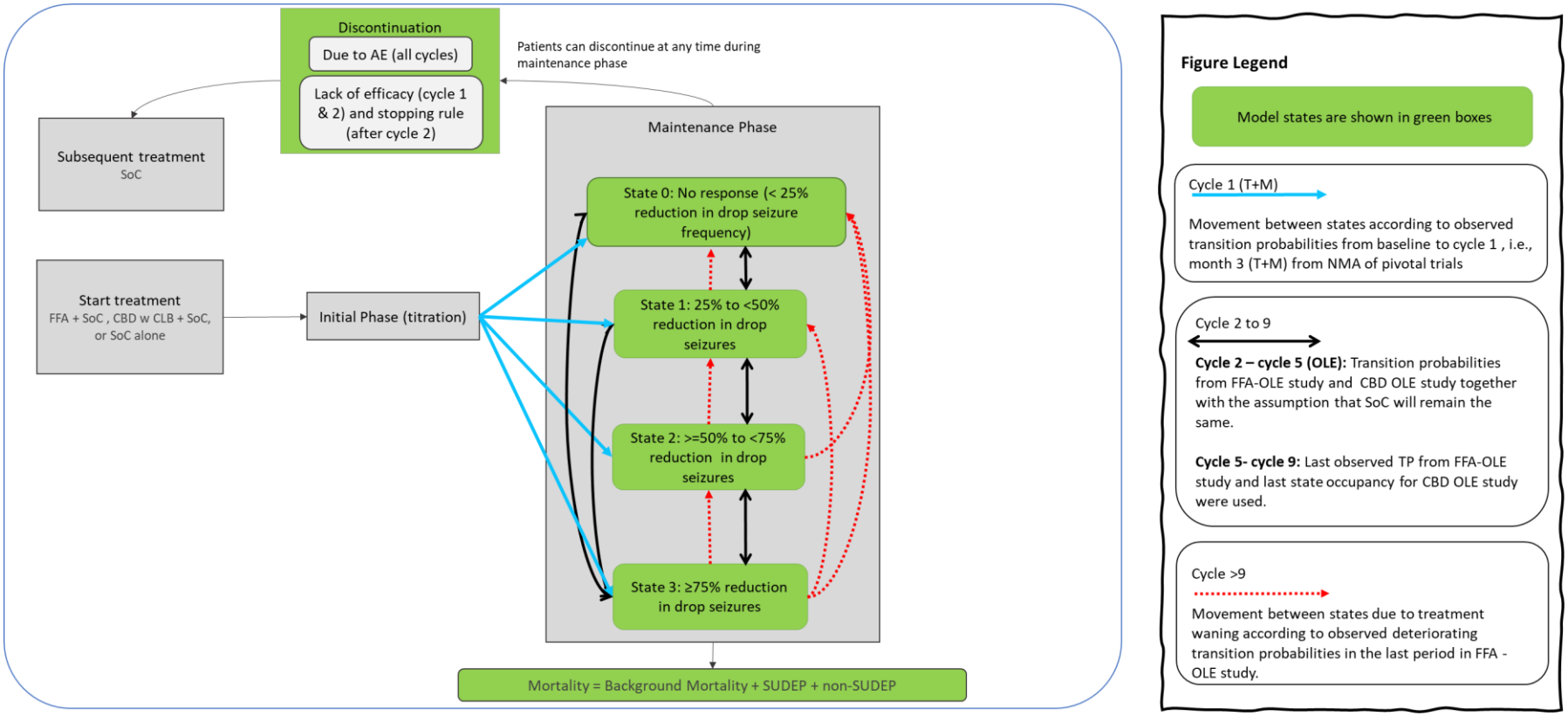
At the beginning of the titration cycle, the initial distribution of patients across health states 0, 1, 2 and 3 respectively, were calculated using quartiles of drop-seizure distribution at baseline in Study 1601 (137). During titration period of 2 weeks, apart from discontinuation or death occurring, the model assumes patients would remain at their respective health states (only dosing and cost is affected by titration period). At the end of cycle 1 (3 months) patients would move to corresponding health states according to efficacy data from ITC of pivotal trials (see section B2.9). Once in a response state, transition probabilities or state occupancies determined movement between health states up to 15 months (up to cycle 5). Transition probabilities and state occupancies in this time period were estimated from FFA and CBD OLE studies respectively. Similar to the NICE - cannabidiol submission (TA615) (40), and the NICE fenfluramine for DS submission (4), the model assumed that treatment effect would be applied up to 27 months, after which patients would stay in their corresponding state with potential competing occurrences of discontinuation or death.

Treatment discontinuation varied across the time horizon. Patients could discontinue due to adverse events (at all cycles), from lack of efficacy (cycles 1 and 2) and through stopping rules (after cycle 2). Discontinued patients were assumed to go to the discontinuation state which is equivalent to state 0), to remain in the discontinuation state unless they die, and to follow the same trajectory in terms of costs, utilities, and mortality as patients on state 0 of the SoC treatment arm.

Treatment efficacy waning was accounted in the model and applied after cycle 9 as a proportion of patients assumed to undergo waning calculated from OLE study (12). The same value was applied to patients receiving fenfluramine and cannabidiol due to lack of cannabidiol deterioration rates.

All-cause mortality was applied using a background mortality rate applied to all patients (15, 70). In addition, all patients were at risk of SUDEP as well as death from other non-SUDEP causes such as status epilepticus and accidents. SUDEP mortality was assumed to be dependent on health states and the frequency of seizures per 28 days (138).

Figure 26. Schematic diagram of cost-effectiveness model (CEM)



Abbreviations: AE, Adverse event; CBD, cannabidiol; CBD w CLB, cannabidiol with clobazam; FFA, fenfluramine; NMA, network meta-analysis; OLE, Open label extension; SoC, Standard of Care; SUDEP, Sudden unexpected death in epilepsy; T+M, Titration and Maintenance; TP, transition probability.

Table 32. Model description

Parameter	Application in the model	Related sources
Health States **State 0: No response** < 25% reduction in frequency of drop-seizure since baseline **State 1: Low response** 25% to <50% reduction in frequency of drop-seizure since baseline **State 2: Medium response** 50% to <75% reduction in frequency of drop-seizure since baseline **State 3: Higher response** ≥75% reduction in frequency of drop-seizure since baseline	•Titration: The initial distribution of patients across health states were used from FFA Study 1601 baseline. At the end of the titration cycle, the model assumes patients will remain at their respective states (only discontinuation, mortality, dosing and cost is affected by titration period). • T+M (cycle 1): NMA results for relative risks of each state is used together with proportion of patients in SoC arm Study 1601 to calculate state occupancy at cycle 2 • Cycle 2 - cycle 5 (OLE): Transition probabilities from FFA-OLE study (137) and CBD OLE study (139) together with the assumption that SoC will remain the same. • Cycle 5 - cycle 9: Last observed data from FFA-OLE study (137) and CBD OLE study(139) were used. • After cycle 9, treatment waning is applied in which a proportion of patients was assigned to undergo waning using last deteriorating TP from FFA-OLE study (137). • Patients who do not undergo waning remain in the same state and only discontinuation or death can occur after this time.	• T+M (cycle1): Study 1601 and NMA • Cycle 2 - cycle 5: OLE study • Cycle 5 - cycle 9: assumption based on FFA and CBD OLE studies • >Cycle 9: assumption
Discontinuation	• Discontinuation can occur at any cycle including titration, due to AE (all cycles), lack of efficacy (cycles 1 and 2) or stopping rule (after cycle 2). Discontinued patients were assumed to go to the discontinuation state (equivalent to state 0). • Discontinuation due to AEs could occur at very cycle (including titration) at cycle 1 NMA results were used to calculation discontinuation for each study arm. For follow-up cycles, observed values from FFA and CBD OLE were used. For the SoC arm, AE rates from Study 1601 were used and assumed to be the same at every cycle throughout the time-horizon • Discontinuation due to lack of efficacy was applied at cycles 1 and 2 and assumed to be the same for FFA and CBD. SoC arm did not experience any discontinuation due to lack of efficacy (only due to AE). • After cycle 2, a stopping rule at 3 months was applied, all patients with response of <25% discontinue treatment	• Discontinuation due to AE: ○ NMA results for cycle 1 (140) ○ OLE studies for follow-up cycles (12, 139) • Discontinuation due to lack of efficacy: ○ Cycle 2: OLE study for FFA (12) ○ > Cycle 2: stopping rule

Parameter	Application in the model	Related sources
Mortality	• Mortality can occur at any cycle including titration due to General mortality (All-cause age-dependent mortality rate) and SUDEP or non-SUDEP causes. • Non-SUDEP deaths include status epilepticus and accidental deaths •The SUDEP and non-SUDEP rates were assumed to be the same as in DS patients (due to a lack of LGS-specific data)	• Assumption: Similar to DS – Cooper et al. 2016 (138) Same assumption as NICE CBD submission 2019 (TA615)(40)

Abbreviations: AE, Adverse Event; CBD: Cannabidiol; DS, Dravet Syndrome; FFA, Fenfluramine; LGS, Lennox-Gastaut Syndrome; NMA, Network Meta-Analysis; OLE, Open-Label Extension; SoC, Standard of Care; SUDEP, Sudden Unexpected Death in Epilepsy; TP, Transition Probability.

Improvements in QoL (141) were linked to the percentage reduction in drop seizure frequency reflected through the model health states.

As some seizure-related outcomes from the literature (e.g., resource use or mortality) relied on absolute number of drop seizure rather than rate of response to treatment (e.g., percentage reduction in seizures), the average number of drop seizures per 28 days was determined for each health state in the model. For health states 0 and 3, the mean drop seizures per 28 days were the observed median drop-seizure in Study 1601. For states 1 and 2, an approach described by Neuberger et al. (2020) (134) in LGS patients was used. The approach consisted of multiplying the baseline number of drop seizures by 1 minus the mid-point value in each health state. For example, the mid-point value of state 1: 25% to <50%, was 37.5%. The mid-point estimates and average number of drop seizures per 28 days for each health state used in the model can be seen in Table 33. Mid-point estimates for state 0 and 3 were back calculated as the percentage of change in number of average drop seizures compared to baseline number of drop seizures.

Table 33. Estimated mid-point and number of drop seizures per 28 days per model health state

Health State	Estimated mid-point (%)	Number of drop seizures per 28 days	References
Baseline	0%	70.5	Study 1601 (15)
State 0: <25% reduction	-43.8%	101.38	Study 1601 (median % change in state 0 for FFA 0.7 mg) (15)
State 1: 25% to <50% reduction	37.5%	44.06	Calculated using mid-point estimates according to Neuberger et al. (2020) (134)
State 2: 50% to <75% reduction	62.5%	26.44	Calculated using mid-point estimates according to Neuberger et al. (2020) (134)
State 3: >75% reduction	85.0%	10.58	Study 1601 (median % change in state 3 for FFA 0.7 mg) (15)

Abbreviations: mg, Milligram;

The base case analysis used a lifetime horizon. The titration cycle had the duration of 2 weeks for both fenfluramine and cannabidiol as per the duration in respective trials. The model used a 3-month length for each cycle as the clinical outcomes in fenfluramine and cannabidiol trials were reported at this time interval. The titration length was accounted for in cost, life year and QALY gain calculations. A standard half cycle correction was applied to account for the fact that events and transitions could occur at any point during the cycle and not strictly at the start or end of each model cycle.

The analysis was conducted from the perspective of the NHS and personal social services in England and Wales, in line with current NICE guidelines (141). The base case analysis thus considered only direct healthcare costs. Costs and outcomes were discounted at an annual rate of 3.5%, in line with the NICE reference case. Key features of the economic analysis are provided

in Table 34. These are compared to the company submission for cannabidiol in NICE TA615 (40), with justification for differences in the approach.

Table 34. Features of the economic analysis

Factor	Previous evaluation	Current evaluation	
	CBD + CLZ TA615	Chosen values	Justification
Perspective	NHS/ Personal Social Services (PSS)	NHS/PSS	NICE guidelines (141)
Time horizon	Lifetime (90 years)	Lifetime (86 years)	Long enough to reflect all important differences in costs or outcomes as per the NICE reference case (141)
Cycle length	3 months	3 months	Aligned with the maintenance period duration of the Study 1601 (15)
Discount for utilities and costs	3.5% for QALYs and costs	3.5% for QALYs and costs	NICE guidelines (141)
Source of efficacy	GWPCARE 3 and GWPCARE 4 phase 3 trials (88, 89)	Study 1601 (15) and OLE (12) NMA (140)	Pivotal trial data for patients with LGS and treated with FFA NMA used to mitigate the direct comparative efficacy data gap between CBD and FFA
Source of utilities	Health states: utilities based on visual analog scale (VAS) from online survey conducted by GW (the manufacturer)	Health states: utilities based on EQ-5D scores from Verdian et al. 2008 (130, 142)	The Verdian study provided LGS-specific EQ-5D scores that are aligned with the present model design
Source of costs	NHS reference costs Personal Social Services Research Unit (PSSRU) British National Formulary (BNF) Published literature Expert opinion	NHS reference costs PSSRU BNF Published literature Expert opinion	NICE guidelines (141), economic data reflective of the UK setting
Source of safety	GWPCARE3 and GWPCARE4 phase 3 trials(88, 89)	Study 1601(15) and OLE (15) NMA (140)	Pivotal trial data for patients with LGS and treated with FFA NMA used to mitigate the direct comparative safety data gap between CBD and FFA
Mortality rates	ONS life table for England (143) Published literature	ONS life table for England (baseline) (143) Published literature: SUDEP-related: Neuberger et al. 2020 (134) SE-related: Cooper et al. 2016 (138)	Similar to Neuberger et al. (2020) (134) approach, the model assumes patients in each health state experienced a reduction in SUDEP-related mortality based on the midpoint of each health state. Similar to NICE-DS submission (2022), the model assumes non-SUDEP mortality is a proportion of SUDEP and SE-related mortality. The proportion is used from Cooper et al. (2016) (138) for DS due to limited data available

Factor	Previous evaluation	Current evaluation	
	CBD + CLZ TA615	Chosen values	Justification
Treatment waning effect	Not included	Included	Implemented conservatively due to lack of long-term data. There is currently no evidence that the effect would be maintained beyond 27 months.

Abbreviations: BNF, British National Formulary; CBD, Cannabidiol CLB, Clobazam; DS, Dravet Syndrome; FFA, Fenfluramine; LGS, Lennox-Gastaut Syndrome; NHS, National Health Services; NICE, National institute of Health and Care Excellence; OLE, Open-Label Extension; ONS, Office for National Statistics; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, Quality-Adjusted Life Years; SUDEP, Sudden Unexpected Death in Epilepsy; UK, United Kingdom.

B.3.2.3 Intervention technology and comparators

Cannabidiol is currently the only existing add-on therapy to have been formally appraised and accepted as a clinically and cost-effective treatment option for LGS by NICE. It is also the only therapy with sufficient trial data to permit a robust comparison (129). As such, the model evaluates (in its base case) the incremental cost-effectiveness of fenfluramine + SoC compared with cannabidiol (with clobazam) + SoC. Comparison is also made vs SoC alone.

Based on OLE data, the base case analysis used an average maintenance dose 0.5 mg/kg/day for fenfluramine to most closely reflect the clinical practice dose of fenfluramine, which is based on a balance between efficacy and tolerability (as per the guidance in the SmPC for fenfluramine)(1). The efficacy within the OLE for fenfluramine also improved despite the majority of patients being on a dose of 0.2 - 0.5 mg/kg/day, which alleviates any concerns on dosing within the model (0.5mg/kg/day) not reflecting the dosing within the trials (0.7mg/kg/day) that were used to inform the indirect treatment comparison (12, 15). For cannabidiol, the base case analysis utilised the initial cycle dose of 12mg/kg/day and maintenance dose after T+M of 14mg/kg/day as expected to be used in clinical practice as per advice from UK clinical opinion (34, 40, 144). As highlighted in the NICE cannabidiol submission (TA615), "*based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk" (40)*. Based on real world data (145) and expert opinion (34), the cannabidiol average dose beyond the initial cycle was increased to 14mg/kg/day (i.e., 60% of patients on a dose of 10 mg/kg/day, and 40% of patients on the maximum dose of 20 mg/kg/day). The above assumptions reflect the dose of fenfluramine and cannabidiol expected to be used in clinical practice as per UK clinical opinion.

In terms of the SoC, a basket of treatments including: clobazam; levetiracetam, valproate, lamotrigine, topiramate, and rufinamide was used. The SoC was in line with published evidence on current clinical practice and the final scope published by NICE and has also been validated by clinical experts to be appropriate and representative of the UK clinical setting (34).

The NICE scope includes felbamate, ketogenic diet and VNS as potential comparators. However, these treatments were not considered within this economic analysis. Felbamate is only available in Europe on a patient-by-patient basis due to a risk of aplastic anaemia and acute liver failure

(40). In England, only a very small number of patients have access to felbamate (on a named-patient basis) as NICE recommended that felbamate is used only in centres providing tertiary epilepsy specialist care and when treatment with sodium valproate, lamotrigine, rufinamide and topiramate are ineffective or not tolerated (40, 70).

Regarding non-pharmacological interventions, those were excluded from the comparators list. Whether these non-pharmacological treatments should be included in the analysis was discussed with NICE during the TA615 submission for cannabidiol: "*As the effects of VNS are durable, these interventions are already included in the comparator by virtue of their contribution to transition probabilities in both cohorts of the model as part of the CCM (current clinical management) mix*" (40). As patients in both treatment arms in the model are assumed to receive pharmacological treatments only, as part of their SoC, the exclusion of the non-pharmacological interventions from the current analysis is expected to have no impact on the ICERs.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline patient characteristics

Patient characteristics used in the model were sourced from Study 1601; the baseline model population had a mean starting age of 13.7 years and 55.5% were male (Table 35). As the treatment dosages for cannabidiol and some other ASMs are weight-based, the trial population was split into five age groups (2-5 years, 6-11 years, 12-17 years, 18-35 years and >35 years) and mean weight for each group was used to ensure more precise estimation of the treatment dosages, in line with respective SmPC (Table 36). The model used weight for patients in each age group at baseline from Study 1601 (4, 15) as shown in Table 36.

Table 35. Baseline patient characteristics included in Study 1601 (aggregate across treatment arms FFA 0.2mg/kg/day, FFA 0.7mg/kg/day, and placebo)

Measures at baseline	Proportion of patients (%)	Reference
Average age at model initiation, mean	13.7 years	Based on Knupp et al. 2022 (15)
Proportion male, %	55.5%	Based on Knupp et al. 2022 (15)
Median number of drop seizures per 28 days, median	70.50	UCB 2022 Fenfluramine Study Statistical Analysis (137)
Health state baseline distribution, %		UCB 2022 Fenfluramine Study Statistical Analysis (137)
State 0 (No response; < 25% reduction)	32%	
State 1 (Response group 1: 25% to <50% reduction)	22%	
State 2 (Response group 2: 50% to <75% reduction)	38%	
State 3 (Response group 3: ≥75% reduction)	8%	
Proportion of GTC, %	62.0%	Strzelczyk et al. 2023 (146)
Rescue medications (Diazepam), %	67.0%	UCB Data on file Internal Adelphi survey results, 2023 (67)
Rescue medications (Midazolam), %	33.0%	Based on Knupp et al. 2022 (15) Calculated (100% - 67%)
Titration FFA (length in weeks)	2 weeks	Knupp et al. 2022 (15)
Titration CBD (length in weeks)	2 weeks	Clinical expert (KOL) (34)
Age distribution, %		Based on Knupp et al. 2022 (15) (calculated for all arms)
2-5 years of age	14.4%	
6-11 years of age	27.4%	
12-17 years of age	29.3%	
≥18 years of age	28.9%	
ASM distribution, %		Knupp et al. 2022 (15)
Valproate	56%	
Clobazam	44%	
Lamotrigine	33%	
Levetiracetam	23%	
Rufinamide	21%	

Abbreviations: ASM, Antiseizure Medications; CBD, Cannabidiol, GTC; Generalised Tonic-Clonic, KOL, Key Opinion Leader; mg, Milligram.

Table 36. Weight parameters

Age groups	Mean weight, in kg (SD)	Reference
2-5 years of age	17.63 (3.68)	Study 1601 (15)
6-11 years of age	30.11 (9.74)	
12-17 years of age	48.07 (14.02)	
18 -35 years of age	62.11 (18.86)	
>35 years of age*	78.00 (15.6)	Last age group was used from DS patients (NICE-fenfluramine for DS submission) (4)

*Notes: * Due to lack of data, SD was calculated using 20% variation around the mean.*
Abbreviations: DS, Dravet Syndrome; SD, Standard Deviation.

B.3.3.2 Transition probabilities

The model starts first by removing discontinued patients and then mortality in the Markov traces. Different transition probabilities were then used to estimate health state occupancies according to treatment response (states 0 to 3) for each treatment arm at different time epochs:

- T+M cycle 1 covering a 3.5-month time-period.
- First year of follow-up: from maintenance cycle 2 to 5 (months 4 to month 15)
- Second year of follow-up: from maintenance cycle 6 to 9 (months 16 to 27)

B.3.3.2.1 Transition probabilities for T+M period (ITC of pivotal trial results)

Cycle 1 in the model corresponded to titration plus maintenance (T+M) months, i.e., 3 months following titration. The initial distribution of patients across health states 0, 1, 2 and 3 respectively, were calculated using quartiles of drop-seizure distribution at baseline in Study 1601 (137). Relative risks estimated from the ITC (Table 37) were used to assess the effect of treatments on the distribution across health states.

The model used a stepwise approach to calculate state occupancy after T+M. First, binomial relative risks for each percentage of drop-seizure reduction category were multiplied by baseline proportions (Table 37). Next, difference within each cut-off points were calculated for state occupancy (Table 38).

Binomial relative risks for the sub-population on clobazam (CBD w CLB) was selected for the base case analysis, as displayed in Table 37. As explained in section B2.9.4, the NMA analysis on ITT patient population included patients not systematically receiving clobazam with cannabidiol, which is required by the EMA and MHRA label. Since the EMA dataset did not provide all relevant outcomes needed for our economic analysis, a second NMA analysis was performed on published CBD w CLB sub-population data from German HTA body (GBA). Since definition of drop seizure varied, convulsive seizures were considered similar to drop seizures in this data set.

Table 37. Binomial relative risks for proportion in each state - Binomial relative risks at cycle 1 (T+M), FFA-PBO-CBD w CLB (GBA) (NMA results)

Cohorts	FFA 0.7 mg/kg/day, RR (95% CI)	CBD 10 mg/kg/day, RR(95% CI)	CBD 20 mg/kg/day, RR(95% CI)	Baseline: proportion of patients in each state at T+M (Study 1601)	Reference
>=25%					NMA (140)
>=50%					
>=75%					

Abbreviations: CBD, cannabidiol; CBD w CLB, Cannabidiol with Clobazam; CI, Confidence interval; FFA, fenfluramine; FFA-PBO-CBD, fenfluramine-Placebo-Cannabidiol; GBA, Federal Joint Committee of Germany (Gemeinsamer

Bundesausschuss); kg, Kilogram; mg, Milligram; NMA, network meta-analysis; RR, relative risk; SoC., standard of care, T+M, Titration and Maintenance.
Note: All credible intervals are overlapping

Table 38. Calculated state occupancy at cycle 2 (after T+M)

Cohorts	State 0: No response (< 25% reduction)	State 1: Response group 1: 25% to <50% reduction	State 2: Response group 2: 50% to <75% reduction	State 3: Response group 3: >=75% response	Reference
SoC	69.0%	20.7%	5.7%	4.6%	Study 1601 (15)
FFA +SoC	[redacted]	[redacted]	[redacted]	[redacted]	Data on File - NMA(140)
CBD +SoC*	[redacted]	[redacted]	[redacted]	[redacted]	Data on File - NMA(140)

Abbreviations: CBD, cannabidiol; FFA, fenfluramine; kg, Kilogram; mg, Milligram; NMA, network meta-analysis; SoC, Standard of care; T+M, Titration and Maintenance.
*Notes: * CBD proportions are weighted by 10 and 20mg/kg/day dosage using relative risks from Table 37.*

B.3.3.2.2 Transition probabilities for cycle 2 to cycle 5 (analysis of OLE studies)

The efficacy for the SoC in the model was extracted from the SoC + placebo arm of the fenfluramine trial (15, 34). The model assumed patients would stay at their respective state at T+M for the rest of the time-horizon with potential for discontinuation or death.

For fenfluramine and cannabidiol arms, transition probabilities and state occupancies from cycle 2 to cycle 5 were estimated from the respective OLE studies, as displayed in Table 39 (139). As shown in (Figure 27), cannabidiol state occupancy was stable after 12 months since T+M. On the other hand, fenfluramine state occupancy significantly changed which justified the longer projection of efficacy period from cycle 5 to 9 (27 months). NICE - cannabidiol submission (2019) and NICE-fenfluramine for DS submission (4) also assumed the efficacy period to cycle 9 (Figure 27).

B.3.3.2.3 Transition probabilities from cycle 6 to cycle 9 (Long-term efficacy)

For fenfluramine, observed transition probability from OLE data in the last cycle (cycle 4 to 5) was applied from cycle 6 to cycle 9. State occupancies observed from NICE - cannabidiol submission (2019) from cycle 4 to 5 shows stabilisation and, therefore, no change in state occupancy of cannabidiol was applied from cycle 6 to 9 (Figure 27) (Table 39).

B.3.3.2.4 Transition probabilities from cycle 10 (Long-term efficacy)

The model assumed that treatment effect would be applied only up to 27 months (end of cycle 9). From cycle 10 onwards, patients would stay in their corresponding state and were only subjected to potential competing occurrences of discontinuation or death.

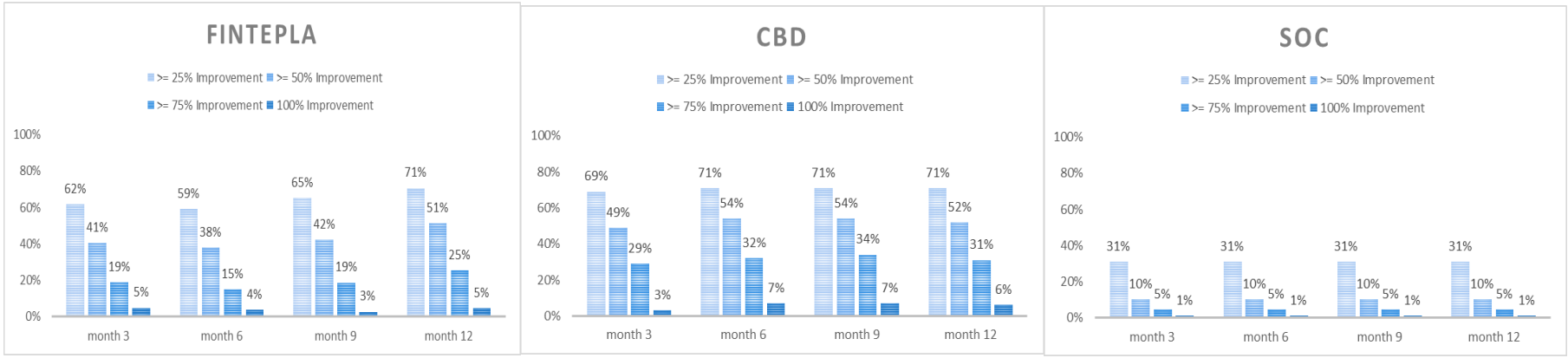
Table 39. Transition probabilities after T+M

Variable		Value				Reference
Transition probabilities (from cycle 2)						
FFA						
TP matrices		S0	S1	S2	S3	
Cycle 2 (3-6 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	Transition probabilities from cycle 2 to cycle 5 were estimated from the fenfluramine OLE study (137).
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 3 (6-9 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 4 (9-12 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 5 (12-15 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 6-9 (up to 27 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	Observed transition probability from OLE data in the last cycle (cycle 4 to 5) was applied from cycle 6 to cycle 9 (137).
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycles 10+		Patients remain in the same health state				Assumption
CBD						
State occupancy		S0	S1	S2	S3	
Cycle 2 (3-6 months)		0.308	0.201	0.201	0.291	State occupancies from cycle 2 to cycle 5 were estimated from the CBD OLE study (139).
Cycle 3 (6-9 months)		0.291	0.170	0.220	0.319	
Cycle 4 (9-12 months)		0.291	0.170	0.201	0.338	
Cycle 5 (12-15 months)		0.291	0.190	0.209	0.310	
Cycles 6-9		Last observed data				State occupancies observed from NICE - cannabidiol submission (TA615) (2019) from cycle 4 to 5 shows stabilisation and, therefore, no change in state occupancy of cannabidiol was applied from cycle 6 to 9 (40)
Cycles 10+		Patients remain in the same health state				Assumption

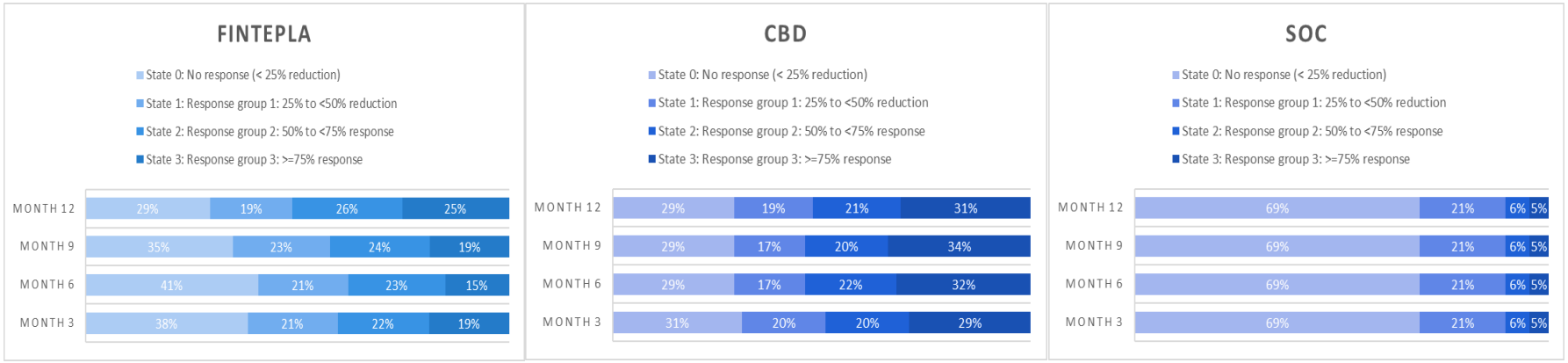
Abbreviations: CI, confidence interval; S0, health state 0; S1, health state 1; S2, health state 2; S3, health state 3

Figure 27. State occupancy of treatment arms in the first-year follow-up after T+M (data from OLE studies)

Clinical trial data



Model Health states data



Abbreviations: CBD, Cannabidiol; SoC, Standard of Care;

B.3.3.3 Supplementary efficacy outcomes

The percentage reduction in number of generalised tonic-clonic (GTC) seizures (as part of the drop seizures) was necessary to inform HCRU costs.

B.3.3.3.1 Reduction in GTC seizures to inform healthcare resource use costs

To demonstrate the higher clinical and economic burden associated with GTC seizures, secondary care seizure-related events were stratified into GTC and other drop seizures.

In the initial cycle, patients were assumed to experience a median of 70.5 drop seizures per 28 days (Knupp et al 2022 (15)), of which 62% were GTC seizures (Strzelczyk et al 2023 (146)) (Table 40). The reduction in GTC seizures after the initial cycle of treatment was based on the findings of the ITC analysis (Table 40) (140). The ITC analysis is described in section B2.9.4.2

Table 40. Reduction in GTC seizures from baseline based on the ITC analysis

	% GTC seizures at baseline	% GTC seizures reduction
SoC	62.0%	[redacted]
FFA + SoC	62.0%	[redacted]
CBD w CLB + SoC*	62.0%	[redacted]

** GTC % in seizure reduction for CBD+SoC arm was calculated using weighted results for the 10 and 20mg/kg/day doses of CBD.*
Abbreviations: CBD w CLB, Cannabidiol with clobazam; FFA, Fenfluramine; GTC, Generalised tonic clonic; kg, Kilogram; mg, Milligram; SoC, Standard of Care.

Based on these data, the number of GTC seizures at initial cycle (baseline) was calculated as 43.71 per 28 days and was independent of any treatment arm. After titration and the initial cycle of treatment (T+M), the number of GTC seizures was calculated based on the median number of drop seizures at T+M (determined from cost-effectiveness traces), the proportion of GTC seizures at baseline (62%), and the reduction in GTC seizures according to the following equation:

$$\mathrm{GTC}_{\mathrm{T+M}} = \mathrm{Drop\ Seizures}_{\mathrm{T+M}} \times \%\mathrm{GTC}_{\mathrm{Baseline}}(1 + \%\mathrm{GTC}_{\mathrm{Reduction}})$$

The proportion of GTC seizures at T+M was calculated by dividing the median number of GTC seizures by the total number of drop seizures at T+M. The results can be found in Table 41. It was considered the proportion of GTC seizures remains constant after T+M period.

Table 41. Number of drop seizures and GTC seizures

	Total number of drop seizures		Median number of GTC seizures		Proportion of GTC seizures among each group at T+M and after
	Baseline	T+M	Baseline	T+M	
SoC	70.5	[redacted]	43.71	[redacted]	[redacted]
FFA + SoC	70.5	[redacted]	43.71	[redacted]	[redacted]
CBD w CLB + SoC	70.5	[redacted]	43.71	[redacted]	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; GTC, Generalised Tonic-Clonic; SoC, Standard of Care; T+M, Titration and Maintenance.

The proportion of GTC calculated were then used together with HCRU for hospitalisation, emergency visits and outpatient clinic data. Details on the calculations are provided in section Health-state unit costs and resource use).

B.3.3.4 Treatment discontinuation

As mentioned previously in section Model structure, discontinuation could occur due to AEs, lack of efficacy or stopping rule. Few patients during Study 1601 were reported to discontinue treatment with fenfluramine because of AE at titration. Hence, treatment tolerability was modelled and differentiated between titration and maintenance periods by considering respective discontinuation rates in the two periods. Additionally, stopping rule was considered for patients with no or limited reduction in drop seizures.

B.3.3.4.1 Treatment discontinuation due to AE

Discontinuation due to AE was applied each cycle according to cycle specific proportions sourced from the Study 1601, the NMA, and fenfluramine and cannabidiol OLE studies.

Discontinuation due to AE at titration

The model used observed values for discontinuation titration for SoC and fenfluramine from the Study 1601. Due to lack of data for cannabidiol discontinuation at titration, we assumed same proportion of discontinuation for fenfluramine and cannabidiol at titration (Table 42).

Table 42. Discontinuation due to AE at Titration

Cohorts	Proportion (n/N)	Reference
FFA + SoC	2.3% (2/87)	Study 1601(15) FFA 0.7mg/kg/day
CBD w CLB + SoC	2.3%	Assumption*
SoC	0%	Study 1601(15)

*Notes: * Due to lack of data for CBD discontinuation at titration, we assumed same proportion of discontinuation for FFA and CBD at titration.*
Abbreviations: CBD w CLB, cannabidiol with clobazam; FFA, Fenfluramine; n, Sample Size; N, Population Size; SoC, Standard of Care.

Discontinuation due to AE at cycle 1 (T+M)

The model used NMA results (see Table 23, section B.2.9.4.2) together with the baseline SoC discontinuation from Study 1601(15) to calculate discontinuation for each study arm at T+M (Table 43).

Table 43. Discontinuation due to AE at T+M

Cohorts	Relative risk for discontinuation at T+M vs. SoC (95% CI)	Mean discontinuation at T+M*	Reference
CBD (10mg/kg/day)	[redacted] (0.048, 24.651)	[redacted]	NMA(140)
CBD (20mg/kg/day)	[redacted] (2.526, 66.882)		
FFA (0.7 mg/kg/day)	[redacted] (0.950, 189.500)	[redacted]	
SoC, % (n/N)	1	1.1% (1/87)	

Abbreviation: CI, confidence interval; kg, Kilogram; mg, Milligram; n, sample size; N, population size; T+M, Titration and Maintenance; NMA, network meta-analysis; SoC, standard of care.
*Notes: * Mean discontinuation for CBD was calculated using weighted average on the dosing.*

Discontinuation due to AE at follow-up (>cycle 2)

For the fenfluramine arm, OLE data from cycle 2 to 5 was used. AE rate was assumed to be 0% after cycle 5 throughout the time-horizon as the rate turns to 0% at cycle 5. For the CBD arm, respective OLE data was also used. As this proportion becomes zero in cycle 7, we assumed no further discontinuation due to AE event will occur after this cycle for CBD arm. For SoC, AE rates from Study 1601 were used (1.1%) and assumed to be the same at every cycle throughout the time-horizon (Table 44).

Table 44. Discontinuation due to AE at follow-up

Time point	FFA Proportion, % (n/N)	CBD Proportion % (n/N)	SoC proportion % (n/N)
Cycle 2 (6-month follow-up)	3.7% (6/164)	6.8% (25/366)	1.1% (1/87)
Cycle 3 (9-month follow-up)	4.1% (6/146)	5.9% (20/341)	1.1% (1/87)
Cycle 4 (12-month follow-up)	1.6% (2/128)	4.7% (15/321)	1.1% (1/87)
Cycle 5 (15-months follow-up)	0.0% (0/116)	1.3% (4/306)	1.1% (1/87)
Cycle 6 (18-months follow-up)	0.0% (0/116)	1.0% (3/302)	1.1% (1/87)
Cycle> 7 (>21-months follow-up)	0.0% (0/116)	0.0% (0/299)	1.1% (1/87)
Reference	FFA-OLE study(12)	CBD-OLE study(139)	Assumption - SoC discontinuation from Study 1601(15) }

Abbreviation: CBD, Cannabidiol, FFA, Fenfluramine; n, Sample Size, N, Population Size;

B.3.3.4.2 Treatment discontinuation due to lack of efficacy and stopping rule

In the case of discontinuation due to lack of efficacy, cycle specific proportions of discontinuation were applied for the T+M period and cycle 2, collected from the Study 1601 and OLE study, as shown in Table 45.

After cycle 2, discontinuation was captured by a stopping rule for patients in the state 0 evaluated every 3 months. The stopping rule combined with the treatment waning of efficacy (explained in the next section) triggered patients with no or limited reduction in drop seizures to discontinue treatment.

No discontinuation due to lack of efficacy or stopping rule was applied to SoC as patients are expected to remain on treatment during all model duration.

Table 45. Discontinuation proportion due to lack of efficacy at cycle 1 (T+M) and cycle 2

Cohorts	T + M (cycle 1)	cycle 2 (6-month follow-up)	Reference
FFA +SoC, % (n/N)*	0.0%	7.3% (12/164)	FFA-OLE study (12)
CBD w CLB + SoC, %	0.0%	7.3%	Assumed same as FFA + SoC

** Used the first cycle of OLE data (12 patients discontinued among 164 due to lack of efficacy).*
Abbreviation: CBD w CLB, Cannabidiol with Clobazam, FFA, Fenfluramine, n, Sample Size, N, Population Size, OLE, Open-Label Extension, SoC, Standard of Care; T+M, Titration and Maintenance.

B.3.3.5 Treatment waning

Applying treatment waning effect over time was requested by the External Advisory Group (EAG) during discussions within TA615 for cannabidiol to capture uncertainty over long-term efficacy (40). Although there is no evidence from fenfluramine OLE study to suggest wanning of its effect with LGS patients, a waning approach has been applied in this analysis (12).

After cycle 9 (month 27), treatment waning was applied as a proportion of patients assumed to undergo waning of efficacy. This was implemented using the last deteriorating transition probability observed from the OLE study from month 9 to 12 of follow-up and was applied to both fenfluramine and cannabidiol arms - due to lack of data for cannabidiol deterioration rates (12). Proportion of patients for treatment waning were calculated from OLE study in the last 3 months of observation (5.2%). The same value was applied to patients receiving fenfluramine and cannabidiol. (Table 46)

Table 46. Treatment waning per cycle (after cycle 9)

Cohorts	Proportion of patients undergoing waning due to lack of efficacy	Reference
FFA + SoC	5.2%	Calculated from OLE study in the last 3 month of observation (12).
CBD w CLB + SoC	5.2%	Assumed similar to proportion used in FFA arm due to lack of CBD deterioration data.
SoC	0.0%	Assumption

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; SoC, Standard of Care.

B.3.3.6 Treatment-emergent adverse events

To calculate costs and HRQoL-related outcomes, TEAEs of special interest that were the most commonly reported in both fenfluramine and cannabidiol trials were included in the analysis. The AEs were assumed to occur in cycle 1. TEAEs of special interest (see Section B.2.10.3) included rash, somnolence, fatigue, diarrhoea and decreased appetite. In the model, the adverse event rates for fenfluramine and SoC were based on the safety data reported in Study 1601(15). The adverse event rates for cannabidiol were sourced from the safety data of the GWPCARE4 trial (Table 47).

Table 47. Treatment-emergent adverse events at cycle 1(by treatment)

Cohorts	Occurrence of TEAEs (3-months probabilities)					Reference
	Diarrhea	Somnolence	Pyrexia	Decreased appetite	Vomiting	
SoC	0.05	0.10	0.11	0.11	0.06	Knupp et al. 2022(15)
FFA+SoC	0.13	0.17	0.08	0.36	0.08	Knupp et al. 2022(15)
CBD w CLB + SoC	0.13	0.14	0.01	0.09	0.07	Thiele et al. 2018(89)

Abbreviation: CBD, Cannabidiol; CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; TEAEs, Treatment-Emergent Adverse Events; SoC, Standard of Care.

B.3.3.7 Mortality

The model accounted for the general population mortality, as well as sudden unexpected death in epilepsy (SUDEP) and non SUDEP.

General population mortality was informed from age- and sex-adjusted national life tables in the UK (143). SUDEP mortality was informed from a DS publication due to lack of data for LGS – in line with the NICE- cannabidiol submission (TA615) (2019) (40).

An incidence rate of SUDEP of 9.32 per 1000 person-years was translated into a cycle probability (0.00233) (NICE- fenfluramine for DS submission (4, 138)). SUDEP mortality in Dravet et al. (2016) was observed in severe epilepsy patients (4, 138). Patients in the model experienced health state specific SUDEP-related mortality based on the calculated seizure frequency mid-points of each

health state described in section B3.2.2 Model structure (i.e., SUDEP-related mortality in a 50% to < 75% reduction state was the product of baseline SUDEP-related mortality multiplied by [1–0.625]) (Table 48). This mid-point approach was also used in Neuberger et al. (2020) (134) for LGS patients. With this approach, patients experiencing a higher number of drop seizures incurred an increased risk of SUDEP (Table 48).

Table 48. SUDEP mortality

SUDEP mortality	Cycle probability	Reference
Baseline SUDEP, proportion (95% CI)	0.00233 (0.001; 0.004)	NICE- FFA for DS submission (TA808) (4)
State 0: No response (< 25% reduction), proportion	0.00335	Using same approach described in Neuberger et al. (2020) (134)
State 1: Response group 1: 25% to <50% reduction, proportion	0.00146	
State 2: Response group 2: 50% to <75% reduction, proportion	0.00087	
State 3: Response group 3: >=75% response, proportion	0.00037	

Abbreviations: DS, Dravet Syndrome; FFA, Fenfluramine; NICE, National Institute for Health and Care Excellence; SUDEP, Sudden Unexpected Death in Epilepsy.

Non-SUDEP mortality in the model captured both status epilepticus-mortality and accidental-mortality. In the absence of LGS-specific data, evidence was sourced from Cooper et al. 2016 on DS patients (Table 49) (138).

Accidental mortality was calculated from Cooper et al. 2016 as a proportion of additional accidental deaths observed given SUDEP and SE mortality (138). To determine accidental deaths in the model, the calculated proportion (21.40%) was multiplied each cycle (except titration) by SUDEP and SE deaths.

Table 49. Non-SUDEP: SE and accidental mortality

Non SUDEP: SE and accidental mortality	Probability*	Reference
Probability of SE mortality for DS patient	0.093%	Cooper et al. 2016 (138)
Additional proportion of accidental mortality compared to SE + SUDEP mortality	21.40%	

*Notes: * Following the CBD NICE submission (2019), epilepsy-related rates for Dravet syndrome were used as a proxy.*
Abbreviations: DS, Dravet Syndrome; SE, Status Epilepticus.

B.3.3.8 Validation of the clinical parameters

Overall, the clinical data described in the section above were primarily informed from the clinical studies of fenfluramine and cannabidiol and hence provide realistic estimates for the expected LGS population as confirmed by UK clinical opinion. The only exception is for mortality due to a lack of mortality data in LGS. However, UK experts highlighted that mortality remains low in practice and is not the primary outcome of interest. Extrapolation curves of mortality within the cost-effectiveness model met the expectations of the clinical experts, as they validated this is reflective of UK clinical practice. (34).

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

As described in section B.2.6., in Study 1601 and the OLE study, data were collected for patient HRQoL measures using QOLCE-16. However, those were not considered for inclusion in the cost-effectiveness analysis because it is a disease-specific measure and long-term data were not yet available. Furthermore, the EQ-5D questionnaire was not collected in Study 1601. Therefore, no health state utility (HSU) values were derived directly from trial data and alternative sources were searched instead (see section B.3.4.3 below).

B.3.4.2 Mapping

As previously mentioned, HSU values were not directly derived from the fenfluramine trial, hence, no mapping was undertaken for this economic evaluation. Instead, scientific literature was searched for EQ-5D data for LGS patients to meet NICE guidelines requirements.

B.3.4.3 Health-related quality-of-life studies

B.3.4.3.1 Identification and key characteristics of the HrQoL studies

An SLR was conducted to identify HRQoL and utility/disutility values relevant to patients with LGS and their caregivers. Full details of methodology and results of the SLR are available in Appendix H. The search was conducted on 05 October 2022 and was re-run on 07 June 2023. After full-text screening, eight unique publications were included. No records were identified from other sources.

B.3.4.3.2 Baseline patient characteristics for the selected HrQoL studies

A summary of baseline patient characteristics for selected HrQoL studies are presented in Table 50. Four of the eight publications reported outcomes only on children aged 18 years or under, (58, 147-149) while two reported on a mixed aged population(15, 80, 88). One study focused on the health utility of caregivers and children with LGS (150).

In terms of the other demographic characteristics, all but one study reported a majority of male participants (range 52-90%) (58). The median number of prior ASMs ranged from ~3 to 7(15, 148), in 3 of the 8 studies, whereas information on the number of concomitant medications was only reported by one study(88). The mean age of LGS patients ranged from 6.6 to 16 years across all studies (15, 149).

Table 50. Summary of baseline patient characteristics for selected HRQoL studies

Author, year (Study name)	Intervention (N)	Age, median (range)	Male (%)	Body Mass Index (BMI), median (range)	Number of previous ASMs (median)	Concurrent ASMs (median)	Convulsive seizure frequency (median)
Humanistic burden							
Qualitative study							
Gallop, 2010 (151)	NR (N=40)	Parent: 39 (23 - 69) Child: 12 (4–43)	Parent: 4 (10%) Child: 26 (65%)	NR	NR	NR	NR
Impact of intervention on HRQoL							
RCTs							
Devinsky, 2018 (NCT02224560) (88)	Placebo (N=76)	Mean (SD): 15.3 (9.3) range: 2.6–43.4	44 (58%)	NR	6 (1–22)	3 (1–5) Clobazam: 37 (49) Valproate (all forms): 30 (39) Levetiracetam: 23 (30) Lamotrigine: 25 (33) Rufinamide: 20 (26)	Drop attacks: 80.30 (47.8–148.0) Total seizures (all types combined): 180.60 (90.40–431.30) Non-drop attacks: 78.0 (22.0–216.0)
	Cannabidiol oral solution 10 mg/kg (N=73)	Mean (SD): 15.4 (9.5) range: 2.6–42.6	40 (55%)	NR	6 (0–21)	3 (1–5) Clobazam: 37 (51) Valproate (all forms): 27 (37) Levetiracetam: 22 (30) Lamotrigine: 22 (30) Rufinamide: 19 (26)	Drop attacks: 86.9 (40.6-190) Total seizures (all types combined): 165 (81.3- 359.0) Non-drop attacks: 95.7 (14.0-280.0)
	Cannabidiol oral solution 20 mg/kg (N=76)	Mean (SD): 16 (10.8) range: 2.6–48	45 (59%)	NR	6 (1–18)	3 (0–5) Clobazam: 36 (48) Valproate (all forms): 28 (37) Levetiracetam: 24 (32) Lamotrigine: 20 (26) Rufinamide: 26 (34)	Drop attacks: 85.5 (38.3–161.5) Total seizures (all types combined): 174.3 (82.7– 392.4) Non-drop attacks: 93.7 (22.2–278.4)

Author, year (Study name)	Intervention (N)	Age, median (range)	Male (%)	Body Mass Index (BMI), median (range)	Number of previous ASMs (median)	Concurrent ASMs (median)	Convulsive seizure frequency (median)
Knupp, 2022 Study 1601 (15)	Fenfluramine (0.2 mg/kg) (n=89)	13 (3–35)	46 (52%)	19 (20–47)	7	3	Drop attacks: 85 Motor seizures: 106 Motor and non-motor seizures: 138
	Fenfluramine (0.7 mg/kg) (n=87)	13 (2–35)	54 (62%)	9 (10–37)	7	3	Drop attacks: 83 Motor seizures: 111 Motor and non-motor seizures: 152
	Placebo (n=87)	13 (2–35)	46 (53%)	18 (11–36)	6	3	Drop attacks: 53 Motor seizures: 68 Motor and non-motor seizures: 120
Non-randomised studies							
Ding, 2016 (147)	Resective surgery (N=20)	Mean (SD): 9.70 (3.66)	13 (65%)	NR	NR	NR	NR
	Resective surgery plus Corpus Callosotomy (CCT) (N=23)	Mean (SD): 9.48 (3.88)	11 (47.8%)	NR	NR	NR	NR
	Medicine group (n=25)	Mean (SD): 9.40 (3.32)	12 (48%)	NR	NR	NR	NR
Liang, 2014 (148)	Anterior CCT (N=23)	Mean (SD): 9.48 (2.21)	16 (70%)	NR	Mean ASM 2.96 ± 0.93	NR	NR
	Rational multiple ASMs therapy* (N=37)	Mean (SD): 9.73 (2.39)	22 (60%)	NR	Mean ASM 2.71 ± 0.87	NR	NR
Case series							
Weinstock, 2019 (149)	Clobazam (N=10)	Mean (range): 6.6 (3–12)	9 (90%)	NR	NR	NR	18, range (0–94)
Utility							
Cross-sectional study							

Author, year (Study name)	Intervention (N)	Age, median (range)	Male (%)	Body Mass Index (BMI), median (range)	Number of previous ASMs (median)	Concurrent ASMs (median)	Convulsive seizure frequency (median)
Auvin, 2021 (58)	NR (subgroup: UK, N=30)	NR	6 (20%)	NR	NR	NR	NR
	NR (subgroup: France, N=20)	NR	7 (35%)	NR	NR	NR	NR
Lo, 2021 (150)	NR (subgroup: UK, N=150)	Mean (SD): 40.3 (15.2)	70 (47%)	NR	NR	NR	NR
	NR (subgroup: Sweden, N=50)	Mean (SD): 37.8 (15.8)	25 (50%)	NR	NR	NR	NR

Abbreviations: ASM, Antiseizure Medication; BMI, Body Mass Index; CCT, Corpus Callosotomy; kg, Kilogram; mg, Milligram; N, Population Number; NR, Not Reported; RCT, Randomised Controlled Trial; SD, Standard Deviation; UK, United Kingdom.

B.3.4.3.3 Summary of the HrQoL studies' results

In the next section we provide a brief summary of the utility studies. Full summary of all included HRQoL studies is provided in Appendix H.

(i) Utilities / Disutilities

As previously noted, only two cross-sectional studies reported health utility data for patients with LGS, Auvin et al. 2021 and Lo et al. 2021 (58, 150).

For Auvin et al. 2021 , surveys were conducted in the UK (n=30) and France (n=20), whereby patients and/or caregivers of patients with LGS (n=12), DS (n=3) or other epilepsies (n=35) were asked to score health state vignettes for a hypothetical patient with LGS (58, 150). Respondents reported QoL estimates for health states based on the number of seizures and seizure-free days per month using a VAS. These VAS scores were converted to the 0 to 1 scale as a proxy estimate for utility values. For both countries, as the number of seizures per month increased and the number of seizure-free days per month, utility scores, and thus QoL also decreased (Figure 28). Seizure-free days had a greater effect on utility than seizure frequency ($p < 0.001$). QoL estimates were generally higher from caregivers than patients when evaluating the impact of seizures, although the seizure-free health state was given a similar score by both caregivers and patients.

Figure 28. Mean health state utility scores for a hypothetical patient with LGS

Number of seizure-free days in an average month[a]	Lennox-Gastaut syndrome: Number of drop seizures in an average month[a]													
	UK							France						
	130	110	80	60	45	20	0	130	110	80	60	45	20	0
1	0.21	0.24	0.29	0.30	0.33			0.14	0.17	0.19	0.34	0.24		
3	0.26	0.28	0.32	0.30	0.33			0.16	0.19	0.23	0.27	0.28		
6	0.35	0.29	0.37	0.37	0.37			0.19	0.21	0.31	0.23	0.36		
9	0.36	0.39	0.38	0.40	0.39			0.22	0.22	0.28	0.32	0.34		
12	0.41	0.35	0.43	0.43	0.41	0.52		0.26	0.20	0.38	0.33	0.32	0.52	
15	0.43	0.44	0.48	0.49	0.49	0.54		0.29	0.31	0.37	0.41	0.41	0.41	
18	0.46	0.47	0.45	0.49	0.53	0.59		0.32	0.35	0.36	0.43	0.51	0.51	
30							0.83							0.79

Reference: Auvin et al. 2021 (58)
Notes: Colours illustrate the degree that frequency of drop seizures and seizure-free days impact the health state utility scores. Red shades highlight low utility scores/worse health (scores <0.3; <0.4); white, intermediate scores (0.4–0.5); green, high utility scores (>0.5; 0.7)/good health; and grey indicates comparisons that were not applicable (since the number of seizure-free days limits the maximum number of seizures per month). The mean utility score associated with each health state was obtained by converting the VAS scores to the 0–1 scale (dividing by 100). Higher frequency of drop seizures resulted in significantly lower utility scores (p=0.02, UK; p < 0.001, France), while fewer seizure-free days also resulted in lower utility scores (p<0.001, UK and France).

In Lo et al. 2021 , health state vignettes for living and caring for a child with LGS or DS were developed based on a targeted literature review and feedback from interviews with LGS and DS clinical experts and DS caregivers(150). Vignettes varied by the number of seizures and seizure-free days per month, with vignettes being evaluated via interviews from the general population in the United Kingdom and Sweden using a VAS and time trade-off (TTO) method. Health utility decreased notably for both patient and caregiver utility measures with an increase in seizure frequency (Table 51 & Table 52). Patient TTO utility values range from -0.186 (>110 seizures per month) to 0.754 (seizure-free state).

Table 51. Patient utility measures

No. of drop-seizures per month	No. of Seizure-Free Days	TTO Weights Mean (SD)	VAS Ratings Mean (SD)
Drop seizure free	>15	0.754 (0.371)	0.687(0.16)
≤45	>3–≤15	0.375 (0.575)	0.423 (0.21)
>45–≤110	>15	0.228 (0.598)	0.317 (0.19)
>45–≤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)

Reference: Lo et al. 2021 (150)
Abbreviations: SD, Standard Deviation.

Table 52. Caregiver utility measures

No. of drop-seizures per month	No. of Seizure-Free Days	TTO Weights Mean (SD)	VAS Ratings Mean (SD)
Drop seizure free	>15	0.810(0.281)	0.702 (0.18)
≤45	>3–≤15	0.572(0.479)	0.492 (0.23)
>45–≤110	>15	0.424(0.554)	0.397 (0.22)
>45–≤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)

Reference: Lo et al. 2021 (150)
Abbreviations: SD, Standard Deviation.

The SLR also conducted HTA review of previous technologies' submissions to supplement the utilities database search. The utility data included in the economic model in the recent NICE TA for cannabidiol in combination with clobazam was redacted from the submission papers and unavailable for inclusion in this SLR.

B.3.4.4 Adverse reactions

Beyond the AEs leading to treatment discontinuation (see sections B.3.3.4.1 and B.3.3.6), TEAEs of special interests were included to assess their impact patient's QoL. Those included rash, somnolence, fatigue, diarrhoea, and decreased appetite. The TEAEs used in the model were most common adverse events according to both published pivotal trials of FFA (Knupp et al. 2022) and CBD (Thiele et al. 2018) (15, 89).

In the absence of data available directly from Study 1601, a unique disutility of (-0.060) was applied to all TEAEs based on the Matza et al. 2019 study, (152) This study assessed the disutility associated with AEs of oral medications including antiepileptic treatments. In this group of treatments, disutility from AEs ranged from – 0.010 to − 0.098. Fatigue had a disutility score (-0.060), and in the absence of scores for other TEAEs of special interest, fatigue disutility was applied to all TEAEs. TEAE's was assumed to occur once in the initial cycle only and would not occur in any subsequent cycles.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Based on the SLR findings, only two studies provided health utility data (58, 150). Auvin et al. 2021 examined various types of epilepsies including DS and others, which did not align with the specific patient population mentioned in the draft scope for fenfluramine(129) . The study by Lo et al. 2021 (150) provided TTO weights and VAS ratings based on vignettes. The vignettes were developed to assess the patients and their caregivers HrQoL status, however, health states were based on the total number of drop seizures per month rather than treatment response as structured in our modelling approach.

In the absence of relevant data from the fenfluramine clinical trial and the HrQoL SLR, additional searches were conducted within the papers retrieved in the SLR one economic evaluations and NICE TA615 submission in LGS. Health utility data from a 2008 conference abstract by Verdian et al. was found to be used in several subsequent studies (142). Verdian et al. referenced this data in another 2010 cost-effectiveness analysis study (130), and Clements et al. applied it in a 2013 trial-based study (133). It was also mentioned in the previous NICE TA615 submission (40). This abstract study reported patient utilities using EQ-5D, TTO and VAS measures for four health states, categorised by the percentage reduction in seizures. These states ranged from <25% reduction in drop seizure frequencies to ≥75% reduction response.

Utility scores from Verdian et al. 2008 were the preferred choice for the base case, since these closely match EQ-5D reporting requirements as per NICE guidelines. They were also used in similar cost-effectiveness studies in LGS, and were aligned with the model's relative health state structure(130, 133). The anchor state from Verdian, defined as frequency of 21-28 drop seizures per week which is equivalent to 84+ seizures per 28 days, was considered similar to the median number of seizures in our model (70.5 per 28 days). This anchor state was therefore matched with our health state 0; the other health states used in Verdian were defined with the same level of seizure reduction categories, ≥25 - <50%, ≥50 - <75% and ≥75% reductions (Table 53).

No caregiver specific utility scores were provided by Verdian et al. so the same utility values were assumed for both patients and caregivers (130, 142). To comply with committee comments in NICE TA615 evaluation (40, 153), the base case assumes 1.8 caregivers per LGS patient. Due to the paucity of data, the effects on QoL of the siblings of children or young people with LGS were not considered. Table 53. Utility measures used in the model for patients and caregivers summarises utility measures used in the model for LGS patients and caregivers.

QALYS in the model were adjusted using mean health state utility value for individuals in the general population obtained from an EQ-5D questionnaire conducted in England as described by Ara and Brazier 2010 (154).

Table 53. Utility measures used in the model for patients and caregivers

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

Reference: Verdian et al. 2008 (142)
Abbreviations: EQ-5D, EuroQol 5 Dimensions; TTO, Time Tradeoff; VAS, Visual Analogue Scale; HS, Health State.

Table 54. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	Reference in submission (section and page number)	Justification
State 0: No response (< 25% reduction)	0.020	EQ-5D via Verdian et al. 2008 (142) Section Health-related quality-of-life data used in the cost-effectiveness analysis	• LGS patients within Study 1601 havesimilar baseline characteristics as those quoted within the clinical paper (Verdian et al. 2008) • Anchor point for drop seizures of 17.6 per week is close to the 21-28 range for the patients of the present analysis • EQ-5D scores are requested to be reported as per NICE guidelines • Utilities and health states are aligned with the current CEA in this dossier and used in previous similar studies
State 1: 25% to <50% reduction	0.100		
State 2: 50% to <75% reduction	0.500		
State 3: >=75% response	0.596		
Treatment emergent adverse event (all)	-0.060	Matza et al. 2019 (152)	• Fatigue disutility was the only TEAEs of special interest to be found in Matza et al. In the absence of other TEAEs of special interest fatigue disutility was applied to all TEAEs in the model.

Abbreviations: CEA, Cost-Effectiveness Analysis; EQ-5D, EuroQol 5 Dimensions; LGS, Lennox- Gastaut Syndrome; NICE, National Institute of Health and Care Excellence; SE, Standard Error.

B.3.5 Cost and healthcare resource use identification, measurement, and valuation

B.3.5.1 Cost and healthcare resource use studies

The SLR identified eight unique publications that reported data on the HCRU and costs for LGS patients from publications globally. Of these eight studies, five were conducted in the US and three were conducted in Europe (Netherlands, Germany, and the UK).

The SLR also conducted HTA review of previous submissions to supplement the HCRU database search. The primary care resource use data included in the recent NICE TA615 for cannabidiol in combination with clobazam was used in this analysis (40). Two further studies were identified through a desk search on general epilepsy, Tobochnik et al. 2015 and Kurth et al. 2010. These were used in the model to estimate healthcare resource use for GTC versus other types of seizures (155, 156).

Details of how relevant cost and healthcare resource data were identified and results are presented in Appendix I.

B.3.5.2 Intervention and comparators' costs and resource use

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 was calculated using the proportion of patients across age groups.

The dosing of several drugs considered in the model were weight-dependent; the model considered a fixed weight approach, based on inputted patients' mean weight by age group based on Study 1601 as summarised in Table 55 (15).

Table 55. Age distribution at start of model and mean weights by age group

Age groups	Proportion of patients used to calculate average dose (%)	Mean weight (kg)	Reference
2-5y	14.4%	17.63*	Study 1601 (15, 80)
6-11y	27.4%	30.11*	
12-17y	29.3%	48.07	
≥18y	28.9%	62.11	

**Mean weight not used in base case analysis as average age at model initiation is 13.7 years old*

B.3.5.2.1 Drug dosing

Drug dosing for the various drugs included in the basket of SoC (clobazam, levetiracetam, valproate, lamotrigine, topiramate, rufinamide) were sourced from their SmPCs.

For both cannabidiol and fenfluramine, the titration period was spread over a 2-week time period, based on respective trials and UK clinical opinion (15, 88, 89).

Fenfluramine dosing should start at 0.2mg/kg/day to gradually reach 0.4 mg/kg/day at day 7, based on the SmPC. Accordingly, the average titration dose for fenfluramine was estimated at 0.3 mg/kg/day. If well tolerated, the maximum maintenance dose is 0.7 mg/kg/day at day 14 with a cap at 26 mg/day. Patients should be tolerated up until the maximum licensed dose based on a balance between efficacy, safety and tolerability, as such a maintenance dose of 0.5mg/kg/day was implemented in the model based on the mean dose within the OLE study and from validation by UK clinical experts(1, 12, 34).

Based on the SmPC for cannabidiol, the titration period consists of progressively increasing the starting dose from 5mg/kg/day to the target maintenance dose of 20 mg/kg/day over 2 weeks. The model assumed the maintenance dose of cannabidiol in the initial maintenance cycle to be 12 mg/kg/day to align with NICE TA615 submission (40). The maintenance dose after T+M for cannabidiol was based on real-world use of cannabidiol for DS described in Silvennoinen, 2021 (145) and expert opinion stating that the dose is not expected to exceed 14mg/kg/day, as patients are titrated up to their maximum tolerable dose (34). In the CBD OLE study, the mean modal CBD dose of 24 mg/kg/day was generally consistent across each 12-week period as well as in the last 12 weeks of data for each patient. Based on response and tolerability, CBD could be reduced or increased up to 30mg/kg/day; patients who tolerated CBD were more likely to receive a higher

dose of CBD than those who did not (157). The summary of the titration dosing and maintenance dosing are presented in Table 56 and Table 57, respectively. As all drugs were administered orally, it was assumed that no cost would be associated with administration.

Table 56. Drug dosing - titration

Titration dosage / Drug	Average dose mg/kg/d	Average dose mg /d	Max dose mg/d	Reference
Fenfluramine	0.30	-	26.00	Fenfluramine SmPC (1)
Cannabidiol	5.00	-	-	Cannabidiol SmPC (72)

Abbreviations: d, Day; kg, Kilogram; mg, Milligram; SmPC, Summary of Product Characteristics.

Table 57. Drug dosing – maintenance phase

Maintenance Dosage / Drug	Age 2-5y			Age 6-11y			Age 12-17y			Age ≥18y			Reference
	Avg dose mg/kg/d	Avg dose mg/d	Max dose mg/d	Avg dose mg/kg/d	Avg dose mg/d	Max dose mg/d	Avg dose mg/kg/d	Avg dose mg/d	Max dose mg/d	Avg dose mg/kg/d	Avg dose mg /d	Max dose mg/d	
Fenfluramine	0.50	-	26.00	0.50	-	26.00	0.50	-	26.00	0.50	-	26.00	Fenfluramine SmPC (1)(Provisional), OLE, Expert opinion
Cannabidiol (after T+M)	14.00	-	-	14.00	-	-	14.00	-	-	14.00	-	-	Silvennoinen, 2021 (145) Expert opinion (34)
Clobazam	0.65	-	60.00	0.65	-	60.00	0.65	-	60.00	-	25.00	60.00	Clobazam SmPC (158)
Levetiracetam	-	-	-	-	1,000.00	-	-	1,000.00	-	-	2,000.00	-	Levetiracetam SmPC (159)
Valproate	20.00	-	2,500.00	25.00	-	2,500.00	25.00	-	2,500.00	25.00	-	2,500.00	Valproate SmPC (160)
Lamotrigine	3.00	-	200.00	3.00	-	200.00	-	150.00	-	-	150.00	-	Lamotrigine SmPC (161)
Topiramate	7	-	-	7	-	-	7	-	-	-	300	-	Topiramate SmPC (162)
Rufinamide	37.50	-	800.00	-	400.00	1,500.00	-	400.00	1,500.00	-	400.00	2,000.00	Rufinamide SmPC(163)

Abbreviations: d, Day; DS, Dravet Syndrome; kg, Kilogram; mg, Milligram; SmPC, Summary of Product Characteristics; y, Years old.

B.3.5.2.2 Drug costs

The list prices of fenfluramine and its comparator (cannabidiol) are detailed in Table 58 for their different presentations. A discount of [redacted] was applied to the list price of fenfluramine, based on the existing simple patient access scheme (PAS) discount within the DS indication.

Costs were sourced from British National Formulary 2023 (164). As SoC drugs are available in different formulations, a weighted average price per mg was calculated based on prescribing percentages obtained from the Prescription Cost Analysis (PCA)– England – 2022 shares of each formulation in England (165). Unit costs of SoC drugs are presented in Table 59.

Standard of care includes a basket of ASMs according to baseline distribution observed in Study 1601 (Table 60). The distribution of drugs in the SoC basket within the model was in line with the SoC arm from fenfluramine pivotal trial (15), except for one ASM within the cannabidiol arm where clobazam was used by 100% of patients as per the cannabidiol label (72). The total regimen cost in the first year included the cost of the titration period and the maintenance period; the cost of subsequent years only accounted for the cost of the maintenance period.

Note that Appendix K provides price details of treatments included in the submission.

Table 58. Unit cost of the compared new adjunctive therapies (FFA & CBD)

Drug	Formulation	Pack size	Cost per Pack (list price)	Dose	Cost per mg	PAS	Cost per mg after PAS	Reference
FFA	Oral solution	120ml	£1,808.88	2.2 mg/ml	£6.851	[redacted]	[redacted]	BNF UK 2023 (164)
FFA	Oral solution	360ml	£5,408.65	2.2 mg/ml	£6.829			BNF UK 2023 (164)
CBD	Oral solution	100ml	£850.29	100 mg/ml	£0.085	0%	£0.0850	BNF UK 2023 (164)

Abbreviations: BNF, British National Formulary; CBD, Cannabidiol; FFA, Fenfluramine; kg, Kilogram; mg, Milligram; PAS, Patient Access Scheme; UK, United Kingdom.

Table 59. Unit cost of the standard of care drugs and PCA shares

Drug	Cost per pack/vial (£)	Formulation	Pack/vial size	Unit strength per pack or vial (mg)	Cost per mg (£)	PCA share	Avg cost/mg (£)	Reference
Clobazam	£76.55	Oral solution	150.0	1.0	£0.5103	7.9%	£0.0734	**Drug cost:** BNF UK 2023 (164) **PCA share**: Prescription Cost Analysis – England – 2022. National summary tables - financial year (165)
	£88.14	Oral solution	150.0	2.0	£0.2938	4.9%		
	£6.43	Tablets	30.0	10.0	£0.0214	87.2%		
Levetiracetam	£1.96	Tablets	60.0	250.0	£0.0001	27.5%	£0.0001	
	£3.96	Tablets	60.0	500.0	£0.0001	39.5%		
	£4.26	Tablets	60.0	750.0	£0.0001	8.6%		
	£6.28	Tablets	60.0	1000.0	£0.0001	16.6%		
	£22.41	Granules	60.0	250.0	£0.0015	0.3%		
	£39.46	Granules	60.0	500.0	£0.0013	0.3%		
	£76.27	Granules	60.0	1000.0	£0.0013	0.1%		
	£6.89	Oral solution	300.0	100.0	£0.0002	7.1%		
Valproate	£2.31	GR tablets	30.0	200.0	£0.0004	37.0%	£0.0004	
	£5.78	GR tablets	30.0	500.0	£0.0004	33.2%		
	£5.67	MR tablets	30.0	500.0	£0.0004	5.0%		
	£1.68	Tablets	30.0	100.0	£0.0006	8.7%		
	£8.24	Oral solution	300.0	40.0	£0.0007	12.6%		
	£3.40	MR tablets	30.0	300.0	£0.0004	3.5%		
Lamotrigine	£1.48	Tablets	56.0	25.0	£0.0011	20.4%	£0.0007	
	£1.16	Tablets	56.0	50.0	£0.0004	29.2%		
	£1.58	Tablets	56.0	100.0	£0.0003	33.2%		
	£2.31	Tablets	56.0	200.0	£0.0002	12.3%		
	£13.90	Dispersible tablets	56.0	100.0	£0.0025	2.3%		

Drug	Cost per pack/vial (£)	Formulation	Pack/vial size	Unit strength per pack or vial (mg)	Cost per mg (£)	PCA share	Avg cost/mg (£)	Reference
	£8.72	Dispersible tablets	56.0	25.0	£0.0062	2.7%		
Topiramate	£1.34	Tablets	60.0	25.0	£0.0009	38.7%	£0.0015	
	£1.71	Tablets	60.0	50.0	£0.0006	32.4%		
	£2.25	Tablets	60.0	100.0	£0.0004	20.2%		
	£23.83	Tablets	60.0	200.0	£0.0020	2.9%		
	£14.79	MR capsules	60.0	15.0	£0.0164	0.9%		
	£22.18	MR capsules	60.0	25.0	£0.0148	3.0%		
	£36.45	MR capsules	60.0	50.0	£0.0122	2.0%		
	£186.00	Oral solution	150.0	10.0	£0.1240	0.0%		
	£285.00	Oral solution	280.0	20.0	£0.0509	0.0%		
Rufinamide	£5.15	Tablets	60.0	100.0	£0.0009	15.0%	£0.0042	
	£61.77	Tablets	60.0	200.0	£0.0051	23.6%		
	£102.96	Tablets	60.0	400.0	£0.0043	38.6%		
	£94.71	Oral solution	460.0	40.0	£0.0051	22.7%		

Abbreviations: BNF, British National Formulary; GR, Gastroresistant; kg, Kilogram; mg, Milligram; MR, Modified Release; PCA, Pharmacy and Appliance Contractors; UK, United Kingdom.

Table 60. Distribution of patients taking SoC ASMs in each arm

Technology	FFA +.SoC	CBD w CLB + SoC	SoC only	Reference
Clobazam	44%	100%	44%	Study 1601 (15) ASM distribution at baseline in the SoC arm. CBD SmPC for 100% concomitant clobazam (72)
Levetiracetam	23%	23%	23%	
Valproate	56%	56%	56%	
Lamotrigine	33%	33%	33%	
Topiramate	0%	0%	0%	
Rufinamide	21%	21%	21%	

Abbreviations: ASM, Antiseizure Medications; CBD, Cannabidiol, CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; SoC, Standard of Care; SmPC, Summary of Product Characteristics.

B.3.5.3 Subsequent treatment costs

The model assumes a basket of treatment in subsequent lines will be given to patients who discontinue either fenfluramine or cannabidiol treatments . The distribution of the treatments within the basket is assumed to be the same as the SoC arm of the Study 1601 (15) and applied for both cannabidiol and fenfluramine arms once patients discontinue either treatment (as is presented in Table 61).

Table 61. Patient distribution in subsequent treatment applied to all patients

Technology	Patient distribution (%)	Reference
Clobazam	44%	Study 1601 (15) ASM distribution at baseline in the SoC arm.
Levetiracetam	23%	
Valproate	56%	
Lamotrigine	33%	
Topiramate	0%	
Rufinamide	21%	

Abbreviations: ASM, Antiseizure Medication; FFA, Fenfluramine; SoC, Standard of Care.

B.3.5.4 Health-state unit costs and resource use

Two types of HCRU costs are considered in the model: primary care (also referenced as LGS routine care) and secondary care (also referenced as seizure associated care). Health states were 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. Calculation to obtain this equivalence was described in section B.3.2.2 Model structure.

Resource use for primary care routine-care cost was estimated across categories of mean number of drop seizure, i.e., (0, <45, 45-110 and >110) from NHS - cannabidiol submission (2019) (40).

Resource use for seizure-associated secondary care costs was estimated separately for GTC and other seizure types. Distribution of GTC and other seizures at T+M for each arm was estimated

based on the observed GTC seizure reduction in the Study 1601 (15). Calculation was described in section Reduction in GTC seizures to inform healthcare resource use costs.

B.3.5.4.1 Primary care

Health state costs in the model were 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 was matched (as best as possible) to three seizure frequency ranges for the purpose of estimating the resource use consumption associated to each health state (Table 62).

Table 62. Mean number of drop seizures for each health state

Median points (T+M)	Calculated mid-point (number of drop-seizures per last 28 days)	Matched ranges of seizures frequencies for HCRU estimation	References
State 0: < 25% reduction	101.40	> 110	Using Study 1601 data (median % change in state 0 for FFA 0.7 mg)
State 1: 25% to<50% reduction	44.06	>45 to ≤ 110	Mid-points are used between 25 and 50%
State 2: 50% to<75% reduction	26.44	≤ 45	Mid-points are used between 50 and 75%
State 3: >75% response	11.20	≤ 45	Using Study 1601 (median % change in state 0 for FFA 0.7 mg)

Reference: UCB 2022 Fenfluramine Study Statistical Analysis (137)
Abbreviations: FFA, Fenfluramine; HCRU, Healthcare Resource Use; kg, Kilogram; mg, Milligram; T+M, Titration and Maintenance.

The HCRU inputs associated with the number of seizures were sourced from UK clinical experts and obtained from the NICE cannabidiol submission (TA615)(40).

The HCRU were 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 63.

Table 63. Number of annual primary care visits per seizure numbers and per age groups

Healthcare resource utilisation (seizure number-related)	Age <12y			Age ≥12y			Reference
	≤ 45	>45 to ≤ 110	> 110	≤ 45	>45 to ≤ 110	> 110	
	# annual visits						
Nurse visit	4.0	8.0	12.0	4.0	4.8	12.0	UK Clinical Experts, NICE TA615 (40)
Specialist visit	2.0	4.0	6.0	1.0	1.2	3.0	
Paediatrician/general practitioner visit	4.0	8.0	12.0	0.0	0.0	0.0	
Phone call follow-up	2.0	5.0	12.0	1.0	2.5	6.0	
Rescue medication per intake	2.0	5.0	8.0	2.0	5.0	8.0	

Abbreviations: HCRU, healthcare resource use; NICE, National Institute of Health and Care Excellence; UK, United Kingdom; y, year

All unit costs for the primary care healthcare resources are reported in Table 64 and were sourced from the NHS reference costs for the year 2021-22 (166) and Personal Social Services Research Unit 2022 (167). It was assumed that the cost for paediatric services would only apply to patients below the age of 12-years old.

Similar to the SoC drugs costs described in section Drug costs, rescue medications are available in different formulations. Hence, a weighted average price per mg was calculated based on prescribing proportions obtained from the Prescription Cost Analysis – England – 2022 shares of each formulation in England (Table 65). Drug dosing for rescue medication is described in Table 66.

Table 64. Healthcare unit costs for primary care

Healthcare Resource (Unit cost)	Cost year	Age < 12y	Age 12-18y	Age >18y	Reference
		Cost per visit (£)	Cost per visit (£)	Cost per visit (£)	
Physician visits (paediatrician)	2022	£224.00	N/A	N/A	PSSRU 2021 - Paediatric consultant-led outpatient attendance for health services
Specialist visit	2022	£416.00	£214.00	£214.00	NHS England 2023 1. Outpatient Attendances Data. Service code: 421 - Paediatric Neurology TOTAL COST 2. Outpatient Attendances Data. Service code: 400 – Neurology Unit cost total
Nurse visit	2022	£57.00	£57.00	£57.00	PSSRU 2022 - Epilepsy nurse specialist visit: 9.2 Nurses - Band 6
Phone Call Follow-up	2022	£41.13	£41.13	£41.13	PSSRU 2022 - Average cost of e-consultation

References: PSSRU 2021 (168), NHS England 2023 (166), PSSRU 2022 (167)
Abbreviations: GP, General Practitioner; N/A, Not Applicable; NHS, National Healthcare Service; PSSRU, Personal Social Services Research Unit.

Table 65. Unit cost of the medications and PCA shares

Drug	Cost per pack/vial (£)	Formulation	Pack/vial size	Unit strength per pack or vial (mg)	Cost per mg (£)	PCA share	Avg cost/mg (£)	Reference
Diazepam	£5.85	2.5 ml rectal solution	5.0	5.0	£0.2340	37.5%	£0.18	Drug cost: BNF UK 2023 (164) PCA share: Prescription Cost Analysis – England – 2022. National summary tables - financial year (165)
	£7.53	2.5 ml rectal solution	5.0	10.0	£0.1506	62.5%		
Midazolam	£75.00	2ml pre-filled oral syringes	4.0	10.0	£1.8750	53.9%	£2.62	
	£65.00	0.5 ml pre-filled oral syringes	4.0	2.50	£6.5000	4.4%		
	£70.00	1ml pre-filled oral syringes	4.0	5.00	£3.5000	18.0%		
	£70.00	1.5ml pre-filled oral syringes	4.0	7.50	£2.3333	17.5%		
	£45.76	1 ml pre-filled oral syringes	1.0	10.00	£4.5760	6.2%		

Abbreviations: BNF, British national formulary; kg, Kilogram; mg, Milligram; PCA, Pharmacy and Appliance Contractors; UK, United Kingdom.

Table 66. Drug dosing – rescue medication

Maintenance Dosage / Drug	Age 2-5y			Age 6-11y			Age 12-17y			Age ≥18y			Reference
	Avg dose mg/kg/d	Avg dose mg/d	Max dose mg/d	Avg dose mg/kg/d	Avg dose mg/d	Max dose mg/d	Avg dose mg/kg/d	Avg dose mg/d	Max dose mg/d	Avg dose mg/kg/d	Avg dose mg /d	Max dose mg/d	
Diazepam	-	7.50	20.00	-	7.50	20.00	-	15.00	40.00	-	15.00	40.00	Diazepam SmPC
Midazolam	-	5.00	10.00	-	7.50	-	-	10.00	20.00	-	10.00	20.00	Midazolam SmPC

Abbreviations: d, Day; kg, Kilogram; mg, Milligram; SmPC, Summary of Product Characteristics; y, Years old.

Costs and HCRU were then weighted by the baseline age distribution found in the fenfluramine trial to obtain an average cost per patient per cycle for each health state. Total routine care cost per patient and per 3-month duration cycle can be found in Table 67.

Table 67. Routine care cost per patient per 3 months cycle

Routine care costs per patients per cycle	≤ 45	>45 to ≤ 110	> 110
Nurse visit	£57.00	£87.47	£171.00
Specialist visit	£105.83	£176.94	£317.50
Paediatrician/general practitioner visit	£93.69	£187.38	£281.06
Phone call follow-up	£14.58	£36.46	£87.50
Rescue medication (per number of medicine intake)	£2.64	£6.59	£10.54
Total routine care cost	**£273.74**	**£494.83**	**£867.60**

Note: Calculated in the cost-effectiveness model

B.3.5.4.2 Secondary care

The model used efficacy data on proportion of reduction in GTC seizure in the fenfluramine and cannabidiol arms to proportionally weight the cost for each state to account for secondary care costs. The way the model accounts for GTC seizure reduction is further explained in section Reduction in GTC seizures to inform healthcare resource use costs.

The HCRU costs for secondary care were based on HCRU hospitalisations (both general ward and intensive care unit inpatient admissions) and emergency department visits to calculate per patient per cycle cost of secondary care for each seizure type.

The HCRU for LGS patients was first calculated to account for patient's age distribution using Chin et al. (2021) data on confirmed LGS, as presented in Table 68. Of note, the proportion of inpatients requiring ICU visits presented in Table 68 was considered independent from seizure type or age distribution and was sourced from Tobochnik et al. (2015)(155).

Then, the HCRU for each seizure type (GTC and other seizures) was estimated from a publication on epileptic patients by Kurth et al. (2010)(156) and is presented in Table 69. These data were used to derive the final HCRU for LGS patients adjusted by seizure type in Table 70.

Cost of secondary care were calculated using the unit costs presented in Table 70.The costs of secondary care per patient per cycle were split between costs incurred for GTC seizure types and costs incurred for other seizure types and are presented in Table 70.

Table 68. Healthcare utilisation per year per LGS patient adjusted for age

Healthcare resource utilisation of LGS patients	Age <12y	Age >12y	Age <12y	Age >12y	LGS HCRU adjusted for age	Reference
	Mean (SD)		Population distribution			
Number of hospital inpatient admissions, PPY	1.50 (1.47)	0.96 (1.78)	41.83%	58.17%	1.19	Chin et al. (2021)(36) - HCRU for confirmed LGS patients in the UK
Hospital inpatient length of stay (LOS), days*	2.48 (6.07)	3.24 (6.80)	41.83%	58.17%	2.92	
Number of A&E visits, PPY	0.85 (1.18)	1.15 (2.17)	41.83%	58.17%	1.02	
Proportion of inpatients requiring ICU visits	N/A	N/A	N/A	N/A	4.2%	Tobochnik et al. (2015)(155)

** This input is used to calculate the number of hospital admissions in Table 69.*
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 69. Healthcare utilisation per year for epileptic patients adjusted for seizure type

Healthcare resource utilisation of LGS patients	GTC seizures	Other seizures	Seizure distribution at baseline		Average HCRU (adjusted for seizure type)	Reference
			GTC	Other		
Hospital admissions*	2.14	0.71	62.00%	38.00%	1.60	Kurth et al. (2010) (156)
Hospital days	6.26	2.08	62.00%	38.00%	4.67	
Emergency department visits	1.52	0.78	62.00%	38.00%	1.24	

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

Table 70. Healthcare utilisation of LGS per patient per year per seizure type

Healthcare resource utilisation of LGS patients	GTC seizures	Other seizures	Reference
Number of hospital inpatient admissions, PPY	1.59	0.53	Calculated: (GTC HCRU in Table 69/Average HCRU adjusted for seizure type in Table 69) * LGS HCRU adjusted for age in Table 68 (Other HCRU in Table 69/Average HCRU adjusted for seizure type in Table 69) * LGS HCRU adjusted for age in Table 68
Hospital inpatient LOS, days	3.92	1.30	
Number of emergency department visits, PPY	1.26	0.65	

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

Table 71. Healthcare unit costs for secondary care

Healthcare Resource (Unit cost)	Cost year	Age < 12y	Age 12-18y	Age >18y	Reference
		Cost per visit (£)	Cost per visit (£)	Cost per visit (£)	
Inpatient admissions (general ward)	2022	£724.10	£607.24	£607.24	1. NHS England 2023. NON ELECTIVE SHORT STAY - Admitted patient care - Code PR02A/PR02B/PR02C : Paediatric Epilepsy Syndrome with CC Score 0 / Score 1-5 / Score 6+ - weighted average 2. NHS England 2023. NON ELECTIVE SHORT STAY - Code [AA26C < > AA26H] : Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC [Score 0-2 < > Score 15+] - weighted average
Inpatient admissions (ICU)	2022	£3,102.49	£2,137.90	£2,137.90	1. NHS England 2023. CRITICAL CARE - PD Paediatric - Code [XB01Z < > XB09Z] - weighted average 2. NHS England 2023. CRITICAL CARE - CCU05 Neurosciences adult patients predominate - Code [XC01Z < > XC07Z] - weighted average
Emergency department (ED) visits	2022	£279.60	£279.60	£279.60	1.Assumed same cost for paediatrics 2. NHS England 2023: EMERGENCY MEDICINE - WEIGHTED AVERAGE. Service code T01A-T03A-1 Currency Code: VB01Z-VB02Z-VB03Z-VB04Z-VB05Z-VB06Z-VB07Z-VB08Z-VB09Z

Reference: NHS England 2023 (166)
Abbreviations: ED, Emergency Department; ICU, Intensive Care Unit; NHS, National Healthcare Service.

Table 72. Secondary care costs per patient per 3 months cycle per seizure type

Secondary care costs per patient per cycle	GTC	Others
Hospitalisation	£292.17	£97.08
Emergency department visits	£87.87	£45.09
Total routine care cost	**£380.04**	**£142.17**

Note: Calculated in the cost-effectiveness model
Abbreviations: GTC, Generalised Tonic-Clonic.

B.3.5.5 Drug monitoring

Patients on fenfluramine 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 (1). The cost associated with an echocardiogram was sourced from the 2022/23 National Tariff Payment system and the yearly costs associated with drug monitoring are summarised in Table 73.

Table 73. Cost of echocardiogram

Monitoring resources	Cost year	Age <18y	Age ≥18y	References
		Average cost (£)	Average cost (£)	
Echocardiogram	2022	£100.00	£83.00	- Code: RD51B and RD51C (Simple Echocardiogram, between 0 and 18 years) - Code: RD51A (Simple Echocardiogram, 19 years and over)

Reference: NHS 2022 (169)
Abbreviations: NHS, National Healthcare Service.

B.3.5.6 Adverse reaction unit costs and resource use

In line with NICE cannabidiol submission (TA615) (40), the cost of managing adverse events was assumed to be equal to that of one visit to a specialised nurse. The cost was sourced from Personal Social Services Research Unit 2022 (167). Adverse event costs are applied as a one-off cost in the first cycle when patients start treatment (Table 74).

Table 74. Adverse event related costs

Adverse events	Unit cost	Cost year
Diarrhoea	£57.00	2022
Somnolence	£57.00	2022
Pyrexia	£57.00	2022
Decreased appetite	£57.00	2022
Vomiting	£57.00	2022

References: PSSRU 2022(167)

B.3.5.7 Mortality costs

In line with the NICE TA615, it was assumed that all patients will require an emergency department visit and an ICU visit prior to death. As a result, a one-off terminal care cost was applied to patients at time of death (Table 75).

Table 75. Mortality costs

Mortality resources	Costs	Age distributions
Emergency department visit <18 years of age	£279.60	71.1%
Emergency department visit >= 18 years of age	£279.60	28.9%
Intensive care unit <18 years of age	£2,795.31	71.1%
Intensive care unit >=18 years of age	£2,137.90	28.9%
Total average cost (£)	**£2,820.94**	

References: NICE [TA615] 2019(40), PSSRU 2022 (167); Knupp et al. 2022 (15)

B.3.6 Severity modifier eligibility

Fenfluramine meets the criteria for a severity weight of x 1.7. According to the SLR findings, there were no QALY shortfall calculated for previous NICE appraisals in this indication. Therefore, it was not possible to provide a summary list of QALY shortfall from previous evaluations.

B.3.6.1 QALY shortfall calculation

To calculate the QALY shortfall, we considered the total quality adjusted life years (QALYs) achieved by LGS patients under NHS standard care and the total quality adjusted life expectancy (QALE) for the general population with same age and sex distribution. The total QALYs for LGS patients were estimated over a lifetime horizon from the cost-effectiveness analysis, focusing on the “patients treated with SoC” arm. The model employed health state utility values from Verdian et al. 2008 EQ-5D study. Details of utility values per health state are outlined in Table 76 and the calculated discounted LYs and QALYs for each health state are provided in Table 77.

The total QALYs for general population’s was estimated using the Schneider et al. calculator (170) with the tool’s reference case scenario by Hernandez Alava et al. 2022 applied (171). Age and

gender parameters were adjusted to match baseline LGS patient characteristics provided in section 3.3.1 (Knupp et al. 2022). A 3.5% discounting rate was applied as per NICE reference case. Features of the QALY shortfall analysis are summarised in Table 78.

Table 76. Summary of utility values for QALY shortfall analysis

Patient states	EQ-5D	Reference
State 0: No response (< 25% reduction)	0.020	Verdian et al. 2008 (142)
State 1: Response group 1: 25% to <50% reduction	0.100	
State 2: Response group 2: 50% to <75% reduction	0.500	
State 3: Response group 3: >=75% response	0.596	

Abbreviations: EQ-5D, EuroQol 5 Dimensions.

Table 77. Summary of health state benefits and utility values for QALY shortfall analysis

Health State - LGS	Total LYs (discounted)	Total QALYs (discounted)
State 0	0.97	0.02
State 1	0.34	0.04
State 2	0.23	0.12
State 3	0.09	0.05
Discontinued	18.52	0.35
Dead	0	0
Total	20.15	0.58

Abbreviations: LGS, Lennox-Gastaut Syndrome; LY, Life Years; QALY, Quality-Adjusted Life Years.

Table 78. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference / note
Sex distribution	55.5% male, 44.5% female*	See section Baseline patient characteristics
Starting age	13.7 years*	See section Baseline patient characteristics
Selected scenario	Reference case: measurement and valuation of health (MVH) value set+ Health Survey for England (HSE) 2014 adjusted limited dependent variable mixture mode (ALDVMM) model	Hernandez Alava et al. 2022 (172)
Discount rate	3.5%	As per NICE base case
Total QALYs of General population (discounted)	23.55	Calculated using current CEA's LGS patients treated with SoC

**The calculator only allows integers, so 45% was applied to the percentage of females and 14 years old to the starting age.*
Abbreviations: ALDVMM, Adjusted Limited Dependent Variable Mixture Mode, CEA, Cost-Effectiveness Analysis; HSE, Health Survey for England; LGS, Lennox-Gastaut Syndrome; MVH, Measurement and Valuation of Health; NICE, National Healthcare Institute; QALY, Quality-Adjusted Life Years, SoC, Standard of Care.

B.3.6.2 Estimated QALY Weight

Based on the abovementioned, results of the QALY calculator were generated as shown in Table 80. The estimated absolute QALY shortfall was 22.97 and the proportional QALY shortfall was 0.98. Both values satisfy thresholds corresponding to a QALY weight of x1.7 (Table 79). Fenfluramine, therefore, meets the criteria for a severity weight of x 1.7. Summary of the analysis results are provided in Table 80.

Table 79. QALY weights for severity

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

Reference: NICE 2022 manual (173)
Abbreviations: QALY, Quality-Adjusted Life Years.

The severity weight calculation relies on assumptions on population age, sex, and the calculated QALYs achieved by LGS patients under NHS standard of care. The severity modifier is applied as a QALY weight on all interventions.

Table 80. Summary of QALY shortfall analysis

Category	Value
Total QALYs - General population	23.55
Total QALYs – LGS patients treated with SoC	0.58
Absolute QALY shortfall	22.97
Proportional QALY shortfall	0.98
QALY weight	x1.7

Abbreviations: QALY, Quality-Adjusted Life Years; SoC, Standard of Care.
Values calculated using Schneider et al. online calculator available at: https://shiny.york.ac.uk/shortfall/

B.3.7 Uncertainty

The principal areas of uncertainty in this analysis relate to the rarity of LGS, its heterogeneous clinical presentation, and variation in the management of patients in clinical practice. These issues are expected to impact the precision of the outcomes in the analysis.

The heterogeneity among LGS patients limits the predictability of clinical effectiveness studies. This would ideally be addressed by collecting data on a larger number of patients. However, this would be extremely difficult to achieve as LGS is rare, patient numbers are small and diagnosis of LGS in clinical practice is not straightforward (174). The latter also compounds complexity as symptoms among patients tend to evolve between childhood and adulthood (78).

Also, as there is no head-to-head clinical trial between fenfluramine and cannabidiol with clobazam, the efficacy data for parts of the analysis were derived from an ITC which makes its own assumption on the transitivity and homogeneity of patients compared across trials, which is bound to increase uncertainty over results.

B.3.8 Managed access proposal

Not applicable

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of the model parameters used for the base case analysis is presented in Table 81.

Table 81. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings			
General options			
Time horizon (years)	86 years	Scenario: 15 y	B.3.2.2
Half-cycle correction	Included	N/A	B.3.2.2
Comparator cohort	CBD w CLB + SoC	SoC in complementary analysis	B.3.2.3
Baseline distribution adjustment	Included (e.g., patients distributed at FFA trial as baseline)	N/A	B.3.2.2
Discounting rate of benefits (%)	3.5%	DSA: 0 – 6%	B.3.2.2
Discounting rate of costs (%)	3.5%	DSA: 0 – 6%	B.3.2.2
Costing options			
Acquisition costs	Included	N/A	B.3.5.2
Drug monitoring costs	Included	N/A	B.3.5.5
Disease management costs (routine care cost)	Included	N/A	B.3.5.4
Disease management costs (secondary care cost)	Included	N/A	B.3.5.4
Mortality costs	Included	N/A	B.3.5.7
Adverse event costs	Included	N/A	B.3.5.6
Indirect costs	Excluded	N/A	N/A
Use of concomitant ASMs	Study 1601	N/A	B.3.5.2
Population used for NMA	on CLB (GBA data)	Scenario: on CLB (EMA data)	B.2.9.4
Patient distribution of ASM			
Proportion with ASM (FFA + SoC) (%)			
Valproate	56%	Deterministic sensitivity analysis (DSA) / Probabilistic sensitivity analysis (PSA): ±20% (Beta)	B.3.5.3
Clobazam	44%		
Lamotrigine	33%		
Levetiracetam	23%		
Rufinamide	21%		
Topiramate	0%		
Proportion with ASM (CBD w CLB+ SoC)			
Valproate	56%	DSA/PSA: ±20% (Beta)	B.3.5.3

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Clobazam	100%	N/A	
Lamotrigine	33%	DSA/PSA: ±20% (Beta)	
Levetiracetam	23%		
Rufinamide	21%		
Topiramate	0%		
Proportion with ASM (SoC)			
Valproate	56%	DSA/PSA: ±20% (Beta)	B.3.5.3
Clobazam	44%		
Lamotrigine	33%		
Levetiracetam	23%		
Rufinamide	21%		
Topiramate	0%		
Subsequent treatments			
Proportion moving to new line (among discontinued patients)	100%	N/A	B.3.5.3
Subsequent treatment basket			
Clobazam	44%	N/A	B.3.5.3
Levetiracetam	23%		
Valproate	56%		
Lamotrigine	33%		
Topiramate	0%		
Rufinamide	21%		
Costing approach			
Seizure-event costing approach	Confirmed LGS	N/A	B.3.5.4.2
FFA discount price (%)	[redacted]	N/A	B.3.5.2.2
Weight calculations			
Weight calculations option	Fixed (based on inputted mean weight per age group)	N/A	B.3.5
Clinical inputs			
Baseline characteristics			
Average age at model initiation (years)	13.7 years	N/A	B.3.3.1
Proportion male (%)	55.5%	DSA/PSA: ±20% (Beta)	
Median number of drop seizures per 28 days	70.50	DSA/PSA: 30 – 110 (Gamma)	
Baseline proportion of GTC (%)	62.0%	DSA/PSA: ±20% (Beta)	
Health state baseline distribution (%)			
State 0 (< 25% reduction)	32%	N/A	B.3.3.1
State 1 (25% to <50% reduction)	22%	N/A	
State 2 (50% to <75% reduction)	38%	N/A	
State 3 (≥75% reduction)	8%	N/A	
Age distribution at start of the model – proportion of patients (%)			
2-5 y of age	14.4%	N/A	B.3.3.1
6-11 y of age	27.4%		
12-17 y of age	29.3%		
>=18 y of age	28.9%		

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Rescue medications (proportion used %)			
Diazepam	67%	DSA/PSA: ±20% (Beta)	B.3.3.1
Midazolam	33%	N/A	
Titration period (weeks)			
Titration FFA + SoC (weeks)	2 weeks	DSA/PSA: ±20% (Lognormal)	
Titration CBD w CLB+ SoC (weeks)	2 weeks	DSA/PSA: ±20% (Lognormal)	
Weight parameters (kg)			
2-5 y of age	17.63kg	DSA/PSA: SE = 3.68 (Normal)	B.3.3.1
6-11 y of age	30.11kg	DSA/PSA: SE = 9.74 (Normal)	
12-17 y of age	48.07kg	DSA/PSA: SE = 14.02 (Normal)	
18 -35 y of age	62.11kg	DSA/PSA: SE = 18.86 (Normal)	
>35 y of age	78.00kg	DSA/PSA: SE = 18.86 (Normal)	
Discontinuation			
Discontinuation due to Stopping rule (from cycle 3 to time horizon)			
Approach	Discontinue if <25% response	Scenario: Discontinue if <50% response	B.3.2.2
Frequency (months)	3 months	N/A	
Discontinuation due to AE			
Relative Risks of discontinuation due to AE at T+M (NMA data)			
Treatment vs SoC			
CBD + SoC - Weighted dosing	[redacted]	DSA: [redacted] PSA: ±20% (Lognormal)	B.3.3.4.1
CBD 10 mg/kg/day + SoC	[redacted]	N/A	
CBD 20 mg/kg/day + SoC	[redacted]	N/A	
FFA (0.7 mg/kg) + SoC	[redacted]	DSA: [redacted] PSA: ±20% (Lognormal)	
Discontinuation due to AE (%) for SoC (at any cycle)			
SoC cohort			
Titration (initial cycle)	0.0%	N/A	B.3.3.4.1
Cycle 1 (T+M) and all follow-up cycles	1.1%	DSA/PSA: ±20% (Beta)	B.3.3.4.1
Discontinuing patients due to AE (%) – FFA + SoC			
Titration	2.3%	DSA/PSA: ±20% (Beta)	B.3.3.4.1
Cycle 1 (T+M)	7.3%		
Cycle 2	3.7%		
Cycle 3	4.1%		
Cycle 4	1.6%		
Cycle 5 (FFA - OLE)	0.0%		
Cycle 6	0.0%		

Variable		Value		Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Cycle >=7 (CBD - OLE)		0.0%			
Discontinuing patients due to AE (%) – CBD w CLB + SoC					
Titration		2.3%		DSA/PSA: ±20% (Beta)	B.3.3.4.1
Cycle 1 (T+M)		8.5%			
Cycle 2		6.8%			
Cycle 3		5.9%			
Cycle 4		4.7%			
Cycle 5 (FFA - OLE)		1.3%			
Cycle 6		1.0%			
Cycle >=7 (CBD - OLE)		0.0%			
Cognitive impact on discontinuation		Excluded		N/A	N/A
Discontinuation due to lack of efficacy (%)		Titration and cycle 1	6 months (cycle 2)		
SoC		0.0%	0.0%	N/A	B.3.3.4.2
FFA + SoC		0.0%	7.3%	DSA/PSA: ±20% (Beta)	
CBD w CLB + SoC		0.0%	7.3%	DSA/PSA: ±20% (Beta)	
Treatment-emergent adverse events, waning and mortality					
Treatment-emergent adverse events – 3-month probabilities (by type and comparator)					
SoC	Diarrhoea	0.05		DSA/PSA: ±20% (Beta)	B.3.3.6
	Somnolence	0.1			
	Pyrexia	0.11			
	Decreased appetite	0.11			
	Vomiting	0.06			
FFA + SoC	Diarrhoea	0.13		DSA/PSA: ±20% (Beta)	
	Somnolence	0.17			
	Pyrexia	0.08			
	Decreased appetite	0.36			
	Vomiting	0.08			
CBD w CLB + SoC	Diarrhoea	0.13		DSA/PSA: ±20% (Beta)	
	Somnolence	0.14			
	Pyrexia	0.01			
	Decreased appetite	0.09			
	Vomiting	0.07			
Treatment waning					
Treatment waning per cycle (after cycle 9)		Included		Scenario: Excluded	B.3.3.5
Proportion of patients undergoing waning due to lack of efficacy (long-run) –	FFA + SoC	5.2%		N/A	
	CBD w CLB +SoC	5.2%		Scenario: 19.6%	
	SoC	0.0%		N/A	

Variable		Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Mortality				
Mortality source		General mortality + SUDEP + non-SUDEP	N/A	B.3.3.7
SUDEP: 3-months probabilities (applied through all model duration)				
Baseline SUDEP		0.00233	DSA/PSA: 0.0015 – 0.0049 (Beta)	B.3.3.7
State 0: No response (< 25% reduction)		0.00335	Scenario: same as baseline SUDEP	
State 1: Response group 1: 25% to <50% reduction		0.00146	Scenario: same as baseline SUDEP	
State 2: Response group 2: 50% to <75% reduction		0.00087	Scenario: same as baseline SUDEP	
State 3: Response group 3: >=75% response		0.00037	Scenario: same as baseline SUDEP	
Status epilepticus and accidental mortality (applied through all model duration)				
Status epilepticus (SE) mortality: 3-month probability		0.00093	DSA/PSA: ±20% (Beta)	B.3.3.7
Additional proportion of accidental mortality compared to SE+ SUDEP mortality		21.40%	DSA/PSA: ±20% (Beta)	
Efficacy inputs				
Efficacy model settings				
Efficacy data – time point (NMA data)		Cycle 1 (T +M)	N/A	B.3.2.2
Efficacy duration		27 months (long-term efficacy)	N/A	
Efficacy parameters impacting transition probabilities: Response proportions at T+M (3 months follow-up)				
Proportion in each state – binomial relative risks (used in the model)				
FFA 0.7 mg/kg/day + SoC	>=25%	[redacted]	DSA/PSA: [redacted] (Lognormal)	B.3.3.2
	>=50%	[redacted]	DSA/PSA: [redacted] (Lognormal)	
	>=75%	[redacted]	DSA/PSA: [redacted] (Lognormal)	
CBD - Weighted dosing + SoC	>=25%	[redacted]	DSA/PSA: [redacted] (Lognormal)	
	>=50%	[redacted]	DSA/PSA: [redacted] (Lognormal)	
	>=75%	[redacted]	DSA/PSA: [redacted] (Lognormal)	
Proportion of patients in each state at T+M for SoC				
>=25%		31%	N/A	B.3.3.2
>=50%		10%		
>=75%		5%		
Calculated state occupancy at cycle 2 (after T+M)				
SoC	< 25%	69.0%	N/A	B.3.3.2
	>=25%	20.7%		

Variable		Value				Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	>=50%	5.7%					
	>=75%	4.6%					
FFA + SoC	< 25%	[redacted]					
	>=25%	[redacted]					
	>=50%	[redacted]					
	>=75%	[redacted]					
CBD w CLB + SoC	< 25%	[redacted]					
	>=25%	[redacted]					
	>=50%	[redacted]					
	>=75%	[redacted]					
Transition probabilities (from cycle 2)							
FFA + SoC							
TP matrices		State 0	State 1	State 2	State 3		
Cycle 2 (3-6 months)	State 0	[redacted]				PSA (Dirichlet)	B.3.3.2
	State 1	[redacted]					
	State 2	[redacted]					
	State 3	[redacted]					
Cycle 3 (6-9 months)	State 0	[redacted]					
	State 1	[redacted]					
	State 2	[redacted]					
	State 3	[redacted]					
Cycle 4 (9-12 months)	State 0	[redacted]					
	State 1	[redacted]					
	State 2	[redacted]					
	State 3	[redacted]					
Cycle 5 (12-15 months)	State 0	[redacted]					
	State 1	[redacted]					
	State 2	[redacted]					
	State 3	[redacted]					
Cycle 6-9 (up to 27 months)	State 0	[redacted]					
	State 1	[redacted]					
	State 2	[redacted]					
	State 3	[redacted]					
Cycles 10+		Patients remain in the same health state					
CBD w CLB + SoC							
State occupancy		State 0	State 1	State 2	State 3		
Cycle 2 (3-6 months)		0.308	0.201	0.201	0.291	PSA (Dirichlet)	B.3.3.2
Cycle 3 (6-9 months)		0.291	0.170	0.220	0.319		
Cycle 4 (9-12 months)		0.291	0.170	0.201	0.338		
Cycle 5 (12-15 months)		0.291	0.190	0.209	0.310		
Cycles 6-9		Last observed data					
Cycles 10+		Patients remain in the same health state					

Variable	Value		Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Number of GTC drop seizures				
Efficacy parameters impacting cost: Proportion change in median number of GTC seizures (Titration + maintenance period)				
GTC seizure (% reduction) - NMA data				
Treatment vs SoC– CBD + SoC – weighted dosing	[redacted]		DSA/PSA: [redacted] (Beta)	B.2.9.4.2
Treatment vs SoC– FFA + SoC – 0.7 mg/kg/day	[redacted]		DSA/PSA: [redacted] (Beta)	
Cost Inputs				
Drug acquisition cost (Average cost /mg)				
Antiepileptic drugs				
FFA	[redacted]		DSA/PSA: ±20% (Gamma)	B.3.5.2.2
CBD	£0.0850			
Clobazam	£0.0730			
Levetiracetam	£0.0001			
Valproate	£0.0004			
Lamotrigine	£0.0007			
Topiramate	£0.0015			
Rufinamide	£0.0042			
Rescue medications				
Diazepam	£0.1818		DSA/PSA: ±20% (Gamma)	B.3.5.4.1
Midazolam	£2.6172			
Dosages				
CBD dosage distribution - T+M period (proportion on 20mg/kg/d)	20.0% (e.g. dose of 12mg/kg/d)		N/A	B.3.2.3
CBD dosage distribution - OLE period (proportion on 20mg/kg/d)	40.0% (e.g. dose of 14mg/kg/d)		Scenario: 20% (e.g. dose of 12mg/kg/d)	
FFA average dosage (mg/kg/day)	0.50		Scenario: 0.7	
Titration dosage				
FFA – average dose (mg/kg/day)	0.30		N/A	B.3.5.2.1
FFA – max dose (kg/day)	26.00		N/A	
CBD (mg/kg/day)	5.00		N/A	
Maintenance dosage				
	Average dose	Max dose (mg/d)		
Age 2-5 years				
FFA	0.50 mg/kg/d	26.00	N/A	B.3.5.2.1
CBD OLE	14.00 mg/kg/d	-		
Clobazam	0.65 mg/kg/d	60.00		
Levetiracetam	0.00 mg/d	-		
Valproate	20.00 mg/kg/d	2,500.00		
Lamotrigine	3.00 mg/kg/d	200.00		
Topiramate	7.00 mg/kg/d	-		
Rufinamide	37.50 mg/kg/d	800.00		

Variable		Value		Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Diazepam		7.50 mg/d	20.00		
Midazolam		5.00 mg/d	10.00		
Age 6-11 years					
FFA		0.50 mg/kg/d	26.00	N/A	B.3.5.2.1
CBD OLE		14.00 mg/kg/d	-		
Clobazam		0.65 mg/kg/d	60.00		
Levetiracetam		1000 mg/d	-		
Valproate		25.00 mg/kg/d	2,500.00		
Lamotrigine		3.00 mg/kg/d	200.00		
Topiramate		7.00 mg/kg/d	-		
Rufinamide		400.00 mg/d	1,500.00		
Diazepam		7.50 mg/d	20.00		
Midazolam		7.50 mg/d	-		
Age 12-17 years					
FFA		0.50 mg/kg/d	26.00	N/A	B.3.5.2.1
CBD OLE		14.00 mg/kg/d	-		
Clobazam		0.65 mg/kg/d	60.00		
Levetiracetam		1000 mg/d	-		
Valproate		25.00 mg/kg/d	2,500.00		
Lamotrigine		150.00 mg/d	-		
Topiramate		7.00 mg/kg/d	-		
Rufinamide		400.00 mg/d	1,500.00		
Diazepam		15.00 mg/d	40.00		
Midazolam		10.00 mg/d	20.00		
Age 18+ years					
FFA		0.50 mg/kg/d	26.00	N/A	B.3.5.2.1
CBD OLE		14.00 mg/kg/d	-		
Clobazam		25.00 mg/d	60.00		
Levetiracetam		2000mg/d	-		
Valproate		25.00 mg/kg/d	2,500.00		
Lamotrigine		150 mg/d	-		
Topiramate		300 mg/d	-		
Rufinamide		400 mg/d	2,000.00		
Diazepam		15 mg/d	40.00		
Midazolam		10 mg/d	20.00		
Health state HCRU routine care - # annual visits					
Severity by DSF (per 28 days)		<12 y	> 12 y		
Nurse visit	≤ 45	4.00	4.00	DSA/PSA: ±20% (Gamma)	B.3.5.4.1
	>45 to ≤ 110	8.00	4.80		
	> 110	12.00	12.00		
Specialist visit	≤ 45	2.00	1.00	DSA/PSA: ±20% (Gamma)	
	>45 to ≤ 110	4.00	1.20		
	> 110	6.00	3.00		
Paediatrician visit	≤ 45	4.00	0.00	DSA/PSA: ±20% (Gamma)	
	>45 to ≤ 110	8.00	0.00		
	> 110	12.00	0.00		

Variable		Value			Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Phone call follow-up	≤ 45	2.00	1.00		DSA/PSA: ±20% (Gamma)	
	>45 to ≤ 110	5.00	2.50			
	> 110	12.00	6.00			
Rescue medication (by intake)	≤ 45	2.00	2.00		DSA/PSA: ±20% (Gamma)	
	>45 to ≤ 110	5.00	5.00			
	> 110	8.00	8.00			
Health state HCRU secondary care – seizure-related						
Healthcare utilisation per patient per year (seizure- associated)						
Age group		<12 y	> 12 y			
Number of hospital inpatient admissions, PPY		1.50	0.96		DSA/PSA: ±20% (Gamma)	B.3.5.4.2
Hospital inpatient LOS, days		2.48	3.24			
Number of A&E visits, PPY		0.85	1.15			
Healthcare utilisation per patient per year by seizure type						
Seizure type		GTC (ICD-9: 345.3)	Other (ICD 9: 345.8)			
Hospital days		6.26	2.08		DSA/PSA: GTC: 0.00 – 17.16 Other: 0.00 – 4.45 (Gamma)	B.3.5.4.2
Emergency department visit		1.52	0.78		DSA/PSA: ±20% (Gamma)	
Other inputs						
Proportion of inpatients requiring ICU visit (%)		4.2%			DSA/PSA: ±20% (Beta)	B.3.5.4.2
Costs for monitoring, disease management, AEs and mortality						
Monitoring cost						
Echocardiogram (age <18 year)		£100.00			DSA/PSA: ±20% (Gamma)	B.3.5.5
Echocardiogram (age >=18 years)		£83.00				
Disease management cost						
Cost per visit per age group		<12 y	12-18 y	>18 y		
Inpatient admissions (general ward)		£724	£607	£607	DSA/PSA: ±20% (Gamma)	B.3.5.4.2
Inpatient admissions (ICU)		£3,102	£2,138	£2,138		
Emergency department visit		£280	£280	£280		
Physician visits (paediatrician/GP)		£224	£224	£224		
Specialist visit		£416	£214	£214		
Nurse visit		£57	£57	£57		
Phone Call Follow-up		£41	£41	£41		
Adverse events management cost (per event)						
Diarrhoea		£57			DSA/PSA: ±20% (Gamma)	B.3.5.6
Somnolence		£57				
Pyrexia		£57				
Decreased appetite		£57				

Variable	Value			Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Vomiting	£57				
Mortality cost (used to calculate cost per death)					
	<12 y	12-18 y	>= 18 y		
Emergency department visit	£280	£280	£280	DSA/PSA: ±20% (Gamma)	B.3.5.7
Intensive care unit <18 years	£2,705				
Intensive care unit >=18 yof age	£2,138				
Utilities					
Utility settings					
AE disutility	Included			N/A	B.3.4.4
Age-adjusted disutility	Included			N/A	B.3.4.3
Caregiver utility	Included			N/A	B.3.4.5
Utility measures – EQ-5D – Patient and caregiver (applied independently of treatment arm)					
Selected patient utility source	Verdian et al. (2008) – EQ-5D			Scenarios: Verdian et al. (2008) – TTO; Verdian et al. (2008) – VAS; Lo et al. (2021) – TTO; Lo et al. (2021) – VAS; Auvin et al. (2021) -VAS	B.3.4.5
Selected caregiver utility source	Verdian et al. (2008) – EQ-5D			Scenarios: Verdian et al. (2008) – TTO; Verdian et al. (2008) – VAS; Lo et al. (2021) – TTO; Lo et al. (2021) – VAS; Auvin et al. (2021) -VAS	
State 0: No response (< 25% reduction)	0.020			DSA/PSA: ±20% (Beta)	
State 1: Response group 1: 25% to <50% reduction	0.100				
State 2: Response group 2: 50% to <75% reduction	0.500				
State 3: Response group 3: >=75% response	0.596				
Number of caregivers	1.8			DSA/PSA: 1.5 – 3.0 (Gamma)	
Treatment-emergent adverse events disutilities					
Diarrhoea	-0.06			DSA/PSA: ±20% (Beta)	B.3.4.4
Somnolence	-0.06				
Pyrexia	-0.06				
Decreased appetite	-0.06				
Vomiting	-0.06				

Abbreviations: AE, Adverse Event; ASM, Antiseizure Medication; CBD, Cannabidiol; CBD w CLB, Cannabidiol with clobazam; CI, Confidence Interval; CLB, Clobazam; d, Day; DSF, DSA, Probabilistic Sensitivity Analysis; DSF, Drop Seizure Frequency; ED, Emergency Department; EMA, European Medicine Agency; EQ-5D, EuroQol 5 Dimension; FFA, Fenfluramine; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); GP, General Practitioner; GTC, Generalised Tonic-Clonic; HCRU, Health Care Resource Use; ICU, Intensive Care Unit; ITT, Intention-To-Treat; kg, Kilogram; LGS, Lennox Gastaut Syndrome; kg, Kilogram; mg, Milligram; N/A, Not Applicable; NMA, Network Meta-Analysis; OLE, Open Label Extension; PPY, Per Patient-Year; PSA, Probabilistic Sensitivity Analysis; SoC, Standard of Care; SUDEP, Sudden Unexpected Death In Epilepsy; T+M, Titration and Maintenance; TEAE, Treatment Emergent Adverse Event; TP, Transition Probability; TTO, Time Trade-Off; VAS, Visual Analog Scale;

B.3.9.2 Assumptions

The model relies on some key assumptions covering its structure, the intervention, comparators, efficacy, safety, treatment discontinuation, subsequent treatments, costs, and death. These are listed in the Table 82 below.

Table 82. Key assumptions used in the model (base case)

Parameter	Assumption	Rationale
Time horizon	Lifetime (86 years).	Appropriate timeline to assess costs and benefits associated with the intervention. Same as the NICE CBD submission 2019 (TA615) after appraisal consultation
FFA dosage	All patients received a maintenance dose of 0.5 mg/kg/day.	To closely reflect the clinical practice dose of fenfluramine, which is based on a balance between efficacy and tolerability (as per the guidance in the SmPC for fenfluramine).
CBD dosage	All patients received a maintenance dose of 12 mg/kg/day during Cycle 1, and a maintenance dose of 14 mg/kg/day for all following cycles	The model assumed the maintenance dose of CBD in the initial maintenance cycle to be 12 mg/kg/day to align with NICE TA615 submission (40). The maintenance dose after T+M for CBD was based on real-world use of cannabidiol for DS described in Silvennoinen, 2021 (145) and expert opinion stating that the dose is not expected to exceed 14mg/kg/day, as patients are titrated up to their maximum tolerable dose.
Standard of Care	Patients in the FFA and CBD arms were assumed to receive the same SoC, except for clobazam (100% of patients under CBD receive clobazam concomitantly as per cannabidiol regulatory label). SoC was assumed to remain the same until patients discontinue add-on treatment; After discontinuation, all patients started subsequent treatment which was equal to SoC in the FFA trial.	SoC basket aligned with FFA trial and SmPC of CBD (that needs to be given in concomitantly with clobazam). Subsequent treatment is not expected to differ from the add-on therapy received beforehand. The proportion of ASM did not have any significative impact on the ICER.
Long-term treatment efficacy and waning	Observed TP from FFA OLE data in the last cycle (cycle 4 to 5) was applied from cycle 6 to cycle 9. Similarly, state occupancies for CBD from cycle 4 to 5 (OLE study) showed stabilisation and, therefore, no change in	This assumption was considered appropriate given that significant improvement in treatment efficacy was observed in patients enrolled in the open label extension study of FFA, while CBD

Parameter	Assumption	Rationale
	state occupancy of CBD was applied from cycle 6 to 9.	state occupancy from observed OLE data was stable after 12 months.
	After cycle 9, in both treatment arms, a proportion of patients were assumed to undergo treatment waning using deteriorating TPs estimated from cycle 4 to 5 from FFA OLE study. Deteriorating TPs assumed patients can only remain in the same state or progress to a worse health state. Deteriorating TPs and proportion of patients undergoing waning of efficacy was assumed to be equal for FFA and CBD arms.	The assumption that treatment waning would occur equally for both FFA and CBD treatment arms was considered conservative and was tested in scenario analysis, where the long-term real-world CBD study in Germany, was used for proportion undergoing waning.
	State occupancies for patients in the SoC arm were assumed to remain the same after cycle 1.	Since no observed data was available on SoC after 3 months, the model assumed stabilisation without deterioration.
Discontinued patients	Discontinuation can be due to AEs or lack of efficacy or through the application of a stopping rule. Discontinued patients were assumed to revert to state 0 (<25% reduction), i.e., the same number of median drop-seizures for patients with state 0 was applied to discontinued patients. Discontinued patients were assumed to remain in the discontinuation state unless they die, and to follow the same trajectory in terms of costs, utilities, and mortality as patients on state 0 of the SoC treatment arm.	Patients discontinuing treatment are expected to lose the benefits of the add-on therapy which can be considered as a conservative assumption.
	For the SoC arm, model assumed no discontinuation due to lack of efficacy.	Since all patients are always on SoC, lack of efficacy is not considered to lead to SoC discontinuation
Stopping rule	After cycle 2, discontinuation due to lack of efficacy was captured by a stopping rule for patients in the state 0 evaluated every 3 months.	Patients with no or limited reduction in drop seizures are expected to discontinue treatment; confirmed by clinical experts
Safety (adverse events)	Two types of adverse events were considered in the model:	TEAE were assumed to not occur in the follow-up cycles as there was less than 2% of severe TEAE in the FFA OLE study, therefore any TEAE are expected to occur upon initiation of treatment.

Parameter	Assumption	Rationale
	1. TEAEs were assumed to occur in the initial cycle and result in cost and disutility 2. Other AEs that resulted in discontinuation, applied in all follow-up cycles.	
Quality of life	Based on Verdian et al.	The SLR did not retrieve any other published studies using similar HS categories than the ones used in this model.
	Model assumed that 1.8 caregivers per patient.	In line with the NICE CBD submission 2019 (TA615)
Mortality	Patients with a higher number of seizures were assumed to be at greater risk of death compared to those with fewer seizures.	Same as CBD submission 2019 (TA615)
	The SUDEP and non-SUDEP rates were assumed to be the same as in DS patients.	Due to a lack of LGS-specific data, as per NICE CBD submission 2019 (TA615)
Resource use associated with disease management	Patients with a higher number of seizures were assumed to be associated with higher levels of resource use compared to those with fewer seizures. Patients experiencing GTC seizures (versus non GTC) were expected to have higher resource use.	Same as NICE CBD submission 2019 (TA615) Based on published literature.
	The average HCRU cost of each health state was based on drop-seizure frequency-specific resource utilisation. To determine the appropriate resource utilisation for each health state, the median number of drop-seizures per 28 days of each state was considered as a good proxy and calculated according to observed data from the Study 1601 (state 0 and 3) or using mid-points (state 1 and 2).	This approach was consistent with the NICE CBD submission 2019 (TA615) Considered an acceptable approach to correspond the health states of this model (based on reduction of seizures) with the health states of the CBD submission model (based on frequency of seizures), and had previously been described by Neuberger et al. (2020) (134) in LGS patients.

Parameter	Assumption	Rationale
	Discontinued patients were assumed to have same seizure-associated costs as state 0 under SoC.	Patients discontinuing treatment are expected to lose the benefits of the add-on therapy and therefore are expected to have the same level of resource use as SoC patients in the most severe health state (<25%)
GTC seizures	Model assumed the proportion of patients experiencing GTC seizures in each study arm will remain the same after T+M. Model assumed no reduction in the proportion of GTC in the SoC arm.	Assumption based on lack of evidence demonstrating otherwise.

Abbreviations: AE, Adverse Event; CBD, Cannabidiol; FFA, Fenfluramine; GTC, Generalised Tonic-Clonic; HCRU, Healthcare Resource Use; kg, Kilogram; mg, Milligram; OLE, Open Label Extension; SoC, Standard Of Care; SUDEP, Sudden Unexpected Death in Epilepsy; T+M, Titration and Maintenance; TEAE, Treatment Emergent Adverse Event; TP, Transition Probability; SmPC, Summary of Product Characteristic; ICER, Incremental Cost-Effectiveness Ratio; SLR, Systematic Literature Review.

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

B.3.10.1.1 Deterministic results

The aggregated base case results for the cost-effectiveness of fenfluramine + SoC compared with cannabidiol (with clobazam) + SoC are presented in Table 83.

Over the lifetime time horizon, treatment with fenfluramine + SoC was associated with a total of 3.71 QALYs at a total cost of [redacted]. Treatment with cannabidiol (with clobazam) + SoC was associated with a total of 2.87 QALYs at a total cost of [redacted]. Compared with cannabidiol, treatment with fenfluramine has resulted in an incremental gain of 0.83 QALYs and an incremental cost of [redacted], yielding an ICER of [redacted] and therefore above the decision-making threshold. However, when the x1.7 severity modifier is applied as a QALY weight, the resulting ICER is below the £20,000/QALY threshold (Fenfluramine meets the criteria for a severity weight of x 1.7, as mentioned in Section B.3.6. Base case results incorporating the severity modifier on QALYs for evaluating the cost-effectiveness of fenfluramine + SoC versus cannabidiol (with clobazam) + SoC, are presented in **Error! Not a valid bookmark self-reference.**. Over the lifetime time horizon, fenfluramine + SoC provides 6.30 QALYs at a cost of [redacted], while cannabidiol (with clobazam) + SoC offers 4.88 QALYs at a cost of [redacted]. When compared to cannabidiol, fenfluramine has produced an additional gain of 1.42 QALYs at an added cost of [redacted]. This leads to an ICER of [redacted], which is below the NICE threshold for cost-effective treatments.

Table 84).

Table 83. Base-case results: FFA + SoC versus CBD w CLB + SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
CBD w CLB + SoC	[redacted]	20.33	2.87	-	-	-	-
FFA + SoC	[redacted]	20.45	3.71	[redacted]	0.12	0.83	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard Of Care.

Fenfluramine meets the criteria for a severity weight of x 1.7, as mentioned in Section B.3.6. Base case results incorporating the severity modifier on QALYs for evaluating the cost-effectiveness of fenfluramine + SoC versus cannabidiol (with clobazam) + SoC, are presented in **Error! Not a valid bookmark self-reference.**. Over the lifetime time horizon, fenfluramine + SoC provides 6.30 QALYs at a cost of [redacted], while cannabidiol (with clobazam) + SoC offers 4.88 QALYs at a cost of [redacted]. When compared to cannabidiol, fenfluramine has produced an additional gain of 1.42 QALYs at an added cost of [redacted]. This leads to an ICER of [redacted], which is below the NICE threshold for cost-effective treatments.

Table 84. Base-case results with severity modifier applied: FFA + SoC versus CBD w CLB + SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
CBD w CLB + SoC	[redacted]	20.33	4.88	-	-	-	-
FFA + SoC	[redacted]	20.45	6.30	[redacted]	0.12	1.42	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard Of Care.

Although treatment and monitoring costs of fenfluramine is higher than cannabidiol, the introduction of fenfluramine resulted in lower disease management costs (seizure associated), ASMs cost, subsequent treatment costs, and mortality costs. This yields a total of [redacted] when doing the sum over the time horizon as detailed below in Table 85.

The clinical outcomes and full disaggregated results from the model are provided in Appendix J.

Table 85. Total costs by category of cost: FFA + SoC versus CBD w CLB + SoC

Item	Intervention cost (FFA + SoC)	Comparator cost (CBD w CLB + SoC)	Increment	Absolute increment	% absolute increment
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	£507	£0	£507	£507	[redacted]
Disease management cost routine care	£38,431	£38,816	-£385	£385	[redacted]

Disease management cost seizure associated care	£29,323	£30,308	-£986	£986	[redacted]
ASM cost	£1,709	£2,256	-£547	£547	[redacted]
Subsequent treatment cost	£11,123	£11,413	-£290	£290	[redacted]
Adverse event cost	£42	£23	£20	£20	[redacted]
Mortality costs	£885	£897	-£12	£12	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Adapted from Pharmaceutical Benefits Advisory Committee (2008).
Abbreviations: ASM, Antiseizure Medication; FFA, Fenfluramine; CBD w CLB, Cannabidiol with Clobazam; SoC, Standard of Care.

B.3.10.1.2 Complementary analysis: cost-effectiveness in comparison of SoC

The aggregated base case results for the cost-effectiveness of fenfluramine + SoC compared with SoC are presented in
Table 86.

The incremental analysis for fenfluramine + SoC was also presented versus SoC alone. Compared to SoC, fenfluramine has resulted in an incremental gain of 3.71 QALYs and incremental cost of [redacted], yielding an ICER of [redacted]. However, when the x1.7 severity modifier is applied as a QALY weight, the resulting ICER is [redacted] (Table 87).

Table 86. Base-case complementary results: FFA + SoC versus SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
SoC	[redacted]	20.15	1.65	[redacted]	-	-	-
FFA + SoC	[redacted]	20.45	3.71	[redacted]	0.30	2.06	[redacted]

Abbreviations: FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; Incr., Incremental; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Table 87. Base-case complementary results with severity modifier applied: FFA + SoC versus SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
SoC	[redacted]	20.15	2.80	[redacted]	-	-	-
FFA + SoC	[redacted]	20.45	6.30	[redacted]	0.30	3.50	[redacted]

Abbreviations: FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; Incr., Incremental; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

The impact of parameter uncertainty in the model was explored through a probabilistic sensitivity analysis. For each parameter in the model for which there was a measure of variance, a new value

was drawn based on an appropriately defined statistical distribution with shape and scale parameters of that distribution determined from the variance of the data (where possible and appropriate). 1000 independent sets of these parameters were drawn and the model re-run for 1000 realisations. An overview of the parameter types that were varied and respective distributions assumed in the PSA are presented in Table 88.

Table 88. Summary of the parameter group evaluated, and distribution type applied in the PSA

Parameter group	Number of parameters	Distribution type applied
Proportion of patients on ASMs at baseline	14	Beta
Proportion male	1	Beta
Median number of drop seizures	1	Gamma
Proportion of GTC seizures	1	Yes
Proportion of rescue medication	1	Gamma
Duration of titration period	2	Gamma
Patient weight by age groups	5	Normal
RR discontinuation due to AEs at T+M	2	Lognormal
Discontinuation rates due to AEs at different time points	12	Beta
Discontinuation due to lack of efficacy (cycle 2)	2	Beta
State occupancies (cycle 1)	12	Dirichlet
Transition probabilities/state occupancies (follow-up period)	80	Dirichlet
RR efficacy T+M	6	Lognormal
Proportion of GTC reduction	2	Beta
Drug costs	10	Gamma
Monitoring costs	2	Gamma
Inpatient costs	6	Gamma
Costs of visits and calls	18	Gamma
Resource use visits and calls	32	Gamma
Resource use rescue medication	8	Gamma
Resource use hospitalisations	22	Gamma
Proportion ICU	1	Beta
Mortality cost	1	Gamma
Utilities patients	4	Beta
Utilities caregivers	4	Beta
Number of caregivers	1	Gamma
Treatment emergent adverse events	15	Beta
AE management costs	5	Gamma
AE disutilities	5	Beta
Mortality	3	Beta

Abbreviations: AE, Adverse Event; ASM, Antiseizure Medication; GTC, Generalised Tonic-Clonic; ICU, Intensive Care Unit; PSA, Probabilistic Sensitivity Analysis; RR, Relative Risk; T+M, Titration and Maintenance.

Cost-effectiveness plane

Results from the PSA are presented in Figure 29.

The cost-effectiveness plane of FFA + SoC versus CBD w CLB + SoC shows that [redacted] of the simulations are located in the North-East quadrant where FFA + SoC is associated with higher costs but also higher QALYs.

The probabilistic mean ICER was [redacted] per QALY gained (Table 89) which is lower than the base case ICER [redacted]. The difference is explained by the incremental costs. While the weight of the patients in each age group is varied in the PSA, there is a cap applied on the dose per day for fenfluramine (26 mg/day), but there is no maximum dose per day for cannabidiol, leading to lower incremental costs of fenfluramine and therefore a lower probabilistic ICER value. Nevertheless, this suggest that the results of the cost effectiveness analysis are robust and consistent when considering inherent uncertainty in input parameters, with the ICER likely to fall within the cost-effectiveness threshold. The cost-effectiveness plane removing the weight parameters is presented in Appendix M.

Figure 29. Cost-effectiveness plane FFA + SoC versus CBD w CLB + SoC

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; QALYs, Quality-Adjusted Life Years; SoC, Standard Of Care.

Table 89. Average results from the probabilistic sensitivity analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
CBD w CLB + SoC	[redacted]	2.87	-	-	-
FFA + SoC	[redacted]	3.69	[redacted]	0.82	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Cost-effectiveness acceptability curves

The results from the cost-effectiveness acceptability curve are presented in Figure 30 below. The cost-effectiveness acceptability curve (CEAC) plots the probability that the intervention is cost-effective at a range of decision thresholds. The probability of being cost-effective at a threshold of £30,000 is [redacted]. However, when the severity modifier of x1.7 is applied on QALYs (Figure 31), the probability of the ICER being below £30,000/QALY is [redacted]

Figure 30. Cost-effectiveness acceptability curve

Abbreviations: CBD, Cannabidiol; CLB, Clobazam; FFA, Fenfluramine; SoC, Standard of Care.

Figure 31. Cost-effectiveness acceptability curve with severity modifier

Abbreviations: CBD, Cannabidiol; CLB, Clobazam; FFA, Fenfluramine; SoC, Standard of Care.

B.3.11.2 Deterministic sensitivity analysis

To understand the impact of variance in individual parameters and determine whether any parameter (or groups of parameters) was a substantial driver of the ICER, deterministic sensitivity analysis was performed. Either the upper and lower bounds of 95% confidence intervals, or 20%

variation were used if confidence intervals were unavailable. The DSA did not include transition probabilities (or state occupancies) as the movement of patients between the different health states at the end of each cycle in the model are interdependent, and all the TPs would have to be changed simultaneously to ensure clinically meaningful results. Therefore, transition probabilities and state occupancies were tested only in the PSA using the Dirichlet method.

The parameters included in the DSA are presented in Table 90.

Table 90. Summary of the parameter group evaluated, and range of variation applied in the DSA

Parameter group	Number of parameters	Range of variation
Discounting rate (costs and outcomes)	2	0% - 6%
Proportion of patients on ASMs at baseline	15	±20%
Proportion male	1	±20%
Median number of drop seizures	1	95% CI from literature
Proportion of GTC seizures	1	±20%
Proportion of rescue medication	1	±20%
Duration of titration period	2	±20%
Patient weight by age groups	5	Mean ±1.96SE
RR discontinuation due to AEs at T+M	2	95% CrI from NMA
Discontinuation rates due to AEs at different time points	12	±20%
Discontinuation due to lack of efficacy (cycle 2)	2	±20%
State occupancies (cycle 1)	12	N/A
Transition probabilities/state occupancies (follow-up period)	80	N/A
RR efficacy T+M	6	95% CrI from NMA
Proportion of GTC reduction	2	95% CrI from NMA
Drug costs	10	±20%
Monitoring costs	2	±20%
Inpatient costs	6	±20%
Costs of visits and calls	18	±20%
Resource use visits and calls	32	±20%
Resource use rescue medication	8	±20%
Resource use hospitalisations	22	±20%; 95%CI from literature for hospital days
Proportion ICU	1	±20%
Mortality costs	1	±20%
Utilities patients	4	±20%
Utilities caregivers	4	±20%
Number of caregivers	1	1.5 - 3
Treatment emergent adverse events	15	±20%
Disabilities with AEs	5	±20%
AE management costs	5	±20%
Mortality: SUDEP	1	95%CI from literature
Mortality: non-SUDEP	2	±20%

Abbreviations: AE, Adverse Event; ASM, Anti-Seizure Medication; CI, Confidence Interval; CrI, Credible Interval; DSA, Probabilistic Sensitivity Analysis; GTC, Generalised Tonic-Clonic; ICU, Intensive Care Unit; N/A, Not Applicable; NMA,

Network Meta-Analysis; RR, Relative Risk; SE, Standard Error; SUDEP, Sudden Unexpected Death In Epilepsy; T+M, Titration and Maintenance.

Figure 32 presents a tornado diagram showing the twenty parameters with the greatest impact on the ICER, with descending ICER sensitivity.

Figure 32. Tornado plot: deterministic sensitivity analyses: FFA + SoC versus CBD w CLB + SoC

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; EQ-5D, EuroQol 5 Dimension; FFA, Fenfluramine; GTC, Generalised Tonic-Clonic; HCRU, Healthcare Resource Use; SoC, Standard of Care; T+M, Titration and Maintenance.

B.3.11.3 Scenario analysis

Scenario were conducted to analytically assess the impact of varying inputs in a number of plausible settings outlined below:

- **Time horizon**: alternative shorter time horizon of 15 years was tested; it was found relevant as after that time, less than 10% of the alive patients in the model will still be on treatment (7% for fenfluramine and 4% for cannabidiol).

- **NMA dataset**: the limited data set specific for the EU-label combination of cannabidiol with clobazam (CBD w CLB) did not provide information for all needed outcomes to be analysed in the NMA. As per the base case, the NMA outcomes combined ITT population dataset (median percent reduction in GTC seizures and discontinuation due to AE) with on-clobazam data published by G-BA (for all three outcomes of reduction in seizure frequency ≥ 25%, ≥ 50% and ≥75%). This approach is limited by breaking the randomisation and by assuming that convulsive seizures reported in G-BA documents is comparable to drop seizures defined in the FFA trial. In an alternative scenario analysis, we replaced the efficacy data from the G-BA data set by the EMA dataset (which provides efficacy values for two of the three outcomes of reduction in drop seizure frequency for the CBD w CLB population: ≥ 50% and ≥ 75%). The missing outcome (≥ 25% response) was calculated by solving the linear equation maintaining the same proportion between the ≥ 25% and ≥ 50% outcomes in EMA as observed in GBA

dataset. Trial data used in this scenario, the network of evidence and results are provided in Appendix D.

- **Stopping rule**: a scenario was applied where discontinuation due to stopping rule was applied at <50% response in drop seizure frequency (for states 0 and 1) instead of under <25%. A UK clinical experts suggested using <25% reduction rate is clinically meaningful response rate (34).

- **Discontinuation due to lack of efficacy for CBD (cycle 2)**: this scenario tested an alternative proportion of discontinuation due to lack of efficacy for CBD at cycle 2 of 19.6% as reported in Kühne et al. 2023 opposed to 7.3% in the base case. In this study, 19.6% of patients reported "no effect" as the reason to end treatment with cannabidiol (as part of a long-term real-world evidence study in Germany on various epilepsy types) (175).

- **Removing waning of efficacy for FFA and CBD**: in this scenario the assumption regarding waning of efficacy was removed for all treatment arms, whereas in the base case it was assumed 5.2% of patients would undergo treatment waning in the FFA and CBD treatment arms starting from cycle 10.

- **Waning of efficacy for CBD (from cycle 10)**: The assumption that treatment waning would occur equally for both FFA and CBD treatment arms was tested in this scenario analysis, where the long-term CBD study from Kühne et al. (2023), a real-world CBD study in Germany, was used for proportion undergoing waning (19.6%) (175).

- **Drug dosages:** Three alternative dosage scenarios were tested,

    - In the first dosing scenario, the average cannabidiol dose was reduced from 14mg/kg/day to 12mg/kg/day. This was done to test the effect of keeping cannabidiol dose in-line with what was accepted in the NICE cannabidiol submission for LGS in 2019 (TA615) (40).

    - In the second dosing scenario, the fenfluramine dose was increased from 0.5mg/kg/day to 0.7mg/kg/day. This was done to test the effect of applying the dose for fenfluramine as used in Study 1601 opposed to what is seen in real-word evidence (RWE) (15).

    - The third alternate dosing scenario involved a combination of changes from the two preceding scenarios (i.e., cannabidiol dosage reduced to 12mg/kg/day and fenfluramine dosage increased to 0.7mg/kg/day). This combined scenario aimed to assess the effects of simultaneously varying the dosages of both treatments.

- **Utilities**: In the base case, utilities for patients and caregivers were derived from Verdian et al. 2008 based on EQ-5D estimates; 5 scenarios were tested, using alternative sources (Lo et al. 2021 and Auvin et al. 2021) and methods to derive utilities such as TTO and VAS.

- **Verdian et al. 2008 patient utilities using TTO and VAS methods**: Since utility measures may vary by method of elicitation, these two scenarios were independently run to explore the impact of using utility rating obtained through TTO interviews and rating obtained through a VAS (142).

- **Lo et al. 2021 utilities using TTO and VAS methods** (for patients' and caregivers' utilities): This study presented dataset of patient and caregiver utilities (Table 91, Table 91 and Table 92) (80). One scenario was run for each elicitation method separately (TTO and VAS) to explore the impact of using a different literature source and elicitation method for utility values (150).

- **Auvin et al. 2021 utilities using VAS method** (for the mixed utilities for patients and caregivers): This study used a mixed sample of patients and caregivers for calculating utilities elicited using the VAS method. This scenario was run to explore the impact of using a different literature source for LGS utility values that combined patient and caregiver utilities (Table 93) (58).

Similar to Lo et al. 2021, Auvin et al. assessed HRQoL statuses for patients and their caregivers based on the total number of drop seizures per month and number of seizure free days. To run these scenarios the model health states had to be categorised by number of drop seizures per month and further segmented by seizure-free days. The utility value for each health state in the model was then determined as the weighted average of each seizure-free (SF) days category within each health state. The proportion of patients within the health state (state 1 – 3) in each SF day category used for the FFA and SoC treatment arms were obtained from the FFA Clinical Study Report (CSR) amend analysis - internal data from 2022. We assumed CBD would have the same distribution as FFA for equality, state 0 would have the same distribution as SoC at baseline. The distribution of seizure-free days were assumed to be fixed in time and only depends on the health states, as displayed in Table 94.

Table 91. Patient utility measures – Lo et al. 2021

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–≤15	0.375 (0.575)	0.423 (0.21)
>45–≤110	>15	0.228 (0.598)	0.317 (0.19)
>45–≤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)

Abbreviations: SD, Standard Deviation; TTO, Time Trade-Off; VAS, Visual Analog Scale.

Table 92. Caregiver utility measures - Lo et al. 2021

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–≤15	0.572(0.479)	0.492 (0.23)
>45–≤110	>15	0.424(0.554)	0.397 (0.22)
>45–≤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)

Abbreviations: SD, Standard Deviation; TTO, Time Trade-Off; VAS, Visual Analog Scale.

Table 93. Patient utility measures - Auvin et al. 2021

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

Abbreviations: UK, United Kingdom.

Table 94. Distribution of seizure free days by health state at T+M (applied at all cycles)

	Group 1: <=3 days, n (%)	Group 2: >3 to <=15 days, n (%)	Group 3: >15 days, n (%)	Total, n (%)
SoC				
HS 0				
HS 1	[redacted]	[redacted]	[redacted]	[redacted]
HS 2	[redacted]	[redacted]	[redacted]	[redacted]
HS 3	[redacted]	[redacted]	[redacted]	[redacted]
FFA + SoC				
HS 0				
HS 1	[redacted]	[redacted]	[redacted]	[redacted]
HS 2	[redacted]	[redacted]	[redacted]	[redacted]
HS 3	[redacted]	[redacted]	[redacted]	[redacted]
CBD w Clobazam + SoC				
HS 0				
HS 1	[redacted]	[redacted]	[redacted]	[redacted]
HS 2	[redacted]	[redacted]	[redacted]	[redacted]
HS 3	[redacted]	[redacted]	[redacted]	[redacted]

Reference: UCB 2022 Fenfluramine Study Statistical Analysis (137)
Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; SoC, Standard of Care; T+M, Titration and Maintenance.

- **Mortality:** in the base case, SUDEP rate depends on the frequency of seizures; in a scenario analysis SUDEP mortality risk was applied by assuming the same risk for all patients independently of their health state, e.g., assumed to be equal to the baseline estimate.

Results of all scenario analysis (with and without severity modifier) are presented in Table 95.

Table 95. Summary of the scenario analyses explored and comparison to the base case

Parameter	Base case	Scenario analyses	FFA+SoC vs CBD w CLB SoC			ICER	ICER with x 1.7 weighting applied to incremental QALYs
			Incremental costs	Incremental QALYs	Incremental QALYs (with severity modifier)		
Base case	**N/A**	**N/A**	[redacted]	**0.83**	1.42	[redacted]	[redacted]
	Varying the time horizon						
Time horizon	Lifetime	15 years	[redacted]	0.72	1.23	[redacted]	[redacted]
	Varying NMA dataset						
NMA dataset	GBA	EMA	[redacted]	0.86	1.46	[redacted]	[redacted]
	Varying the stopping rule						
Discontinuation (all treatment)	Applied if response <25%	Applied if response <50%	[redacted]	0.34	0.58	[redacted]	[redacted]
	Varying the discontinuation due to lack of efficacy for CBD (cycle 2)						
Discontinuation rate (CBD)	7.3%	19.6%	[redacted]	0.91	1.55	[redacted]	[redacted]
	Removing waning of efficacy						
Treatment efficacy (all treatment)	Waning	No waning	[redacted]	1.39	2.36	[redacted]	[redacted]
	Varying the waning for CBD (from cycle 10)						
% of patients undergoing waning	5.2%	19.6%	[redacted]	1.11	1.89	[redacted]	[redacted]
	Varying the drug maintenance dosage						
CBD dosage	14 mg/kg/day	12 mg/kg/day	[redacted]	0.83	1.42	[redacted]	[redacted]
FFA dosage	0.5 mg/kg/day	0.7 mg/kg/day	[redacted]	0.83	1.42	[redacted]	[redacted]
CBD and FFA dosages	14 mg/kg/day (CBD) and 0.5 mg/kg/day (FFA)	12 mg/kg/day (CBD) and 0.7 mg/kg/day (FFA)	[redacted]	0.83	1.42	[redacted]	[redacted]

Parameter	Base case	Scenario analyses	FFA+SoC vs CBD w CLB SoC			ICER	ICER with x 1.7 weighting applied to incremental QALYs
			Incremental costs	Incremental QALYs	Incremental QALYs (with severity modifier)		
	Varying the utilities						
Utilities for patients and caregivers	Verdian EQ-5D	Verdian TTO	[redacted]	0.56	0.95	[redacted]	[redacted]
		Verdian VAS	[redacted]	1.10	1.86	[redacted]	[redacted]
		Lo TTO	[redacted]	0.72	1.23	[redacted]	[redacted]
		Lo VAS	[redacted]	0.48	0.81	[redacted]	[redacted]
		Auvin VAS	[redacted]	0.43	0.72	[redacted]	[redacted]
	Varying the mortality						
Mortality	Dependent of seizure frequency	Independent of seizure frequency	[redacted]	0.84	1.43	[redacted]	[redacted]

Abbreviations: CBD w CBL, Cannabidiol with Clobazam; EMA, European Medicine Agency; EQ-5D, EuroQol 5 Dimension; FFA, Fenfluramine; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); ICER, Incremental Cost-Effectiveness Ratio; kg, Kilogram; mg, Milligram; N/A, Not Applicable; SoC, Standard of Care; TTO, Time Trade-Off; VAS, Visual Analog Scale; QALYs, Quality-Adjusted Life Years.

B.3.12 Subgroup analysis

The submission relates to the full licensed indication of fenfluramine, for which cannabidiol (with clobazam) is the most appropriate clinical and economic comparator. Analyses of fenfluramine plus SoC against comparative SoC alone are also provided in section B.3.10 for completeness. These data support the use of fenfluramine within its full licensed indication. No subgroup of the licensed indication is proposed.

B.3.13 Benefits not captured in the QALY calculation

Beyond the clinical and economic outcomes assessed within the present analysis, fenfluramine provides several l health benefits that were not adequately captured in the CEM. UK clinical experts referred to several benefits for treatment with fenfluramine that extended beyond the seizure frequency reduction effect. This includes reducing duration and severity of individual seizures, improvement effect in other motor functions (e.g., walking), and improvement in cognitive functions of patients, which may specifically benefit children's intellectual development. Other benefits include early response to treatment, tolerability, patient retention, and the minimally sedative nature of the drug, which further contributes to cognitive functions and quality of life (12, 15, 80). Clinicians indicated that considering the resistant nature of seizures in LGS, these benefits carry an important weight in differentiating between ASMs for optimal choice of treatment (34).

The benefits that fenfluramine treatment provides to caregivers and their families could not be fully captured in the QALY calculation as the quality of life of siblings of those living with LGS were not employed in this analysis. Fenfluramine has demonstrated improvement in non-seizure related benefits as demonstrated by the CGI-I scale (see Section B2). One quarter of fenfluramine-treated patients were much or very much improved as assessed by investigators with 14 weeks of treatment. Furthermore, significantly more children and young adults on fenfluramine showed clinically meaningful improvements in global executive functioning with specific improvement in the cognitive regulation Behaviour Rating Inventory of Executive Function 2 (BRIEF®2) index (80). These benefits may not have been captured in full as CGI-I and BRIEF 2 are not directly transferable to how QALYs are calculated or estimated. UK experts reported that these positive outcomes obtained for patients with LGS were considered as uncaptured benefits for fenfluramine in the current analysis (34).

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The model has undergone thorough internal and external validation.

Face validity of the model was assessed by examining the problem formulation, model structure, clinical assumptions and data sources by UK clinical experts. This was done to ensure that the model fully captures LGSs' clinical context and utilises data and assumptions that corresponds with real-world conditions.

External validation was assessed first by examining model comparability and results such as costs and QALYs outcomes with that of the NICE cannabidiol submission 2019 (TA615) (40). It is important to highlight there were methodological differences between our analysis and the NICE cannabidiol submission 2019 (TA615) (40). Unlike in the CBD submission, our model used a semi-Markov approach considering treatment waning, and the health states were based on the percentage of reduction of drop seizures as opposed to seizure frequency.

Overall, the results of both models largely align in terms of the incremental costs and show a modest difference between the incremental estimated life years and QALYs

In this model, the incremental cost of CBD (with clobazam) +SoC compared to SoC over 15 years was estimated to be [redacted], which is similar to the CBD submission's reported cost of £48,907. There were differences in how LY and QALYs were estimated between both models. The NICE cannabidiol submission 2019 (TA615) accounted for disutility assigned to caregivers, while in this model, caregiver utility was directly applied, resulting in a lower incremental QALY gain for CBD compared to SoC (1.14 in our model compared to 1.58 in the CBD submission) (40).

Finally, the mortality rates derived from our model were validated against LGS mortality rates reported in literature. The disease-specific mortality rate in LGS has been reported in the literature at 6.12 per 1,000 person-years (Chin et al. 2016) (36). Using the area under the curve method, the estimated number of deaths in the SoC arm of the model was 7.17 per 1000 person-years, which is relatively close. This corroborates the external validity of the model results.

B.3.14.2 Quality control

The model was reviewed by an independent senior health economist who was not involved in the model development. They reviewed the model for coding errors, inconsistencies, and the plausibility of model inputs and assumptions using a comprehensive checklist detailed in the Table 96 below.

Table 96. Model checklist

Navigation buttons
Form controls
Named cells
User input cells
Extreme input scenario analysis
Worksheets
One-way sensitivity analysis
Probabilistic sensitivity analysis
Hard inputs
Named cell use
Clarity
Accuracy
Internal Consistency
Platform
In-depth check: Model engine/ Traces
Uncertainty analysis
VBA check on
Hypothesis testing (model) and consistency inputs model and report: 1. Sensitivity analyses 2. Scenario analyses 3. Extreme input analyses

Abbreviations: VBA, Visual Basic for Applications.

B.3.15 Interpretation and conclusions of economic evidence

B.3.15.1 Results summary

Fenfluramine is an innovative add-on therapy for patients with LGS that provides a step change in seizure control and is indicated for use with or without concomitant clobazam. This distinct benefit allows fenfluramine to be used throughout the add-on therapy pathway.

The primary base case analysis illustrates fenfluramine's cost-effectiveness as add-on therapy against cannabidiol with concomitant clobazam, within its licensed indication. Considering that cannabidiol is the sole NICE-recommended add-on therapy that has undergone formal appraisal by NICE for LGS and possesses adequate RCT data for a rigorous comparison with fenfluramine, it serves as the most suitable comparator for demonstrating fenfluramine cost-effectiveness in the add-on therapy pathway.

Fenfluramine meets the criteria to be granted the application of the severity modifier at the 1.7 multiplier level and is cost-effective when the severity modifier is applied as a QALY weight when compared with cannabidiol with clobazam.

Deterministic one-way sensitivity analysis (OWSA) and scenario analyses were conducted to assess the influence of parameter uncertainty on the outcomes. A range of sensitivity analyses were explored to test both structural and parametric uncertainties. Fenfluramine remained cost-effective at the 1.7 severity modifier level, with most ICERs falling below the cost per QALY threshold of £30,000 (Table 95).

Probabilistic sensitivity analyses resulted in an ICER lower than the base case, confirming the robustness of the base case analysis considering parameter uncertainty. When considering the severity modifier, there is an [redacted] likelihood that fenfluramine is cost-effective when compared to cannabidiol (plus clobazam) at a willingness to pay threshold of £30,000/QALY. These findings demonstrate that fenfluramine would be regarded as a highly cost-effective intervention for all patients with LGS.

B.3.15.2 Strengths and limitations

Strengths

The de novo economic model optimises the use of the available data in this patient population, while fully accounting for the clinically and economically relevant parameters in the decision problem. The semi-Markov model structure which utilises time-varying transition probabilities is fully aligned with the primary objectives of treatment in LGS population, achieving clinically relevant response rate for frequency of drop-seizure in patients and maintaining that response throughout the treatment horizon. The health states selected are in line with the treatment of LGS according to established drop-seizure reduction categories and reflects the natural disease history of patients with LGS.

The chosen model structure and outcomes are in line and comparable with previous peer reviewed publications and technology appraisals in UK (130, 134). Key model assumptions and uncertainties were extensively explored through sensitivity analyses, which have confirmed the validity and applicability of the model in the context of this rare disease.

Limitations

Despite strengths of the economic model, the analysis has some limitations. First, generating high quality evidence to inform the cost-effectiveness of fenfluramine in LGS may be impacted by the lack of head-to-head comparison versus cannabidiol, and heterogeneity concerning LGS patients and their treatment. Performing an NMA was necessary, but this inherently introduces statistical biases that would not exist with direct treatment comparisons in RCTs.

Moreover, there is a paucity of published data on the relationship between resource use (number of visits/hospital admissions) and frequency of seizures in LGS. This model used the evidence from NICE cannabidiol submission 2019 (TA615), (40) which was established from UK clinical expert opinion. The extent of the savings in resource use associated with improvement in the seizure frequency of patients under fenfluramine is therefore relying on expert opinion.

Clinical efficacy data for fenfluramine was provided by the 20-week trial and the 12-month OLE (12). There is, therefore, uncertainty over the long-term efficacy for fenfluramine. However, this is comparable to the RCT duration for CBD and paucity of efficacy data is expected for a rare disease like LGS. To capture this uncertainty, a treatment waning effect is included in the analysis.

Validation

UK clinical experts were consulted to comment on the above-mentioned strengths and limitations of the analysis. The experts agreed that the NMA results were realistic. Furthermore, whilst confirming LGSs' heterogenous nature and the rarity of the disease, the experts highlighted that decision-making challenges regarding diagnosis and treatment were not specific to fenfluramine but also extended to other key approved ASM therapies including cannabidiol.

B.3.15.3 Conclusion

Fenfluramine provides sustained efficacy and a robust safety and tolerability profile. Accordingly, fenfluramine can be considered a much-needed additional treatment option for patients and carers that is cost-effective compared to cannabidiol (with clobazam) for patients two years of age or older with a diagnosis of LGS.

Due to a lack of restrictions on prior or concomitant ASMs, fenfluramine, unlike cannabidiol, can be taken with or without clobazam, offering flexibility to be used as an add-on therapy to any ASM regimen taken by the patients. This also provides further options for clinicians to balance tolerability of different ASMs and consequently enhance treatment retention, especially in the long term as experts have indicated that uncontrolled LGS in conjunction with poor treatment retention are amongst largest unmet needs in the current management of LGS (34).

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Summary of Information for Patients (SIP)

August 2023

File name	Version	Contains confidential information	Date
ID1651_Fenfluramine_LGS_SIP form	1.0	No	25th August 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine

Both generic and brand name.

Fenfluramine hydrochloride (Fintepla®).

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

People with Lennox-Gastaut syndrome (LGS) who are 2 years of age and older and whose seizures are not controlled by existing treatments (1).

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Fenfluramine was granted a European marketing authorisation on January 24th, 2023. Marketing authorisation for the UK was granted on July 5th, 2023 (2). Fenfluramine was also granted orphan drug designation, which can be provided to drugs that could be used for treating, preventing or diagnosing a rare and serious condition and seen to improve patients' current treatment, having considered what else is available (3). (GB Orphan designation number: PLGB 00039/0804 – 0010OD2)

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

- **Young Epilepsy** – conference sponsorship in 2023, £10,000
- **Neurological Alliance** – annual associate membership £11,000 per year and £9,000 for a service development toolkit in 2022
- **Dravet Syndrome UK** – conference sponsorship, website development and family weekend support in 2023, £20,000
- **Epilepsy Action** – Step Together Toolkit development sponsorship in 2021-2022, £30,000
- **Brain and Spine Foundation** – NeuroLifeNow sponsorship in 2023, £10,000

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

LGS is a severe, rare, difficult-to-treat childhood-onset epilepsy, with approximately 3,500 patients currently living with it in England and Wales (see Budget Impact Analysis of this submission).

People living with LGS often have a high number and different types of seizures which often do not respond to medicines. In some cases, patients can have more than 100 seizures per day, which can lead to a reduction in thinking ability combined with behavioural complications (4-6).

The most common type of seizures in LGS are drop seizures, which result in a loss of muscle tone or stiffening of muscles (7-9). These seizures often result in unpredictable falls, which can lead to serious injury and hospitalisation. There is an increased risk of sudden unexpected death in epilepsy (SUDEP), which is closely linked to the number of seizures patients experience (10, 11).

Each patient has unique and complex signs of both mental and physical disabilities. Most patients' seizures remain uncontrolled as existing medicines do not work well enough (12-14).

The impact of LGS extends beyond the patient, as the condition also has a negative impact on the quality of life of carers and families. Patients require 24-hour care as carrying out normal activities, such as walking, eating, and speaking are challenging. Patients will never have normal development into adulthood, causing lots of emotional stress, worry and difficulty for all involved (15-17).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diagnosing LGS is complicated due to every patient having a unique set of symptoms and disease severity (6, 12). Carers usually find out about LGS when a child is between 3 and 5 years of age (18). Diagnosis can take several years following many physical observations and scanning tests.

The signs and symptoms of LGS change over time. Delayed diagnosis, misdiagnosis and under-recognition in adulthood are common (12, 13, 18). No additional diagnosis tests are required with fenfluramine.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

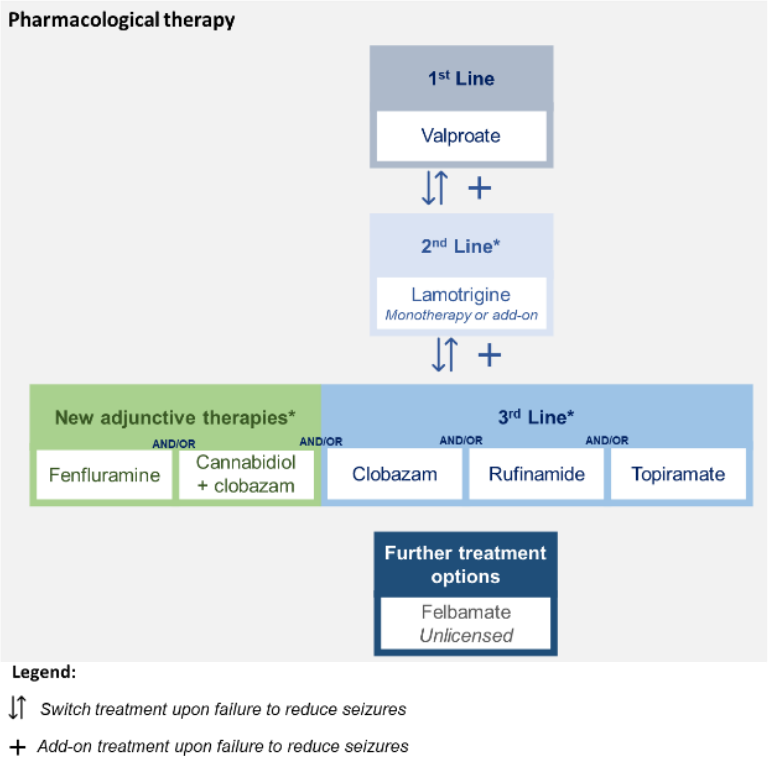
The goal of treatment for LGS is to reduce the complications that seizures cause to patients and their carers/families. This can be achieved by decreasing the frequency and severity of drop seizures. These drop seizures are the key seizures in LGS that can result in falls, serious injury, pain, hospitalisation and death (4, 12, 14, 15, 19). Reducing the frequency of seizures and increasing seizure-free days is key to preventing thinking problems and reducing risks of death (12). Seizure control would also greatly improve patients' and family/caregiver's quality of life as patients would require less care (15, 19).

Taking antiseizure medications are the main way of treating LGS, despite this, seizures often do not respond to treatment (20). That is why a combination of multiple antiseizure medications are usually required, where commonly three are used at the same time (21).

The NICE guideline NG217 is the current treatment guideline for LGS. It recommends drug treatment in a step wise sequence, with sodium valproate as first-line and lamotrigine as second-line (added-on or alone). If seizures remain uncontrolled, third-line option treatments such as rufinamide or cannabidiol + clobazam can be considered.

Fenfluramine is expected to be used as an alternative treatment option following treatment with the first- and second-line antiseizure medications (see **Figure 1** below). Fenfluramine can be used on its own (unlike, for example, cannabidiol, which always requires use with clobazam).

Figure 1. Position of fenfluramine in the current clinical management guideline



Note: adjunctive means when something is added on to something else to help.

Other non-medicinal therapies such as surgery and dietary changes also exist; however, these are considered separately to medicinal therapies and do not form the main part of treatment.

There is no one medicine that is definitively used the most. Each medicine also has many drug-drug interactions or has a key contraindication (e.g., patients with liver problems cannot use cannabidiol or sodium valproate, and sodium valproate is contraindicated in women of childbearing age). Treatment is therefore often individualised to patients (22).

Many patients have tried the several antiseizure medications available or continue to receive treatment while their seizures remain uncontrolled; therefore, new treatment options are required that have a different way of working to help improve the symptoms of LGS (23).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Fenfluramine (Fintepla®) for treating Lennox-Gastaut syndrome.

Given the severity of LGS, patients' carers have been asked to provide details on what it is like for patients to live with LGS and what carers experience when they care for someone with LGS (24). Information was collected by email communications to relevant members of Epilepsy Action and through social media requests.

The key theme in the responses was around the level of care needed, as most carers state 24-hour care is required, and it is noted that seizures can happen through the day and night.

LGS prevents patients from being able to look after themselves and denies them their independence. Carers state: *'My son is 16 with LGS, he is unable to do anything for himself so we have to provide 24 hour care' 'He has no independence and requires continual supervision and support'*

Other respondents highlight the impact of seizures on heart rate and breathing, whereby patients cannot be safely left alone. There is often a requirement for large quantities of numerous medicines that patients need to take to try and gain seizure control. One carer mentioned: 'He needs medicating 6 times a day…he requires supplementary milk feeds through the tube due to weight loss and not willing to eat sufficiently'.

Another carer highlighted the type, frequency, and severity of uncontrolled seizures. Where it is noted that *'We can go for days on end with continuous seizure activity and no rescue meds make any difference'*

In addition to the core issues relating to seizures, patients experience a large range of comorbidities (related impacts of the disease). One parent carer noted that their son also had *'severe learning difficulties'* while another explained that their son was *'significantly cognitively impaired'.*

A result of the seizures and associated comorbidities is the increased risk SUDEP. One parent carer noted their son *'continues to carry five risk factors around SUDEP'* which causes untold anxiety and hinders recruiting paid support to care for him.

Another parent carer noted the wider risk of seizures associated with LGS, their son broke his leg after a drop seizure further exacerbating his care and support needs. They went on to succinctly note: *'LGS and the seizures it causes have major knock-on effects on people lives, that severely exacerbate the already huge challenges that affect the individual and their family.'*

As above, the impact of the condition on parent carers and other family members was made clear by a number of respondents. One parent carer noted *'the impact on our mental health and wellbeing has been significant.'* Another parent carer mentioned that they had suffered a recent period of serious ill health attributable in part to a weakened immune system they link to the exhaustion of caring for their son.

Overall, there continues to be an unmet need for treatments, as carers state:

'The drugs available only seem to provide partial benefit and only reduce seizures and improve behaviour and mood to an extent. The condition is still hugely debilitating'

'It appears to be a guessing game and the only solution is to increase one drug or introduce something else. We might see a difference for a few days until his body gets used to it.'

'My son is treated the same as others with epilepsy, yet he never gets a day without some type of seizure.'

'Yes, there is an unmet need…it's called drug resistant epilepsy and he is continuing to have weekly seizures. This has been the case for 34 years.'

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Fenfluramine causes the release of a natural substance called serotonin in the brain and acts on the sigma-1 receptor, which can result in the reduction of seizures (2), however, the exact way by which fenfluramine works in LGS is unknown. Fenfluramine can be considered innovative as it has a new and double way of working (as it works on multiple types of receptors), which is unlike any other therapy seen to reduce seizures in LGS. This provides the possibility for patients who have tried several medications that have not given them seizure control, to see an improvement with fenfluramine because it works in a different way.

See below links to the patient information leaflet and Summary of Product Characteristics for fenfluramine:

Fintepla 2.2 mg/mL oral solution - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Fintepla 2.2 mg/mL oral solution - Patient Information Leaflet (PIL) - (emc) (medicines.org.uk)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No. Fenfluramine can be used in combination with any other therapy within the treatment pathway; however, is not specifically intended for use with another medicine, and therefore can be used on its own to manage seizures.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Fenfluramine is conveniently given as a cherry-flavoured, oral solution twice daily that can be given with or without food by parents/carers at home and can be used alongside a ketogenic diet. It will be available to be collected from hospital or community pharmacies. It has a long shelf-life (4 years, to be used within 3 months of first opening the bottle) and does not require any special storage conditions (e.g., refrigeration) (2).

Figure 2. Fintepla® packaging

For illustration purposes only

Fenfluramine can be used with feeding tubes that are available from most hospitals. It is supplied with two oral dosing syringes (3mL or 6mL) for accurate and flexible dosing (which is typically altered over 3 weeks) (2).

The recommended maintenance dose of fenfluramine is 0.7 mg/kg daily (**Figure 3**); however, most patients do not reach this dose as seizure control is achieved at doses of 0.3 – 0.5 mg/kg/day (25). Treatment should continue for the duration that seizures continue and patients receive a benefit.

Table 1. Dosing for LGS in children (aged 2 years and older) and adults (2)

Starting dose – first week	0.1 mg/kg taken twice daily (0.2 mg/kg/day)
Day 7 – second week**	0.2 mg/kg twice daily (0.4 mg/kg/day)
Day 14 – maintenance dose**	0.35 mg/kg twice daily (0.7 mg/kg/day)
Maximal recommended dose**	26 mg (13 mg twice daily, i.e. 6.0 mL twice daily)

**The dosage should be increased as tolerated to the recommended maintenance dosage (i.e. Day 14).

Cannabidiol is also given as an oral solution twice daily. The dose of cannabidiol has no maximum and so patients can continue to have increases in doses. Clobazam, which is required along with cannabidiol, is also given orally, and can be given as a liquid or tablets. Most other treatments are also given as oral solutions.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical evidence for fenfluramine for the treatment of LGS comes from a phase 3 randomised controlled trial (RCT) and its open label extension (OLE) study, which is a longer-term study for the patients that joined the RCT:

- Study 1601 (NCT03355209) part 1 (26)
- Study 1601 (NCT03355209) part 2 (OLE) (25)

Study 1601 assessed the efficacy and safety of fenfluramine as an add-on therapy in patients who have been unable to achieve acceptable seizure control on their existing medication. Patients who completed treatment in Study 1601 were invited to enrol in the OLE study. Both studies assessed the impact of fenfluramine across a range of seizure and non-seizure-related measures. A summary of trial methodologies is provided in **Table 2**.

Note: Placebo is used as a dummy/fake medicine to show the real impact of fenfluramine.

Table 2. Summary of trial methodology

Study name	Study 1601 part 1 (26-28)	Study 1601 part 2 (OLE) (25, 27, 28)
Trial design	Phase 3 double-blind, placebo-controlled, multicentre, multinational RCT (20-week trial duration)	Open-label extension study
Locations	65 study sites across North America (Canada, United States, Mexico), Europe (Spain, Italy, Poland, France, Germany, Belgium, Netherlands, Denmark, Sweden and Australia.	
Eligibility criteria for participants	• Aged between 2 and 35 years, ESC–confirmed LGS diagnosis, using stable ASMs. • Age of seizure onset: 11 years or younger, multiple seizure types (including tonic and tonic or atonic seizures), stable 4-week seizure baseline with 2 or more drop seizures per week, abnormal cognitive development, medical history showing EEG pattern of slow spike-and-wave complexes, (<2.5 Hz).	• Patients with a confirmed LGS diagnosis who completed Study 1601 part 1 (aged 2–35 years at entry into the core study).
Trial drugs (number in each group)	Fenfluramine 0.2 mg/kg (n=89), fenfluramine 0.7 mg/kg/day (n=87), placebo (n=87) Fenfluramine was administered orally twice daily as an oral solution of fenfluramine hydrochloride containing 2.2 mg/mL fenfluramine. Starting dose was 0.2 mg/kg/day, titrated up to target dose over 2 weeks, followed by a 12-	N= 247, no comparator group. A subject who completed Maintenance and was eligible for enrolment in the OLE study entered the Transition Period lasting 14 days between Visits 12 and 15, where patients were titrated to 0.2 mg/kg/day fenfluramine and remained at this dose for 1 month regardless of their randomised treatment arm in the RCT.

	week maintenance period. The maximum dose of fenfluramine was 26 mg per day.	After Month 1, patients were flexibly titrated by effectiveness and tolerability, up to a maximum of 0.7 mg/kg/day.
Permitted and disallowed on-going medication	Other ASMs permitted but had to be stable dose for 4 weeks before screening and during trial; Excluded if other use of cannabis evidenced by positive laboratory test, drugs that interact with central serotonin or current use of felbamate for <1yr.	
Primary 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 DSF between baseline and the combined Titration + Maintenance Periods	To assess the long-term safety and tolerability of fenfluramine in children and adults with LGS regarding AEs, laboratory parameters, physical examination, neurological examination, Tanner Staging, cognition, vital signs, ECGs, ECHO, body weight, and body mass index

Abbreviations: AEs, Adverse Events; ASMs, Antiseizure Medications; DSF, drop seizures frequency; ECG, Electrocardiogram; ECHO, Echocardiogram; ESC, Epilepsy Study Consortium; LGS, Lennox-Gastaut Syndrome; RCT, Randomised Controlled Trial.

Study 1601 and interim results of its accompanying OLE study are available online as per the links below (25, 26). The completion of the OLE study is expected at the start of 2025 (28).

Study 1601: Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome: A Randomized Clinical Trial - PubMed (nih.gov)

OLE: Fenfluramine provides clinically meaningful reduction in frequency of drop seizures in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study - PubMed (nih.gov)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Detailed efficacy data in support of fenfluramine are available from one robust, phase 3 RCT (Study 1601; NCT03355209) and its subsequent OLE study providing efficacy data for up to 1 year of treatment.

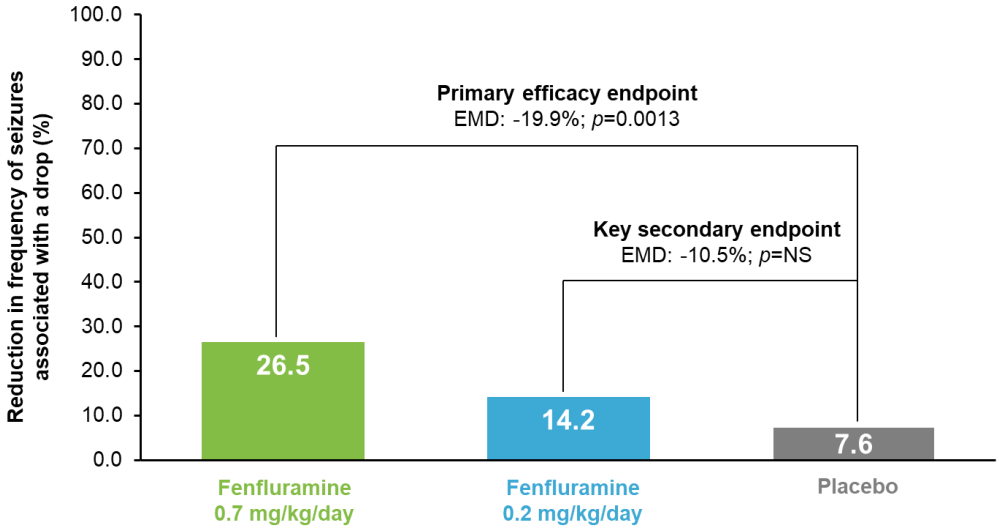
Study 1601 met its primary endpoint (main outcome aim):

- Fenfluramine 0.7 mg/kg/day significantly reduced drop seizure frequency (DSF; estimated median difference vs placebo: -19.9%; p = 0.001).
    - Note: Something is statistically significant if the p-value is less than 0.05 (which is the same as 5%); this means that there is a 95% chance that the results seen will reflect what happens in real life.
    - Note: responses to different doses of a medicine are often tested in clinical trials e.g., 0.7 and 0.2 mg/kg/day of fenfluramine
- Add-on fenfluramine was effective in reducing generalised tonic-clonic (GTC) seizures (which are some of the worst seizures a patient can experience), with 45.7% and 58.2%

reductions seen in the 0.7 and 0.2 mg/kg/day fenfluramine patient groups, respectively, compared with a worsening of -3.7% in the placebo group.

- Significantly more patients on fenfluramine than placebo achieved a clinically meaningful reduction in DSF of at least 50%: one quarter of patients (25%) achieved a ≥50% reduction in DSF with fenfluramine 0.7 mg/kg/day at Week 14 compared with 10% with placebo (p=0.02)
    - Note: something is clinically meaningful if clinicians consider it a big enough change to someone's health in real life
- Children and young adults with LGS treated with fenfluramine were more likely to show clinically meaningful improvement in global executive functioning (measured by something called BRIEF®2) than those receiving placebo.

Figure 3. Primary and key secondary efficacy endpoint – Study 1601 (26)



Abbreviations: EMD, Estimated Median Difference (Hodges-Lehmann estimate), NS, Not Significant.

In the OLE study, patients with LGS experienced continued (39.4% at Month 3 – 51.8% at Month 12) clinically meaningful reductions in DSF during treatment with fenfluramine for up to 1 year. In addition, the median percentage reduction in all seizures not associated with a drop was -66.9% after 1 year. 51.2% of patients responded with a clinically meaningful (≥50%) reduction, and 25.3% of patients demonstrated profound (≥75%) reduction in DSF for the overall OLE Treatment Period. 6.5% patients were near seizure-free (0 or 1 seizures observed) for typical drops during the entire OLE treatment period (29), showing that fenfluramine can completely remove seizures in some patients.

Whilst the placebo-controlled trial of fenfluramine demonstrated the efficacy and safety of its use in LGS, this does not inform the comparative clinical effectiveness of fenfluramine versus alternative add-on therapies. There are no direct comparative data between fenfluramine and the main comparator in this appraisal (cannabidiol with clobazam). Therefore, a network meta-analysis (NMA) was performed to provide the relevant comparative data for fenfluramine as an add-on therapy option versus cannabidiol with clobazam.

Note: An NMA is where you use results of medicines from different RCTs and compare them to one another.

The NMA showed that fenfluramine was ranked first among four treatments (fenfluramine 0.7 mg/kg, cannabidiol (10 mg/kg), cannabidiol (20 mg/kg and placebo) for all the efficacy outcomes (i.e., median percent reduction in frequency of GTC seizure, ≥25%, and ≥50% reduction in DSF) except for the ≥75% reduction in DSF where it ranked third. In addition, fenfluramine showed a better safety profile compared to cannabidiol (20mg/kg), which had the highest probability of patients stopping treatment due to side effects of the medicine .

The NMA provides strong evidence of the clinical efficacy of fenfluramine against cannabidiol (with clobazam) in similar patient populations and confirms that fenfluramine outranks cannabidiol (with clobazam) for the majority of efficacy and safety outcomes.

Collectively, these data clearly demonstrate the significant reductions in drop and non-drop seizure frequency in high proportions of LGS patients when fenfluramine is added to other available antiseizure medications.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In Study 1601, parents/caregivers and study investigators independently rated how patients' symptoms had improved or worsened relative to baseline using the Clinical Global Impression of Change – Improvement (CGI-I) scale.

- Note: the CGI-I scale provides an overall evaluation of a patient's response to treatment taking into consideration how well the medicine works, how safe it is, and how easy it is to continue taking it.

Significantly more patients receiving fenfluramine 0.7 mg/kg/day were rated as "Very much", "Much improved" or "Minimally improved" by parents/caregivers (61.3%) and investigators (48.8%) compared with patients receiving placebo at the end of their treatment period (37% and 33.8%, p=0.0023 and p=0.0567 respectively) (26).

The percentage of patients rated on the CGI-I by the Investigator as having met a more stringent threshold of improvement (much improved or very much improved, indicating a clinically meaningful improvement) at Visit 12 (end of study/early termination) was highly statistically significant in favour of patients receiving fenfluramine 0.7 mg/kg/day compared with patients receiving placebo (26.3% versus 6.3%, respectively; p=0.0007) (26).

This result indicates that the reduction in DSF in the fenfluramine 0.7 mg/kg/day group was associated with clinically meaningful improvements in clinical status as reflected by the CGI-I score.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

During clinical development in LGS, fenfluramine showed a good safety and tolerability profile. The majority of patients continued to stay on fenfluramine during the OLE study, supporting that fenfluramine is a generally well-tolerated antiseizure medication. No case of serious heart problems was reported at any point.

Treatment emergent adverse events (TEAEs) are problems that can occur because of taking a medicine. The most common TEAEs in Study 1601 included decreased appetite (not feeling hungry; 22% of patients), somnolence (feeling sleepy; 13% of patients), and fatigue (feeling tired; 13% of patients). More patients in the fenfluramine treatment groups than in the placebo group experienced decreased appetite (36% in the 0.7 mg/kg/day fenfluramine group; 20% in the 0.2 mg/kg/day fenfluramine group; and 11% in the placebo group).

The most frequent TEAEs leading to patients leaving the study were seizures (3 patients in the 0.2 mg/kg/day fenfluramine group) and somnolence (3 patients in the 0.7 mg/kg/day fenfluramine group) (26).

In the OLE study, the most common TEAEs were decreased appetite (16%) and fatigue (13.4%) (25).

Furthermore, treatment with fenfluramine was not associated with clinically meaningful worsening in cognition compared to placebo ($p>0.05$). Indeed, in combined analysis, including both 0.2 mg/kg and 0.7 mg/kg dosing, significantly more children and young adults on fenfluramine showed clinically meaningful improvement in global executive functioning with specific improvement in cognitive regulation ($p<0.05$; RCI ≥95% certainty) (30). Approximately twice as many children and young adults showed clinically meaningful improvement after fenfluramine than after placebo when measuring cognitive regulation (27% vs. 13%) and global executive functioning (25% vs. 11%).

- Note: executive function refers to the higher-level brain skills used to control and coordinate other cognitive abilities and behaviours. Cognitive regulation refers to one's ability to control and manage brain processes and to problem solve.

As reported in the fenfluramine SmPC (2), findings from Study 1601 (26) are consistent with the observed safety and tolerance outcomes in Dravet syndrome (another rare epilepsy for which fenfluramine is used). The most reported adverse reactions in Dravet syndrome were decreased appetite (44%), diarrhoea (31%), fever (26%), fatigue (26%), upper respiratory tract infection (21%), lethargy (18%), somnolence (15%), and bronchitis (12%).

Long-term safety data is available from various studies, including the OLE study conducted in Dravet syndrome, which provided data for up to 3-years (31). Other studies have also contributed

data with up to 5 years of follow-up (32, 33), one in particular provided data for up to 27 years (34).

The collective findings from these studies indicate little uncertainty regarding the long-term safety of fenfluramine. Notably, there have been no clinically significant cases of cardiovascular or cardiopulmonary events observed in these studies. Furthermore, in real practice, the requirement of routine echo monitoring and safety reporting has not found any significant cases so far.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

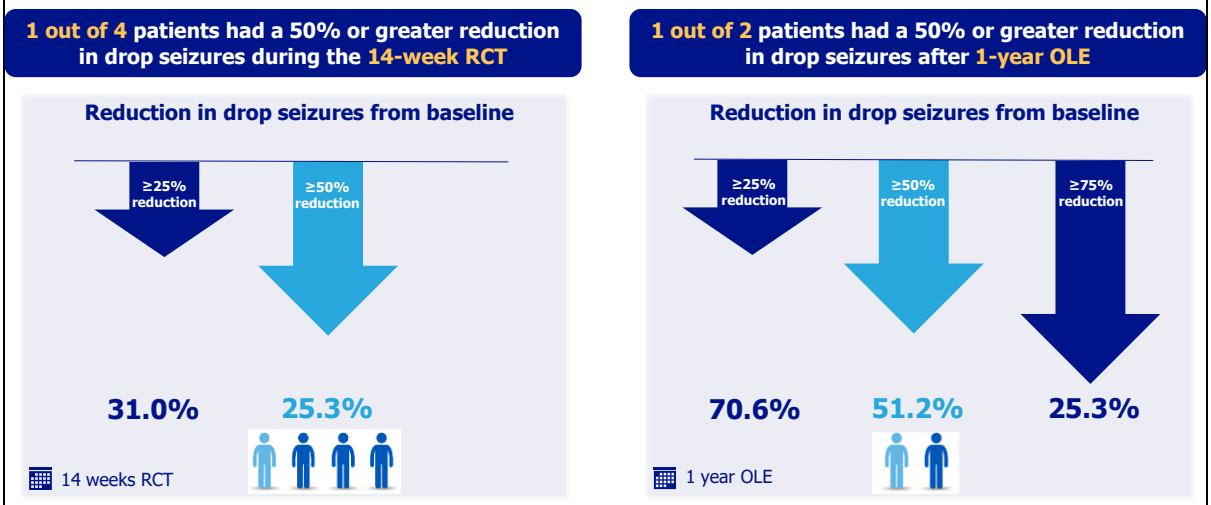
- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The aim of current treatment for LGS is to reduce the impact of seizures on developmental comorbidities, and subsequently improve patient and caregiver's abilities to perform daily living activities and improve their quality of life (18). Despite multiple currently approved medicines, the condition remains largely uncontrolled in most patients. A high unmet need exists for additional treatment options with new ways of working and proven seizure control for LGS patients who have previously failed multiple antiseizure medications.

The dual mode of action for fenfluramine is clinically demonstrated to promote antiseizure activity and improve cognition in patients with severe epilepsies (35, 36). Fenfluramine offers a different way of working from current medicines for patients with LGS, which will help the current treatment for LGS and provide clinicians with more options for new combinations of treatment (26).

In the fenfluramine clinical trials, treatment resulted in a significant reduction in the median frequency of drop seizures by up to 20% from baseline vs placebo, offering the potential of reduced risk of seizure-related injury in the high number of patients that do not respond to treatment (26). Fenfluramine treatment is associated with a clinically meaningful ≥50% reduction in DSF for 1 out of 2 patients with LGS in the long-term **(Figure 4)**.

Figure 4. Clinically meaningful reduction in drop seizure frequency with fenfluramine (25, 26)



Abbreviations: OLE, open-label extension; RCT, randomised controlled trial

Patients with LGS are at increased risk of SUDEP, which is highly linked with the experience of multiple GTC seizures. Fenfluramine treatment resulted in an up to 50% reduction in the number of GTC seizures from baseline vs placebo, offering the potential of reduced risk of SUDEP and seizure-related deaths.

Another key benefit of fenfluramine is that it offers clinically meaningful improvements in cognitive regulation and executive functioning that can improve patient quality of life in both young and adult patients. Fenfluramine has no negative brain side effects, causes no serious heart problems, and a low number of people stop treatment due to side effects of fenfluramine. These all indicate a strong and lasting safety and tolerability profile.

Fenfluramine is a safe treatment option that can easily be used with existing antiseizure medications due to a low risk of drug-drug interactions. Unlike cannabidiol, it does not require co-treatment with another medication, thereby lowering the burden of taking multiple drugs. Taking it as a cherry-flavoured oral solution twice daily also provides a convenient way of giving the medicine.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Patients receiving fenfluramine are required to have a heart scan every six months for the first two years and once a year after that. A final scan is done if a patient stops treatment (2). Though some patients may need to visit a specialist centre, a scan is a common, non-invasive (no needles) procedure that usually does not take too long.

It is important to note that to date there have been no cases of serious heart problems across the clinical trials, registries, or real-world evidence studies.

Although patients on fenfluramine may experience side effects mentioned earlier, such as not feeling as hungry, these side effects are common for these types of treatments and are very similar in other medicines provided for LGS.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

An economic model was created with the aim to accurately show how taking fenfluramine would impact patients through time. The model compares fenfluramine with cannabidiol plus clobazam.

How the model reflects the condition

- The model is structured so that patients move into different health states depending on how they respond to medicines. In real-life, an LGS patient's response to medicines is based on the percentage reduction in seizures that a medicine brings. This model captures this response alongside cost every 3 months for the lifetime of a group of patients that were in the clinical trial. Clinical experts confirmed that this model reflects real life (22).

Modelling how much a treatment extends life

- The OLE study provides data for up to one year, which is not long enough to say that fenfluramine can extend life. However, the reduction of seizures observed with fenfluramine (more than other medicines) is linked to lower rates of SUDEP. Therefore, it is expected that fenfluramine may prolong life; however, due to uncertainty the model also provides results where this is not assumed.

Modelling how much a treatment improves quality of life

- Due to greater seizure reduction that fenfluramine provides compared to other medicines, fenfluramine is expected to improve a patient's quality of life because of improved cognition and better control of bodily movements. This was measured in the model by looking at how fenfluramine reduced the number of drop seizures in clinical trials and converting this to an overall measure of a patients' health, which is measured by

quality adjusted life years (QALYs). Because fenfluramine's side effects are comparable to other medicines for LGS, but is thought to work better, fenfluramine results in more overall QALYs compared to cannabidiol plus clobazam.

Modelling how the costs of treatment differ with the new treatment

- Fenfluramine is a newer medicine with improved efficacy, which costs slightly more than other medicines. However, the additional cost is much lower than the budget limits provided to companies by the NHS and is in the acceptable range. It is also key to consider that there are many benefits expected from fenfluramine that have not been captured within the modelling, as described in **section 3k**.
- The long-term benefits of fenfluramine are thought to lead to an overall cost saving when considering the big impact reducing seizures has on patients and their carers'. Patients are expected to remain on fenfluramine slightly longer than cannabidiol plus clobazam and that is one of the reasons a larger cost is expected.
- Patients taking fenfluramine need to have their heart monitored with a scan every 6 months for the first two years and then once a year after that. It should be noted however that no patients have ever experienced heart problems with fenfluramine in LGS, these concerns came historically when much higher doses of fenfluramine were used to reduce weight in patients. Unlike fenfluramine, other medicines used for LGS can require more extensive monitoring or require invasive blood tests, which can be a difficult and an anxious experience for LGS patients.

Uncertainty

- LGS is a rare disease, meaning that obtaining information for a large number of patients is difficult. Evidence on a lower number of patients makes the data less certain, however this is something that will always remain a challenge for rare diseases
- One of the key uncertainties within the submission is around the comparison against cannabidiol plus clobazam, which is currently used at a similar point in a patient's treatment pathway and is the medicine that fenfluramine is most likely to be considered instead of. In clinical trials, fenfluramine has not been compared directly to cannabidiol plus clobazam, but instead it was indirectly compared to cannabidiol plus clobazam using the clinical trial information of cannabidiol plus clobazam (using an NMA, **see 3e**).
- Due to each patient being treated differently, it is difficult to identify average values for different outcomes. For example, the average number of other medicines patients use. For both treatments, assumptions for averages were therefore made, with clinicians being asked to help understand what values for the model reflect the real-life situation.
- Many assumptions were tested to see the impact these had on results, such as dose, how long the treatments work and how quickly patients stop taking them. When tested, the end results did not change much, indicating that the model is well-built. Therefore, even if in real-life parameters may be slightly different to what is used in the model, prescribing fenfluramine can still be a sensible option.

Cost-effectiveness results

- Although survival when using both medicines is similar (as discussed earlier), the model shows that patients who take fenfluramine over a lifetime can achieve, on average, 0.83 more quality adjusted life-years (QALYs) than if they were taking cannabidiol plus clobazam. This results in an ICER of just above £30,000.

Note: QALYs are a measure of how well someone feels in one year with 0 being the lowest and 1 being the highest. Here, the 0.83 reflects total QALYs for the lifetime of the patient. ICERs are calculated from QALYs and calculate how much each QALY would cost to the NHS. The NHS

accepts ICERs up to £30,000 (a cost of £30,000 for every additional QALY a new medicine can provide) but can make exceptions for rare diseases, especially if there is a big need for treatment.

- NICE give the option for companies to consider a severity modifier. This is a tool that can help the appraisal by adding more QALYs to the medicine a company is trying to bring to patients.
- Because LGS is such a severe condition that has detrimental impact on the life of patients and their carers, the severity modifier should be applicable at its highest level. When this is applied the ICER moves below NICE's threshold of £20,000.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Most treatments currently recommended by NICE for patients with LGS are given as an add-on therapy and require to be given alongside one particular medicine. Fenfluramine can be given by itself (with or without clobazam), providing flexibility in the management of LGS.

As an efficacious treatment option with a new, double mechanism of action compared with other antiseizure medication, fenfluramine can complement existing LGS therapies and provide patients and clinicians with a much-needed alternative option which can create new combinations of medicines.

There are many benefits of fenfluramine that cannot be captured in the model because either it would make the model too complicated or there is not enough information available to compare against cannabidiol plus clobazam. These include:

- Benefits of fenfluramine for beyond the reduction in seizure frequency. For example, reducing the duration and severity of each seizure. Other benefits include improvements in patients' movement and improvement in their brain function.
- Additional benefits are in the early response patients have to fenfluramine, how easy it is to stay on fenfluramine for long periods of time, and the low levels of sleepiness it causes (compared to cannabidiol). All of these are thought to further improve brain function and the quality of life of patients.
- Improvements in the quality of life of siblings of those living with LGS.
- Improvements in other measures of how well a medicine works that measure improvements in behaviour and overall wellness, which cannot be included in QALY calculations.

The abovementioned factors are difficult to include in the modelling, because they can often only be described without being put into numbers.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

No equality issues are expected with fenfluramine.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

- Young Epilepsy – Young Epilepsy | Homepage
- Epilepsy Society – Epilepsy Society | Transforming lives through advocacy, research and care
- Epilepsy Action – Home - Epilepsy Action
- Efficacy and safety results for Study 1601: Efficacy and Safety of Fenfluramine for the Treatment of Seizures Associated With Lennox-Gastaut Syndrome - PMC (nih.gov)
- Long-term efficacy and safety results from the OLE (interim analysis): Fenfluramine provides clinically meaningful reduction in frequency of drop seizures in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study (nih.gov)
- Fenfluramine SmPC: Fintepla 2.2 mg/mL oral solution - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Fenfluramine Patient Information Leaflet: Fintepla, INN-fenfluramine (medicines.org.uk)

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe:

http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event: An unintended or unfavourable sign, symptom, or disease in a patient who has been administered therapy (may or may not be drug-related).

BRIEF®2: An individualised, norm-referenced instrument designed to assess executive function in children and adolescents ages 5 to 18 years.

Chronic disease: A long-term condition that requires ongoing management over a period of years or decades, that cannot currently be cured but can be controlled with medication and/or other therapies.

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease.

Comorbidity: The existence of more than one disease or condition.

Contraindication: A specific situation in which a drug, procedure, or surgery should not be used because it may be harmful to the person.

Drop seizure: The most frequent type of seizures occurring in LGS, resulting in a loss of muscle tone or stiffening of muscles.

Efficacy: The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial.

GTC seizure: Generalised tonic-clonic seizure, where the person loses consciousness and has stiffening and jerking of the muscles

NICE: The National Institute for Health and Care Excellence is an independent organisation set up by the Government to decide which drugs and treatments are available on the NHS in England.

Network meta-analysis: A technique used to compare multiple treatments simultaneously by combining evidence from different clinical trials.

Quality of life: A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living.

Randomised controlled trial: A trial where patients are randomly assigned to groups to test a specific drug, treatment or intervention.

SUDEP: The sudden, unexpected death of someone with epilepsy, who was otherwise healthy.

Treatment-emergent adverse event: an adverse event that began after the start of the trial medication.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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Copyright © 2005, Bladon Medical Publishing, an imprint of Springer Science+Business Media.; 2005.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Clarification questions

August 2023

File name	Version	Contains confidential information	Date
ID1651_Fenfluramine_LGS_ Clarification Answers [Redacted]	1.0	No	14th September 2023

[Please note that company answers are provided in blue after each question. As agreed, we will be addressing questions B11c, B23f, B24b, and B28 which require amendments to the cost-effectiveness model by Thursday 21st September 2023. The updated model will also be provided at this date, including changes requested by other questions in this document to have all changes reflected in one update.]

Section A: Clarification on effectiveness data

Literature searches

A1. Priority question. Section D.1.1.1 reports several supplementary searches. Please see the table below for those listed in Appendix D Table 1.

a) Please provide full details, including the search strategies or search terms used, date searched, and hits retrieved per resource for these and any other additional searches not listed below.

b) Please confirm that these additional searches were conducted as a single set of searches and used to inform all sections of the company submission (CS) i.e., clinical and economic.

Resource	Additional literature sources
Conference proceedings	American Epilepsy Society
	The Professional Society for Health Economics and Outcomes Research
	International League Against Epilepsy
	European Epilepsy Congress
Health Technology Assessment (HTA) Global bodies	National Institute for Health and Care Excellence (NICE)
	Scottish Medicines Consortium (SMC)
	Canadian Agency for Drugs and Technologies in Health (CADTH)
	Pharmaceutical Benefits Advisory Committee (PBAC)
	All Wales Therapeutics and Toxicology Centre
	Institute for Quality and Efficiency in Health Care (IQWIG) & Federal Joint Committee (G-BA)
	Institute for Clinical and Economic Review (ICER)
	Haute Autorité de santé (HAS)
	HTA Database of the INAHTA (https://www.inahta.org/)
	National Institute of Health Research (NIHR) HTA (https://www.nihr.ac.uk/)
Trial Registries	National Institutes of Health ClinicalTrials.gov (http://www.clinicaltrials.gov/)

A1a. Table 1, Table 2 and Table 3 provide details of the grey literature searches, including the search terms used, date searched, and retrieved hits for each source.

Table 1: Search conducted on conference websites

Resource	Additional literature sources	Search term	Date searched	Hits
Conference proceedings	American Epilepsy Society	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	113
	European Epilepsy Congress	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	19
	European paediatric neurology society	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	8
	International Society for Pharmacoeconomics and Outcomes Research	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	19
	International League Against Epilepsy	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	10
	American Academy of Neurology	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	21

Note: conferences between January 2020 and June 2023 searched.

Table 2: Search conducted on HTA body websites

Resource	Additional literature sources	Search term	Date searched	Hits	Full TA retrieved for review
Health Technology Assessment (HTA) Global bodies	National Institute for Health and Care Excellence (NICE)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	1	1
	Scottish Medicines Consortium (SMC)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	2	2
	Canadian Agency for Drugs and Technologies in Health (CADTH)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	4	1
	Pharmaceutical Benefits Advisory Committee (PBAC)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	2	0
	Institute for Quality and Efficiency in Health Care (IQWIG) & Federal Joint Committee (G-BA)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	2	0
	Institute for Clinical and Economic Review (ICER)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	0	0
	Haute Autorité de santé (HAS)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	7	0
	Wales: All Wales Therapeutics and Toxicology Centre	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	2	1
	HTA Database of the INAHTA	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	8	0

Resource	Additional literature sources	Search term	Date searched	Hits	Full TA retrieved for review
	National Institute of Health Research (NIHR) HTA	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	0	0

Table 3: Searches conducted on other websites

Resource	Additional literature sources	Search term	Date searched	Hits
Trial Registries	National Institutes of Health ClinicalTrials.gov (http://www.clinicaltrials.gov/)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	55
Guidelines	European Medicines Agency (EMA)	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	1
	NICE	Lennox Gastaut Syndrome	October 5th 2022, updated June 7th 2023	1
UCB	Clinical Study Report	N/A	N/A	N/A

A1b. These grey literature searches were conducted as a single set of searches, and informed all sections of the CS (clinical and economic) and apply to Appendices D, G, H and I.

A2. In Appendix D, Table 4 provided details of the search strategy used to search the CENTRAL database. Line #1 contains the MeSH term for Lennox Gastaut syndrome (LGS). The evidence assessment group (EAG) notes that the following strategies in Tables 5, 6 and 7 for the remaining evidence-based medicine (EBM) resources do not contain this line, please explain the rationale behind this and what effect it may have had on the recall of results. This question applies to similar searches reported in Appendices G (Tables 53, 54 55, 56), H (Tables 63, 64, 65, 66), and I (Tables 78, 79, 80, 81).

A2. Each of the EBM databases has different record fields available which affects the search strings that are used:

- EBM database - Cochrane Database of Systematic Reviews : the CENTRAL database includes MeSH indexing. Therefore, the MeSH term "Lennox Gastaut syndrome" was used in the CENTRAL search as presented in tables 4, 52, 52 and 77 in the appendices of the CS.

- Other EBM databases: However, this syntax is not relevant in the HTA, CDSR, and DARE databases, so a text term search of relevant fields (title, short title, abstract, keywords, full text) was conducted instead.

There is no effect on the number of results since no records would be captured in these databases by using MeSH terms.

A3. Please confirm the date span for all databases for all Sections.

A3. All database searches were originally conducted on 05 October 2022 without any time restriction (i.e., databases were searched since inception), and updated on 07 June 2023. Search updates were performed on 07 June 2023 in all databases apart from 'EBM Reviews - NHS Economic Evaluation Database' and 'EBM Reviews - Health Technology Assessment'. As these databases had been discontinued in 2015, a search update was not warranted in June 2023.

Grey literature searches were originally conducted on 05 October 2022 and updated on 07 June 2023. Conference searches were restricted to the period January 2020 – June 2023 based on the assumption that data presented in older conference abstracts would have been published in full manuscripts by the time of the database searches. No publication time restrictions were applied to the HTA, guideline or trial registry searches.

A4. In Table 1, MEDLINE searches, MEDLINE daily update and MEDLINE epub ahead of print were not included in the list of MEDLINE segments to be searched, please confirm if this was the case.

A4. The MEDLINE search was run in the Ovid MEDLINE ALL database, which includes the following MEDLINE segments:

- Epub Ahead of Print
- In-Process & Other Non-Indexed Citations
- Versions
- PubMed-Not-MEDLINE
- Daily Update
- Front Segment weekly update

- Back files from 1946 to start of front segment

If more information is needed, please refer to the Ovid MEDLINE ALL website (see the link here) for more details.

A5. Please confirm whether any additional searches, other than those reported in Appendix D Section D.1.1, were conducted to retrieve information regarding adverse events (AEs) for fenfluramine and, if so, provide full details including date, resource names and search strategies used.

A5. Additional information on the safety of fenfluramine was retrieved from the UCB clinical study report (CSR), as described in Appendix D, section 1.1.2. No other additional searches were conducted to retrieve data on AEs for fenfluramine.

Decision problem

A6. Priority question. The final scope by the National Institute for Health and Care Excellence (NICE) as well as the decision problem defined the comparison of interest as fenfluramine versus established clinical management (ECM) without fenfluramine hydrochloride. According to Section B.2.3.1 of the CS, in the identified trial (Study 1601), the *"intervention was fenfluramine in addition to SoC [standard of care] and the comparator was SoC without fenfluramine (i.e., SoC plus placebo)".* This makes clinical sense as fenfluramine has been developed as an add-on therapy, not a first line stand-alone drug. Note that ECM and SoC are synonymous, and include concomitant anti-seizure medications (ASMs). However, an important distinction between the trial and the NICE scope/decision problem is that in the trial fenfluramine is given alongside SoC/ECM, but in the NICE scope/decision problem the implication is that fenfluramine is given alone.

a) Please reframe the decision problem to be fenfluramine + SoC vs. SoC (to avoid giving the impression that fenfluramine alone is being compared to the comparators), or justify the current wording.

b) Several specific comparators, such as various ASMs, are listed in the scope and decision problem under the heading of ECM. If fenfluramine is to be an add-on to ECM, then it would seem logical that the appropriate comparison would be between fenfluramine + specific medication vs. specific medication alone e.g., fenfluramine + clobazam vs. clobazam, assuming that patients who would be prescribed clobazam would still be given clobazam and not switched if fenfluramine was added. If patients were on a combination of treatments, then the appropriate comparison would be fenfluramine + specific combination vs. specific combination alone, where some additional therapy could be expressed as SoC e.g., fenfluramine + clobazam + SoC vs. clobazam + SoC. However, this seems to be inconsistent with the NMA where there is no mention of the therapy to which fenfluramine was added or to which any of the other therapies were added except cannabidiol where it is clobazam.

i. Please clarify that fenfluramine would be added to a specific therapy that, without fenfluramine, would be given alone and that no switching would occur.

ii. Please clarify if any patients would be expected to be on combinations of ECM therapies and which comparison is most appropriate e.g., fenfluramine + clobazam vs. clobazam or fenfluramine + clobazam +SoC vs. clobazam + SoC.

iii. Please conduct analyses that are consistent with the most appropriate comparisons using data from the fenfluramine trial and trials of other treatments in a network meta-analysis (NMA) as dictated by these comparisons.

A6a. The intervention in the decision problem is reframed in Table 4 below. Indeed, fenfluramine is not given alone as it is indicated for the treatment of seizures associated with LGS as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older. Therefore, the intervention in the decision problem is fenfluramine + SoC. This is aligned with fenfluramine clinical trial, Study 1601, where

the intervention was fenfluramine in addition to SoC compared to SoC alone (i.e., SoC plus placebo). In response, the comparators in the decision problem have been reframed in Table 4. Indeed, as cannabidiol with clobazam is the only established clinical add-on therapy to have been formally appraised by NICE, and accepted as a clinically and cost-effective option, it is also the only therapy with sufficient trial data to permit a robust comparison. Therefore, the two relevant comparators are: cannabidiol with clobazam + SoC and SoC alone. The other ASMs and the non-pharmaceutical treatments are not considered as comparators but constitute the SoC 'basket.'

A6b.i. In line with the licensed therapeutic indications as per the SmPC, fenfluramine would not be added to a specific therapy. As per the clarification in question A6a. and the reframed decision problem, the intervention is "*fenfluramine in addition to current SoC*". Despite published guidelines, there is no established standard approach to LGS treatment. Physicians typically adjust or change treatments to enhance their effectiveness in reducing seizures. Individualised anti-seizure therapy is initiated based on the patient's syndrome type, treatment goals, AEs and preferences. Current SoC varies due to the refractory nature of LGS; and given the heterogeneity of the disease, it is not clinically or statistically meaningful to compare the intervention to individual or specific combinations of ASMs beside cannabidiol with clobazam + SoC. Indeed, as illustrated in the response of question 0of this document, LGS patients included in Study 1601 received a wide range of possible treatment options. To note, in NICE evaluation of cannabidiol in 2019 (TA615 – the only treatment evaluated by NICE in LGS), the intervention "*cannabidiol with clobazam + SoC*" is compared to "*SoC*" which was defined as a 'basket' of choices of ASMs.

A6b.ii. It is not expected to have patients on specific combinations of ECM therapies. As presented in Table 4, the most appropriate comparison is fenfluramine + SoC vs. cannabidiol with clobazam + SoC. However, the company also provide an analysis to compare fenfluramine plus SoC versus SoC alone.

A6b.iii. As mentioned in A6b.i., due to the heterogeneity of the disease and lack of an established standard approach to LGS treatment., there is no defined SoC and therefore no additional analyses could be performed.

Table 4: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 2 and over with Lennox-Gastaut syndrome whose seizures are inadequately controlled by established clinical management.	People aged 2 and over with Lennox-Gastaut syndrome whose seizures are inadequately controlled by established clinical management.	As per final NICE scope
Intervention	Fenfluramine hydrochloride	Fenfluramine hydrochloride in addition to current standard of care (SoC).	Fenfluramine is not given alone as it is indicated for the treatment of seizures associated with LGS as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.

Comparator(s)	Established clinical management without fenfluramine hydrochloride, which may include combinations of:
	• Anti-seizure medications, including but not limited to:
	  ○ cannabidiol with clobazam
	  ○ sodium valproate
	  ○ lamotrigine
	  ○ rufinamide
	  ○ topiramate
	  ○ felbamate
	  ○ clobazam
	  ○ levetiracetam
	• ketogenic diet
	• vagus nerve stimulation
	• surgery
		Cannabidiol with clobazam in addition to SoC.or SoC alone
		
		SoC may include combinations of:
		• Anti-seizure medications, including but not limited to:
		  ○ sodium valproate
		  ○ lamotrigine
		  ○ rufinamide
		  ○ topiramate
		  ○ felbamate
		  ○ clobazam
		  ○ levetiracetam
		• Ketogenic diet
		• Vagus nerve stimulation
		• Surgery
			Fenfluramine is expected to be provided as an alternative treatment option to cannabidiol plus clobazam (as per fenfluramine's EMA Orphan Maintenance Assessment Report Jan 2023).
			As cannabidiol is the only established clinical add-on therapy to have been formally appraised by NICE, and therefore accepted as a clinically and cost-effective option, it is also the only therapy with sufficient trial data to permit a robust comparison. A primary clinical and economic comparison of fenfluramine plus standard of care against cannabidiol (with clobazam) plus standard of care as the comparator is considered the most appropriate, relevant, and robust comparison to address the decision problem in this appraisal.
			The company also provide an analysis to compare fenfluramine plus standard of care versus standard of care alone.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome 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 • health-related quality of life (patients and carers)	The outcome measures to be considered include: • seizure frequency (drop seizure) • response rate (percentage of reduction of drop seizures within these categories: <25%; 25-50%; 50-75%; >75%) • mortality (SUDEP and non-SUDEP including status epilepticus) • adverse events of treatment • health-related quality of life (patients and carers)	Only drop seizures, characteristic seizures of LGS and primary and key secondary endpoints in the RCT (Study 1601) for fenfluramine, are considered in the company submission. Proportion of people seizure-free is not considered in the model as the proportion of patients who are (drop) seizure-free was very low in the Phase 3 trials of fenfluramine and cannabidiol (either 0 or 1 patient per treatment arm). The severity of seizures was captured through the types of seizures: GTC seizures leading to drops are associated with higher healthcare resource use, and this was captured in the model. Incidence of status epilepticus is not a model outcome *per se* but non-SUDEP was considered including status epilepticus deaths.

A7. Priority question. Please provide an explanation for the specific dosages of fenfluramine chosen in the trial.

A7. In Study 1601, patients were randomised to receive either a 0.7 mg/kg/d or 0.2 mg/kg/d (maximum 26 mg/d) dose of fenfluramine or placebo. These dose-levels were selected based on data from Study S58545 (NCT02655198), a Phase 2 open-label, pilot, dose-finding trial in which a small cohort (n=13 patients with LGS aged 3-18 year) of refractory patients with LGS in Belgium were treated with fenfluramine as an add-on therapy to conventional therapy (Lagae 2018 (1)). Fenfluramine has been generally well tolerated in this ongoing study, with no subject developing valvular heart disease or pulmonary arterial hypertension.

These two doses were also studied in Phase 3, double-blind, placebo-controlled studies of fenfluramine in subjects with Dravet syndrome (DS) based on data from Study ZXIIS2015-04, an open-label proof-of-concept trial of fenfluramine in subjects with DS. (Schoonjans 2017 (2)). Comparison of the seizure reduction results for the two dose-levels of fenfluramine in this study suggested a dose-response effect on seizure frequency. The pattern of individual responses in the fenfluramine 0.2 mg/kg/day group supported the selection of 0.2 mg/kg/day as the minimally effective dose.

A8. Priority question. Please provide an explanation why the outcome of 'seizure severity' was not included in the decision problem, despite being included in the NICE scope. If available, present relevant data on this outcome.

A8. As mentioned in the decision problem of the CS (page 17), the "*seizure severity*" was not listed as an outcome as "*The severity of seizures was captured through the types of seizures: GTC seizures leading to drops are associated with higher healthcare resource use, and this was captured in the model* [through the management costs]." Indeed, GTC seizures are more severe than other types of seizures, for instance, the risk of SUDEP is highly correlated with the experience of uncontrolled and frequent GTC seizures (3, 4). Patients with any number (one or more) of GTC seizures in the previous year are 27 times more likely to die suddenly compared with people with epilepsy who have not experienced any GTC seizures (4). Therefore, the use of GTC seizures was the best proxy possible to capture seizure severity as it was not an

endpoint collected during fenfluramine's clinical trial. To note, in the only NICE evaluation done on LGS (TA615), "*seizure severity*" did not appear as an outcome in the decision problem.

A9. Priority question. Please provide an explanation why the outcome of 'mortality' was not included in the decision problem, despite being included in the NICE scope. If available, present relevant data on this outcome.

A9. Mortality is included in the decision problem (CS, Table 1, page 17). It is explained that, in the model, mortality accounted for SUDEP and non-SUDEP. Non-SUDEP includes death from accidental causes and status epilepticus *"mortality (SUDEP and non-SUDEP including status epilepticus)"*.

A10. The outcome of 'seizure frequency' is restricted to drop seizures in the decision problem, and to drop seizures and tonic-clonic seizures in the CS clinical efficacy report, but other seizure types are not included. This is despite the trial population including patients with "*multiple seizure types, including tonic and tonic or atonic seizures*".

a) Please provide a full justification for this restriction.

b) Provide further data for other seizure types if appropriate.

A10a. As mentioned in the decision problem of the CS (page 17), "*only drop seizures, characteristic seizures of LGS and primary and key secondary endpoints in the RCT (Study 1601) for fenfluramine, are considered in the company submission*." Drop seizures (or drop attacks) can be caused by many different seizure types. In Study 1601, drop seizures are classified as GTC, secondary generalised tonic-clonic (SGTC), tonic, atonic, or tonic/atonic that are reviewed and confirmed as resulting in a drop for each subject based on the definition from Epilepsy Study Consortium (ESC): "*seizures involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface, or that could have led to a fall or injury depending on the subject's position at the time of the seizure*." Measuring and utilising drop seizures therefore encompasses, as per above, the trial population including patients with "*multiple seizure types, including tonic and tonic or atonic seizures*". To

note, since drop seizures result in physical events such as falls and injuries, the data collection for these seizures is considered more easily identifiable, and the accuracy of measurement can be better compared to other seizures. In contrast, the count of non-motor or non-drop seizures tends to vary considerably, likely because of the challenge in consistently counting these subtler seizures.(5, 6).

A10b. As explained in A10a., drop seizures are considered the most appropriate seizures to use in the model for multiple reasons (these seizures are characteristic of LGS, they are the primary endpoint of fenfluramine and cannabidiol trials, they include multiple seizure types and are more accurately measured compared to other seizures) and therefore no additional data are provided.

Systematic review

A11. Eight records were excluded in full-text screening for "*Not in English*", while the PICOS criteria do not mention any restriction on language (Table 8 in CS Appendices). Please clarify the inclusion criteria for language and assess these excluded articles for inclusion.

A11. Systematic literature searches were conducted with the eligibility criterion of being written in English only. Table 8 in CS Appendices should have indicated 'Language: English,' similar to the other tables presenting PICOS (Tables 57, 67, and 82 in the CS Appendices). Figure 1 in the CS Appendices is considered accurate; it shows that eight records were excluded because they were not written in English.

Clinical effectiveness evidence

A12. Priority question. The groups in the 1601 trial appeared to be reasonably well-matched in the proportion of patients taking each of the five concomitant medications. There were also similarities in the number of concomitant medications – three - taken by each patient. However, it is unclear if the groups were similar in terms of the numbers of patients using specific combinations of concomitant medications (for example, how many people were receiving precisely fenfluramine + rufinamide + clobazam).

a) **Please provide the numbers of patients in each arm using any specific combinations of concomitant medications that were used.**

b) **Were any other concomitant medications or non-pharmacological therapies used by any patients?**

A12a. The numbers of patients in each arm using any specific combinations of concomitant medications are listed in Table 5 below:

Table 5: Number of subjects taking combination of five concomitant ASMs in Study 1601 – Safety population

A12b. Regarding other concomitant medications received in Study 1601, the most common concomitant medications and non-pharmacological therapies [redacted] of patients overall) included the following: vagus nerve stimulation (VNS) ([redacted] patients [redacted]%]), paracetamol ([redacted] patients ([redacted]%]), and melatonin ([redacted] patients [redacted]%]). It is noted in the trial that no patients received concomitant stiripentol (STP) (7).

A13. Priority question. Effectiveness is likely to vary according to the combination of concomitant medications to which fenfluramine is added.

a) Please conduct subgroup analyses defined by the specific combinations of concomitant medications to which fenfluramine (or placebo) is added.

b) Please conduct analyses for all efficacy outcomes to estimate the effect of the specific combinations of concomitant medications to which fenfluramine is added, adjusting for any likely treatment effect modifiers.

A13a. and A13b. During an advisory board meeting, clinical experts agreed that patient profiles and treatment pathways in LGS are highly heterogeneous in clinical practice (8). Combining this with the fact that LGS is a rare disease with a relatively limited number of patients it is very difficult to provide/form meaningful subgroups that would represent specific patient groups in clinical practice. Furthermore, current clinical management varies due to the refractory nature of LGS and the course of the disease has no specific patterns that would help establish any meaningful subgroups of patients with ASM combinations. Due to there being such a large variation in the different combinations of concomitant medications used (see answer to question A12a), the analysis would become very complex and potentially lead to implausible conclusions on a small group of patients which are heterogenous in their response to treatments. This observation is in line with clinical expert opinion and this specific issue has been highlighted in other TAs including TA615 (9). In addition, Study 1601 does not have the necessary sample sizes per specific ASM combinations to conduct analyses of efficacy outcomes by these subgroups of patients. To note: the efficacy of different ASM combinations within fenfluramine's DS studies were also assessed, and no significant or plausible differences/impact on efficacy were observed (10).

A14. If effectiveness varies according to the specific combinations of concomitant medications, then it is important to know how similar the concomitant

medications used in the trial are to those used in the target population. How do the specific combinations of concomitant medications used in the trial compare to the specific combinations of concomitant medications used in United Kingdom (UK) clinical practice?

A14. Clinicians who were recently consulted (following receipt of these clarification questions) confirm that LGS treatment consists of a complex mix of treatments, and every patient is treated differently. Treatment is highly individualised, making it difficult to specify how any specific group of patients using a particular combination of ASMs will respond. No combinations have been seen to be more effective than others, and it has been specifically mentioned that combinations used in the fenfluramine trials do reflect that which is seen in clinical practice. This was also observed within the advisory board conducted earlier in 2023, where multiple clinicians practicing the treatment of LGS in the UK were asked to comment on the applicability of data within trials, and it was confirmed that baseline characteristics of patients, including the concomitant medications they are on, do reflect real clinical practice within the UK (8).

A15. No sub-groups based on any other patient characteristics (such as age or ethnicity) were considered by the company during analysis either.

a) Please consider any patient characteristics that might plausibly affect the treatment outcome.

b) Please consider sub-grouping the trial analyses for any patient characteristics that might be thought to influence outcome.

c) Please provide population characteristics for the UK target population so that an evaluation of any differences with the trial population (and thus an inference of external validity) can be made.

A15a. to A15c. Subgroups were examined in efficacy analyses and AE summaries. These included subgroups based on age, sex, weight, number of concomitant ASMs, number of prior ASMs, baseline drop seizure frequency (DSF), race, and region. The subgroup analyses were not adequately powered and therefore should be considered exploratory. The observed ranges of the CIs were what would be expected in exploratory analyses that included a small number of subjects. Generally, the analysis

results were consistent across all relevant subgroups. This is why no subgroup trial analyses based on patient characteristics were presented in the CS.

UK clinical experts were consulted following receipt of these clarification questions, and there was no mention of any patient characteristics (sub-groups) that may impact treatment outcome. Rather overall comments were provided on how patients are managed based on the impact ASMs have on certain aspects such as behavioural changes for all patients. One clinician mentioned that LGS is – "*such an individualised disease with multiple aetiologies so very hard to identify a specific sub-group*". Patient characteristics within the fenfluramine clinical trials have been said to match observed characteristics within UK clinical practice (11). Furthermore, in NICE evaluation of CBD in LGS (TA615), no subgroup on ASMs were presented as the company stated in their clarification questions that "*these subgroups have small population numbers with low statistical powering*" (9).

A16. The validity of the efficacy measures depends on the measurement validity of the eDiary, an electronic, homebased handheld device provided to every subject, used for the recording of seizures. Please provide information about the measurement validity of these devices.

A16. The main efficacy measures were based on seizures reported in the eDiary, an electronic, homebased handheld device (TrialMax Touch™) provided to every subject. Additional scales and questionnaires were administered using a site-based electronic clinical outcome assessment tablet (TrialMax Slate™, "*Slate*") provided to every clinical site. These devices, along with an internet-based data portal (TrialManager®) used for reviewing data, were hosted by Signant Health (previously known as CRF Health, Boston, MA). Design and validation for the TrialMax Touch™ and TrialMax Slate™ were performed in accordance with Signant Health standard operating procedures and the project design documentation.

A custom-designed eDiary was used in the trial to capture seizure information and record daily study medication intake. The seizure module was designed to model the paper seizure diary form provided by the ESC for use in clinical trials since 2009. The use of diary data (either paper or electronic) has been the gold standard for data collection in epilepsy trials.

eDiaries provide a more efficient and accurate means of collecting data in epilepsy trials. They enhance data quality, reduce administrative burdens, and offer a more patient-centered approach to data collection and monitoring. Various studies have demonstrated the accuracy of using eDiaries in epilepsy trials (12-14). The ESC recognise the quality of Signant Health and its devises, acknowledging its "*considerable experience developing complex eDiaries and conducting epilepsy trials*" (15).

A17. There was a large difference in baseline motor seizure frequency between placebo and intervention groups in the 1601 study [median (interquartile range [IQR]) frequency per 28 days: 68 (14 to 1,761) for placebo, 106 (4 to 2,943) for 0.2 mg/kg/day fenfluramine and 111 (10 to 1,897) for 0.7 mg/kg/day fenfluramine]. Although quite possibly a random effect, this appears to be a large enough difference to influence outcome.

a) Please comment on how this discrepancy could influence the outcome.

b) Please provide statistical adjustment to results if appropriate.

A17a and b. All countable motor seizures were an "*additional secondary*" endpoint and not a key outcome of the trial. In order to mitigate baseline variability, the analyses used two approaches: (1) A rank-based, nonparametric model was used. Ranks are much more robust to difference in scales than an untransformed analysis. (2) The outcome measure used in the analysis model was percentage change from baseline. That means each subject was adjusted for their own baseline seizure frequency.

Thus, the difference in baseline motor seizure frequency between treatment arms is a random effect that is not likely to influence the outcome.

A18. There appear to be contradictions in the description of the open label extension (OLE) study. In Figure 8 and Table 7 of the CS it appears that the OLE study did not involve any randomisation to different doses of fenfluramine or placebo. Instead, patients were started on 0.2 mg/kg/day fenfluramine and doses were then adjusted as tolerated, which would fit with the established format of an OLE study. However, in Section B.2.3.1 of the CS it is stated that *"patients who qualified for the OLE study entered the titration period and 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 placebo". Figure 9 in the CS gives a similar impression that randomisation to the three OLE groups was applied. Please clarify this apparent contradiction.

A18. No randomisation was applied in the OLE study, as explained in Section B.2.3.1 (page 40 of the CS) "*During the OLE study, all patients were treated initially with fenfluramine 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study patients. After 1 month at a dose of 0.2 mg/kg/day, the investigator could adjust the dose for each subject based on effectiveness and tolerability."*

At the beginning of the paragraph, as noticed by the EAG, there is a misprint, and it should read "*Upon completion of baseline in Study 1601, patients who qualified for the ~~OLE~~ study entered the titration period and 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 placebo.".* Figure 8, Table 7 and Figure 9 are correct. In Figure 9, the division into three different treatments and dosages does not indicate randomization but rather shows that out of the 247 patients from Study 1601 who continued to the OLE study, 78 received 0.7 mg/kg/day of fenfluramine during Study 1601, 83 received 0.3 mg/kg/day of fenfluramine, and 86 received a placebo.

A19. The CS, the NICE scope, and the European Medicines Agency (EMA) and Food and Drug Administration (FDA) marketing authorisations do not contain information on the appropriate 'stopping rules' for fenfluramine in LGS. This information is important in economic modelling. What would be appropriate 'stopping rules' for fenfluramine in LGS?

A19, Similar to cannabidiol (TA615), 'stopping rules' for fenfluramine are not mentioned within the NICE scope, by EMA or FDA authorities. Therefore, the appropriate stopping rule can be identified by confirming with clinicians what percentage reduction would be applied in UK clinical practice. Following receipt of the clarification questions, UK clinical experts were asked this question and they stated a 25% to 30% reduction in drop seizure frequency would be a reasonable reduction and 6 months should be given before assessing the outcome. This closely aligns with what has been accepted for cannabidiol in treatment LGS (TA615), and clinicians

mentioned that also applying the 30% stopping rule for fenfluramine would be appropriate and implementable in clinical practice. Results from additional scenario analysis implementing the 30% stopping rule at 6 months within the cost-effectiveness model (question B11c) can be observed once the company provides the additional analysis to NICE on 21st September 2023.

Indirect treatment comparison (ITC)

A20. Priority question. The systematic literature review (SLR) identified 16 randomised controlled trials (RCTs) that evaluated Fenfluramine, 8 other anti-seizure medications and 2 electrical stimulation approaches in terms of their efficacy in people with LGS. Of these, 7 were excluded from the NMA because a) outcomes were reported outside the range of 10-20 weeks (n=3), b) there were no matching outcomes for comparison (n=2),c) because a drug was not approved by the EMA (n=1) or d) because of a very high baseline number of seizures (n=1). These exclusions appeared appropriate, leaving 9 eligible RCTs for the NMA. However, the NMA published in the CS appendices excluded a further 6 RCTs, merely including 3 RCTs (that covered only fenfluramine and cannabidiol/clobazam). Therefore, rufinamide, felbamate, lamotrigine, clobazam (alone) and topiramate were not included as comparators in the NMA. Of these, rufinamide, topiramate and clobazam (alone) are included in the scope and recommended as 3rd line medications by NICE (NG217) [which is the line of therapy for which fenfluramine is positioned]. Following on from question A6b, the ideal network would contain all 3rd line medications, and might therefore comprise the following 3rd line comparisons: fenfluramine + SoC vs placebo + SoC; cannabidiol/ clobazam + SoC vs placebo + SoC; clobazam + SoC vs placebo + SoC; rufinamide + SoC vs placebo + SoC and topiramate + SoC vs placebo + SoC. Such a network would allow clinically relevant indirect estimates of the treatment differences between each of these 3rd line drugs (appropriately combined with SoC treatment) – for example, between fenfluramine + standard of care and rufinamide + SoC. The rationale given for the exclusion of these further 6 RCTs was that these

excluded RCTs did not report all outcomes of interest or *"most characteristics relevant to the disease"*, that the data from the excluded trials were outdated, and that *"cannabidiol is the most recently approved LGS medication and is a main comparator to fenfluramine"*. These explanations are not convincing. A separate NMA is normally carried out for each outcome of interest and so each RCT should have been allowed to contribute to the NMA for any relevant outcome that it covered, regardless of whether all outcomes were covered. Furthermore, the reasons related to patient characteristics and recency require considerable strengthening. Finally, the fact that cannabidiol has been most recently approved and is a common comparator to fenfluramine does not justify the exclusion of other comparators. Given that a proper consideration of the relative efficacy and cost effectiveness of add-on fenfluramine is not complete unless all the other add-on third line option drugs are considered in the model, please provide NMAs that include data from all 9 eligible RCTs.

A20. The NMA report provided in the reference pack (UCB data on file NMA report) included the extended (broader) network analysis in Appendix F (including data from 9 RCTs). Major concerns were raised in the feasibility assessment, as the 6 excluded trials did not report all key patient characteristics including: baseline seizure frequency, number of prior ASMs used, and number of concomitant ASMs used (see Table 16 in the CS Document B) and most of these excluded studies were dated from 20-30 years old data and hence do not capture improvement in LGS medical care (concomitant ASMs), which is especially difficult to assess as they do not report information on concomitant ASMs. This transgresses the transitivity assumption needed for conducting the NMA for this network.

Furthermore, although this extended network analysis has been provided separately in the NMA report and enclosed in the reference pack, the outcomes of interest for this network are not fully available. For instance, there were no outcomes available for median percent reduction in GTC seizures from this broader network. Table 6 below provides a breakdown of all five NMA outcomes that were used and the available data from the GBA data network results (subgroup on cannabidiol with clobazam), ITT NMA network (no restriction on cannabidiol), and extended ITT network (no restriction on

cannabidiol). We can note that the relative risk ratios from the ITT data network results (3 RCTs) and the ITT extended network results (9 RCTs) are similar for both the smaller and extended network as shown in Table 6 below.

Table 6: NMA outcomes breakdown by treatment, studied population, and NMA network

		GBA data network results (3 RCTs) – GBA data: (FFA-PBO-CBD w CLB (GBA))	ITT data network results (3 RCTs) – ITT data: FFA-PBO-CBD	ITT extended network results (9 RCTs) – (FFA-PBO-CBD-CLB-TPM-RFM-LTG)
Studied population		Subgroup: cannabidiol with clobazam CBDwCLB (GBA)	No subgroup (no restrictions on cannabidiol) ITT: FFA-PBO-CBD	No subgroup (no restrictions on cannabidiol) ITT: FFA-PBO-CBD-CLB-TPM-RFM-LTG
NMA outcome	Treatment	Risk ratio with 95% CrI – (vs placebo)		
≥25% reduction in drop seizure frequency				
	Fenfluramine (0.7mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (10mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (20mg/kg)	[redacted]	[redacted]	[redacted]
≥50% reduction in drop seizure frequency				
	Fenfluramine (0.7mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (10mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (20mg/kg)	[redacted]	[redacted]	[redacted]
≥75% reduction in drop seizure frequency				
	Fenfluramine (0.7mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (10mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (20mg/kg)	[redacted]	[redacted]	[redacted]
Discontinuation due to adverse events				
	Fenfluramine (0.7mg/kg)	NR	[redacted]	[redacted]
	CBD (10mg/kg)	NR	[redacted]	[redacted]
	CBD (20mg/kg)	NR	[redacted]	[redacted]
Median percent reduction in frequency of GTC seizures				
		Mean difference with 95% CrI – (vs Placebo)		

		GBA data network results (3 RCTs) – GBA data: (FFA-PBO-CBD w CLB (GBA))	ITT data network results (3 RCTs) – ITT data: FFA-PBO-CBD	ITT extended network results (9 RCTs) – (FFA-PBO-CBD-CLB-TPM-RFM-LTG)
	Fenfluramine (0.7mg/kg)	NR	[redacted]	NR
	CBD (10mg/kg)	NR	[redacted]	NR
	CBD (20mg/kg)	NR	[redacted]	NR

Notes: Shaded cells denote outcomes selected for base case NMA analysis.

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA-PBO-CBD, Fenfluramine-Placebo-Cannabidiol; TPM, topiramate; RFM, rufinamide; LTG, lamotrigine; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); GTC, Generalised Tonic-Clonic; ITT, Intention-to-Treat; NMA, Network Meta-Analysis; NR, Not reported.

A21. In order to allow evaluation of the clinical heterogeneity of the NMA, please

a) provide detailed information on the patient characteristics in all the trials included in the NMA,

b) provide a table with all the additional add-on therapies (or concomitant, including non-pharmaceutical therapies) used in the trials included in the NMA. Please include the percentage of patients per therapy and per trial, as well as the numbers with specific combinations of concomitant therapies, and

c) discuss the comparability of the RCTs.

A21a. Detailed patient characteristics for all the trials included in the NMA are provided in B2.9.2.2 Table 15 in p.71-73 in CS Document B. They include age, gender, race, mean weight, number of previous ASMs (median), number of concurrent ASMs (median), 28-day median seizure frequency (all seizures) and 28 median DSF. Table 7 below reported the patient characteristics for all the trials included in the NMA (as extracted from Table 15 of the CS Document B).

A21b. Data on ASM-related inclusion/exclusion criteria and concomitant medications usage (%) in each trial are provided in Appendix D (Section D1.1.4.6 – in table 30 of the Appendices of the CS) and reported here in Table 8 below.

Table 7: Patient baseline characteristics (Table 15 of the CS Document B)

Author, year (study name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF#
Knupp, 2022(16) Study 1601 NCT03355209	Fenfluramine (0.2 mg/kg) (n = 87)	13 (3–35) [paediatrics + adults]	46 (52.0)	75%	42.4 (20.9)	7	3	106	85
	Fenfluramine (0.7 mg/kg) (n = 89)	13 (2–35) [paediatrics + adults]	54 (62.0)	80%	42.2 (21.4)	8	3	111	83
	Placebo (n = 87)	13 (2–35) [paediatrics + adults]	46 (53.0)	82%	43.9 (20.7)	7	3	68	53
Devinsky, 2018(6) GWPCARE3 NCT02224560	Cannabidiol (10 mg/kg) (n = 73)	15.4* (9.5) [paediatrics + adults]	40 (55.0)	84.9%	44.3 (26.2)	6	3	165	86.9
	Cannabidiol (20 mg/kg) (n = 77)	16* (10.8) [paediatrics + adults]	45 (59.0)	88.2%	41 (20.6)	6	3	174.3	85.5
	Placebo (n = 76)	15.3* (9.3) [paediatrics + adults]	44 (58.0)	90.8%	45.7 (23.2)	6	3	180.6	80.3
Thiele, 2018(17) GWPCARE4 NCT02224690	Cannabidiol (20 mg/kg) (n = 86)	14.2 (NR) [paediatrics + adults]	45 (52.0)	87%	41.6 (21.5)	6	3	144.6	71.4
	Placebo (n = 85)	13.3 (NR) [paediatrics + adults]	43 (51.0)	93%	39.6 (23)	6	3	176.7	74.7
Ohtsuka, 2014(18) E2080-J081-304	Rufinamide (1000–3200 mg) (n = 28)	16.0* (7.1) [paediatrics + adults]	17 (60.7)	X	39.0 kg (19.5)	X	X	253.0	X

Author, year (study name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF[#]
NCT01146951	Placebo (n = 30)	13.9* (6.1) [paediatrics + adults]	19 (63.3)	X	40.9 kg (18.0)	X	X	296.7	X
Ritter, 1993(19)	Felbamate (45 mg/kg) (n = 37)	12* (SD: NR) [paediatrics + adults]	27	X	37 kg (SD: NR)	8	≥2[†]	1,617**	X
	Placebo (n = 36)	14* (SD: NR) [paediatrics + adults]	24	X	40 kg (SD: NR)	**8**	≥2[†]	716**	X
Motte, 1997(20)	Lamotrigine (100–400 mg) (n = 79)	9.6* (5.2) [paediatrics + adults]	54 (68.0)	94%	32.5 kg (18.1)	X	≤3[†]	X	14.5[#¤]
	Placebo (n = 90)	10.9* (5.9) [paediatrics + adults]	45 (50.0)	**93%**	34.3 kg (19.7)	X	**≤3[†]**	X	11.6[#¤]
Ng, 2011(5) OV-1012 NCT00518713	Clobazam (0.25 mg/kg) (n = 58)	10.9* (7.2) [paediatrics + adults]	36 (62.1)	56.9%	33.6 kg (22.6)	X	X	X	40.9[#¤]
	Clobazam (0.50 mg/kg) (n = 62)	14.1* (10.4) [paediatrics + adults]	36 (58.1)	56.5%	35.1 kg (20.3)	X	X	X	23.5[#¤]
	Clobazam (1.0 mg/kg) (n = 59)	11.7* (8.5) [paediatrics + adults]	34 (57.6)	62.7%	34.7 kg (22.1)	X	X	X	28.9[#¤]
	Placebo (n = 59)	13.0* (9.2) [paediatrics + adults]	38 (64.4)	71.2%	36.5 kg (22.2)	X	X	X	35.5[#¤]

Author, year (study name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF[#]
Sachedo, 1999(21)	Topiramate (6 mg/kg) (n = 48)	11.2* (SD: NR) [paediatrics + adults]	28	X	36.7 kg (19.0)	X	X	267	90
	Placebo (n = 50)	11.2* (SD: NR) [paediatrics + adults]	25	X	31.6 kg (17.8)	X	X	244	98
Glauser, 2008(22) Study 022	Rufinamide (45 mg/kg) (n = 74)	13 (4.0–35.0) [paediatrics + adults]	46 (62.2)	83.8%	35.9 kg (15.5–138.5)	X	1-3[†]	290	92
	Placebo (n = 64)	10.5 (4.0–37.0) [paediatrics + adults]	40 (62.5)	82.8%	33.5 kg (16.2–86.0)	X	1-3[†]	205	92.5
Jensen, 1994(23)	Felbamate (45 mg/kg)	X	X	X	X	X	X	X	X
	Placebo	X	X	X	X	X	X	X	X

Table 8: ASM-related inclusion/exclusion criteria and baseline concomitant medications usage (%) in each trial (table 30 of Appendix D of the CS)

Trial Name	Author, Year	ASM-related inclusion	ASM-related exclusion	Treatment Arm	VPA	CLB	LTG	LEV	RFM	VNS	KD	CBZ	PHT	TPM	CZP	Other
1601	Knupp, 2022	-	-	Fenfluramine (0.2 mg/kg)	58	40	34	19	19	-	-	-	-	-	-	-
				Fenfluramine (0.7 mg/kg)	53	52	33	26	21	-	-	-	-	-	-	-

Trial Name	Author, Year	ASM-related inclusion	ASM-related exclusion	Treatment Arm	VPA	CLB	LTG	LEV	RFM	VNS	KD	CBZ	PHT	TPM	CZP	Other
				Placebo	56	44	33	23	21	-	-	-	-	-	-	-
GWPCARE3	Devinsky, 2018	Patients taking between one and four antiseizure medications	-	Cannabidiol (10 mg/kg)	37	51	30	30	26	21	8	-	-	-	-	-
				Cannabidiol (20 mg/kg)	37	47	26	32	34	22	8	-	-	-	-	-
				Placebo	39	49	33	30	26	28	8	-	-	-	-	-
GWPCARE4	Thiele, 2018	Patients taking one to four antiseizure medications	-	Cannabidiol (20 mg/kg)	42	48	38	28	28	-	-	-	-	-	-	-
				Placebo	39	51	36	40	26	-	-	-	-	-	-	-
-	Ritter, 1993	Patients taking no more than 2 antiseizure medications	-	Felbamate (45mg/kg)	Not reported											
				Placebo	Not reported											
-	Jensen, 1994	-	-	Felbamate (45mg/kg)	Not reported											
				Placebo	Not reported											
-	Motte, 1997	-	Patients receiving more than three antiseizure medications	Lamotrigine (100-400mg)	67	-	-	-	-	-	-	20	13	-	-	14
				Placebo	56	-	-	-	-	-	-	33	14	-	-	10
OV-1012	Ng, 2011	-	-	Clobazam (0.25 mg/kg)	Not reported											
				Clobazam (0.50mg/kg)	Not reported											
				Clobazam (1.0mg/kg)	Not reported											
				Placebo	Not reported											
Study 022	Glauser, 2008	Patients having a fixed-dose regimen of one to three concomitant antiseizure	Patients receiving more than three antiseizure medications	Rufinamide (45mg/kg)	59.5	-	40.5	-	-	-	-	16.2	-	27	18.9	-
				Placebo	54.7	-	29.7	-	-	-	-	18.8	-	-	26.6	10.9

Trial Name	Author, Year	ASM-related inclusion	ASM-related exclusion	Treatment Arm	VPA	CLB	LTG	LEV	RFM	VNS	KD	CBZ	PHT	TPM	CZP	Other
		medications														
-	Sachdeo, 1999	Patients being maintained on one or two standard ASMs	-	Topiramate (6mg/kg)	Not reported											
				Placebo	Not reported											
E2080-J081-304	Ohtsuka, 2014	-	-	Rufinamide (45mg/kg)	89.3	42.9	46.4	-	-	-	-	-	-	-	-	-
				Placebo	93.3	16.7	73.3	-	-	-	-	-	-	-	-	-

CBZ: Carbamazepine, CLB: Clobazam, CZP: Clonazepam, KD: Ketogenic diet, LEV: Levetiracetam, LTG: Lamotrigine, PHT: Phenytoin, RFM: Rufinamide, TPM: Topiramate, VNS: Vagus nerve stimulation, VPA: Valproate

Additional to the information provided in table 30 of Appendix D of the CS, the median number of previous ASMs and concomitant therapies are provided in Table 9. Data on specific combinations of concomitant therapies were not reported in any of the included studies.

Table 9: Median number of previous ASMs and concomitant therapies

Author, year (study name)	Intervention (N)	Number of previous AED (median)	Concurrent AEDs (median)	Other concomitant therapies, N (%)
Knupp, 2022 1601	Fenfluramine (0.2 mg/kg) (n = 87)	7	3	VGS: 23 (26) Keto diet: 5 (6)
	Fenfluramine (0.7 mg/kg) (n = 89)	8	3	VGS: 27 (31) Keto diet: 5 (6)
	Placebo (n = 87)	7	3	VGS: 32 (37) Keto diet: 1 (1)
Devinsky, 2018 GWPCARE3	Cannabidiol (10 mg/kg) (n = 73)	6	3	VGS: 17 (22) Keto diet: 6 (8)
	Cannabidiol (20 mg/kg) (n = 77)	6	3	VGS: 15 (21) Keto diet: 6 (8)
	Placebo (n = 76)	6	3	VGS: 21 (28) Ket diet: 6 (8)
Thiele, 2018 GWPCARE4	Cannabidiol (20 mg/kg) (n = 86)	6	3	VGS: 26 (30) Keto diet: 4 (5)
	Placebo (n = 85)	6	3	VGS: 25 (29) Keto diet: 10 (12)
Ohtsuka, 2014 E2080-J081-304	Rufinamide (1000–3200 mg) (n = 28)	NR	NR	NR
	Placebo (n = 30)	NR	NR	NR
Ng, 2011 [914](5) OV-1012	Clobazam (0.25 mg/kg) (n = 58)	NR	NR	NR
	Clobazam (0.50 mg/kg) (n = 62)	NR	NR	NR
	Clobazam (1.0 mg/kg) (n = 59)	NR	NR	NR
	Placebo (n = 59)	NR	NR	NR
Glauser, 2008 Study 022	Rufinamide (45 mg/kg) (n = 74)	NR	1-3*	NR
	Placebo (n = 64)	NR	1-3*	NR
Sachedo, 1999 -	Topiramate (6 mg/kg) (n = 48)	NR	NR	NR
	Placebo (n = 50)	NR	NR	NR
Motte, 1997 -	Lamotrigine (100–400 mg) (n = 79)	NR	≤3†	NR
	Placebo (n = 90)	NR	≤3†	NR
Jensen, 1994 -	Felbamate (45 mg/kg)	NR	NR	NR
	Placebo	NR	NR	NR
Ritter, 1993 -	Felbamate (45 mg/kg) (n = 37)	8	≥2*	NR
	Placebo (n = 36)	8	≥2*	NR

*Reported as study inclusion criteria. Median value not reported.
Abbreviations: NR, not reported; VGS, vagal nerve stimulation.

A21c. Comparability of RCTs is discussed in B2.9.2 NMA feasibility assessment. This section provides details of feasibility assessment which discussed comparisons of

RCTs designs and characteristics in section B2.9.2.1, comparison of patient characteristics in B2.9.2.2, and conclusions on the feasibility assessment in B2.9.2.3. Finally, in section B2.9.6 *Uncertainties in the ITC* (p.87) limitations and uncertainties of the ITC analysis were discussed given the study and patient characteristics discussed in B2.9.2.1 and B2.9.2.2.

A22. Of the three studies included in the NMA, two involved cannabidiol given alongside concomitant medications, but neither of these studies wholly utilized the NICE scope and decision problem intervention of cannabidiol combined with clobazam. Instead, both studies used a variety of concomitant drugs, and only a sub-group of participants in each study included clobazam amongst any other concomitant drugs. The drawbacks of using sub-groups in the NMA are correctly highlighted by the company, but it appears unlikely that this will cause significant systematic bias. A more important issue is that the NMA has 33tilized these sub-groups as the source of cannabidiol-clobazam data for only the 'response' outcome (25%, 50% and 75% reduction in frequency). The 'median percent reductions in frequency' and 'discontinuation due to adverse events' outcomes do not appear to use such sub-groups and instead report the results for the overall cannabidiol group, which is not a decision problem comparator. This is despite these two outcomes being drawn from the same two studies.

a) Please explain why it did not use the cannabidiol/clobazam sub-grouped data for the other two outcomes in the NMA.

b) If appropriate, please provide sub-grouped analyses for these two outcomes.

A22a. The two outcomes including median percent reduction of GTC seizures and discontinuation due to AEs were not available from the cannabidiol/clobazam sub-grouped data (CBDwCLB GBA). Please see Question A20 for further details. Therefore, we had to rely on the (FFA-PBO-CBD ITT) network to obtain these two outcomes due to their absence in the cannabidiol/sub-grouped data (CBDwCLB GBA).

A22b. Unfortunately, as mentioned in the previous answer A22.a, the two outcomes including median percent reduction of GTC seizures and discontinuation due to AEs were not available from the cannabidiol/clobazam sub-grouped data (CBDwCLB EMA)

and (CBDwCLB GBA). Therefore, it is not possible to provide sub-grouped analyses for these two outcomes. Please see Table 6 for further details (question A20).

Adverse events

A23. Fenfluramine was developed in the 1970s as a weight-loss drug but was withdrawn due to cardiac toxicity. Please provide data from larger non-randomised sources in related populations to establish if cardiac adverse events have been observed in children using fenfluramine.

A23. In the early 1960s, fenfluramine was introduced as a weight loss treatment for obese adults. However, its use led to reports of pulmonary arterial hypertension and cardiac valvulopathy, particularly when combined with phentermine, resulting in its withdrawal from the US and European markets in the late 1990s (24-26). Notably, fenfluramine was prescribed at 60mg/day[1] with doses as high as 220 mg/day (median 56.5 mg/day), and the association with heart disease was complicated by the lack of pre-treatment echocardiograms and consideration of other risk factors.

Since fenfluramine as a treatment to aid weight loss in obese adults was withdrawn from the market over 20 years ago, no other form of fenfluramine has been made commercially available, for any indication.

The current marketing authorisation application for fenfluramine (as Fintepla®) is indicated in an entirely different population of patients with DS or LGS - two rare, severe and life-limiting forms of epilepsy that emerges in early infancy. The maximum clinical doses of fenfluramine for the treatment of DS or LGS are 0.7 mg/kg/day with a maximum total daily dose of 26 mg. Therefore, regardless of a patient's weight, these doses are substantially lower than those previously used to treat obesity. The risk-benefit profile of fenfluramine (as Fintepla®) in the treatment of DS or LGS is therefore completely different to the risk-benefit profile of the previously marketed fenfluramine product that was used and subsequently withdrawn for the treatment of obesity. As indicated in Section B2.10 of the CS Document B, during clinical development in LGS, no case of valvular heart disease (VHD) nor pulmonary arterial hypertension (PAH)

[1] Ponderax PACAPS UK Product Licence 0093/0013R

was reported at any point. Furthermore, there have been no cases of VHD or PAH in over 1,500 patients treated with Fintepla® in clinical trials and the US registry, which includes all US patients who participated in DS and LGS clinical trials and all patients on the commercial drug as of February, 2022 (some patients have received up to 5 years of treatment) (7, 27, 28).

No evidence of VHD or PAH has been found in over 30 years of safety data including evidence from prior fenfluramine studies in epilepsy and in Fintepla® studies with supporting echocardiogram data (29-31).

Section B: Clarification on cost effectiveness data

Literature searches

B1. There appears to be a disparity in the number of hits reported for Cochrane Database of Systematic Reviews (CDSR) in Appendix G of the CS. Table 55 (n=3) does not match the figure provided in Table 58 (n=4) PRISMA flow diagram. Please confirm which is correct and provide an updated table.

B1. We confirm thePRIMSA flow is correct, the search done on CDSR retrieved 4 hits. Table 55 of Appendix G should be as follow:

Table 10: Search strategy in EBM Reviews - Cochrane Database of Systematic Reviews

No.	Reference	Search hits	
		Original	Update
1	(child* epileptic encephalopath* or lennox or gastaut or lgs).ti,ab,kw.	3	3
2	(2022* or 2023*).dp.	NA	884
3	1 and 2	NA	1

B2. Please confirm that Ovid was the host for all searches in Appendices G, H and I as reported in Appendix D.

B2. We can confirm that Ovid was the host for all searches for the review of cost-effectiveness studies, quality of life studies, and cost & resource use studies (in Appendices G, H and I) as with the review of clinical evidence (reported in Appendix D).

B3. Tables 56, 66 and 81 report a search of the 'database of Abstracts of reviews of effects'. Should this read National Health Service (NHS) economic evaluations database (EED) as in the Prisma flow diagrams (Table 58, Figure 19 and Figure 21)?

B3. Correct, tables 56, 66 and 81 should be headed as 'Search strategy in EBM Reviews - NHS Economic Evaluation Database'

B4. In Appendix I, Table 76 lines 17-21 have numbers in the 'original search' column. These appear to be a repeat of the numbers of the search line, please clarify if these are relevant to the search or included in error.

B4. Apologies, this is an error. There should be no numbers in the original search column for rows 17-21. This should read N/A.

Model structure

B5. Priority question. In the CS page 21 it is stated that "Intense epileptiform activity interferes with brain development, resulting in cognitive slowing or intellectual regression, and is sometimes associated with psychiatric and behavioural consequences. Understanding this concept is crucial for both families and clinicians because it introduces the notion that early effective normalisation of the epileptic activity through early pharmaceutical intervention may improve cognition and behaviour, or at least prevent additional neurocognitive deterioration".

a) **Please elaborate on how cognitive impairment was reflected in the economic model.**

b) **It is stated that *"normalization of the epileptic activity (…) may improve cognition"*, therefore you would expect a positive effect on cognition in a better health state. The current health states based on response rates, however, likely reflect a heterogeneous group of patients with different seizure frequencies (although a similar reduction) and thus different states of cognitive impairment. Please comment on how the current economic model covers the relationship between the number of seizures and cognitive functioning.**

c) **Drop-seizure frequency is the main efficacy driver and health states represent different percentages of decrease of drop seizures. However, this model structure deviates from other published models and the NICE technology appraisal (TA) 615, which implemented health states based on seizure frequency categories. Please justify the use of health states with a relative reduction in drop seizure frequency (DSF) instead of an absolute number of drop seizures.**

d) **Please provide an updated economic model and scenario analysis using health states which are categorized by (absolute) seizure frequency instead of relative reduction in seizure frequency, in line with NICE TA615.**

B5a. Although fenfluramine had extended benefits beyond seizure improvement including on cognitive function (see section B2.10.4), it was not considered possible to reflect this in the economic model. This was also noted in section *B3.13 Benefits not captured in the QALY calculation*. For this reason, we believe that results are conservative with respect to fenfluramine.

B5b. Many factors contribute to cognitive function improvement or impairment (e.g., age of onset of disease, among others) and the independent contribution of decrease in drop seizures with regards to cognitive function is difficult to estimate. According to Hoffmann-Riem 2000, longer-term cognitive and behavioural outcomes are linked to seizure control. However, the independent contributions of drop and non-drop seizures are unknown (32). Given this complexity, it is difficult to model cognitive function improvement associated with normalisation of epileptic activity. This was done in line with TA615 CBD for the LGS submission, where these outcomes were not modelled and considered to constitute a "*hidden upside*"; similar approach was taken in TA808 fenfluramine for DS submission (9, 33).

B5c. Although we acknowledge that NICE TA615 implemented health states based on DSF categories, a Markov model utilising the relative percentage decreases in DSF was deemed a more suitable approach in the fenfluramine LGS submission. The concept of relative reduction in DSF has been applied in previously published cost-

effectiveness analysis (CEA) model adopting a Markov structure in LGS, such as Neuberger *et al.* (2020), Clements *et al.* 2013, and Verdian *et al.* 2010 (34-36). In the current model, relative reduction in the percentage of DSF is translated into absolute DSF values using the midpoint approach (please refer to question B14 for more details), to allow the integration of input parameters stratified by DSF (like resource use). However, using absolute DSF values directly as health states in the model was not feasible in the current model due to the existence of comparators (CBD with clobazam +SoC) for which data was not publicly available (please see detailed discussion in Question B8). Indeed, in all pivotal trials, including the fenfluramine and CBD trials, the established primary clinical endpoint is the percentage reduction in DSF. In addition, the primary rationale for using absolute drop seizures in previous NICE submissions, rather than percentages of decreases, lies in the associations between QoL and absolute DSF in conjunction with seizure-free days. It was possible in the CBD submission as no ITC was used, the only comparator being SoC (+placebo). In our case (when the comparison of efficacy is informed through an ITC), the association between QoL and absolute DSF in conjunction with seizure-free days can be accommodated in the percentage decrease approach, by employing the baseline number of drop seizures and changes in the median drop seizures frequency of each state. This allowed the model to compute absolute drop seizures for each health state, based on the method described in Neuberger et al. (2020) (34), where the midpoint of each health state is used to derive the absolute number of drop seizures (please refer to B14 below for more details).

B5d. The model was structured using percentage reduction in DSF mainly because it allows to include the comparison versus CBD with clobazam. As such, it is not possible to provide an updated model with health state (HS) representing absolute frequencies.

B6. Priority question. In the CS, a 'semi-Markov' model was used. It is intended to add a form of memory to the model and alter the likelihood of transitioning to discontinuation state based on the time spent in health state 0. Commonly, memory is built in by adding additional tunnel states (Briggs et al. 2006).

a) Please explain what the 'semi-Markov' approach entails and how it compares to using tunnel states and justify the choice of this model type

for this population of LGS based on the natural course of the disease, its clinical pathways, and expected outcomes.

b) **Modelled patients could discontinue as from cycle 1, when no or limited reduction in drop seizures was observed (i.e., when they are in state 0). Please elaborate on how memory is incorporated in the model for both the 3 and 6 month stopping rules. Please include a detailed explanation on how it is implemented in the Excel file, using cell numbers if necessary.**

B6a. We have reviewed the model description initially included in section B.3.2.2 and we acknowledge the correction needed.

The model should be considered a Markov model instead of a semi-Markov model. The original description of semi-Markov features was related to the application of time-dependent efficacy which changes between T+M and cycle 1, cycle 2-5 and cycle 6-9 and cycle 10 onwards. The application of these features does not require memory of time spent in health states and hence no tunnel states were needed.

B6b. We apologise for the confusion, in fact, memory is not used to implement the stopping rule in the model.

The stopping rule aims to discontinue treatment for patients with no or limited reduction in drop seizures. This was implemented in the model by transitioning patients that are in health state 0 (<25% response) to the discontinuation health state. The model offers the choice between two time points for the stopping rule: 3 months and 6 months. In the base case the stopping rule is applied every 3 months, or at the end of each cycle. For the alternative time point, 6 months, patients in health state 0 discontinue treatment every other cycle. The stopping rule is applied from cycle 3 throughout the model time horizon.

B7. Priority question: In the model, health states are defined based on the percentage decrease in drop-seizure frequency. However, as mentioned in clarification question A10, based on the clinical data (i.e., Study 1601, FFA OLE study, GWPCARE3, GWPCARE4, and GWPCARE5) a substantial number of non-drop seizures is reported for fenfluramine, cannabidiol, and

the SoC group. Non-drop seizures appear to be ignored in the model (e.g., in terms of estimated utility values, costs, and transition probabilities).

a) **Please justify this assumption based on published data and clinical expertise. Please elaborate on the potential implications of including non-drop seizures for the cost-effectiveness.**

b) **Please update the economic model and scenario analyses to include non-drop seizures, including its impact in the quality-adjusted life years (QALYs) and costs.**

B7a. The presence of treatment-resistant seizures (tonic, atonic and tonic-clonic) is a key feature of LGS and forms part of the diagnostic criteria for the condition (37). The temporary loss or gain of muscle tone associated with atonic, tonic and tonic-clonic seizures leads to sudden falls, often resulting in injury (38). Falling is a major contributor to the physical morbidity and complications of the disease. As such, the fenfluramine trials, like previous clinical trials in LGS, were designed to investigate the effect of a new intervention on drop seizures; the effect on non-drop seizure types was only an exploratory endpoint. The studies were not powered to evaluate the effect on non-drop seizures; the counts of these seizures are highly variable, likely due to imprecision of consistently counting these more subtle seizures, as highlighted in Devinsky 2018 (6).

The model focussed on modelling the primary endpoint of the fenfluramine study, the reduction in drop seizures, which is considered relevant from both the clinician and patient perspective (8).

It is reasonable to assume that there would be additional QoL gains associated with reduction in non-drop seizures as fenfluramine showed a large reduction in non-drop seizures, however as explained above it would have added too much complexity to the model. This is another reason why we propose the modelled benefits are conservative.

Regarding healthcare resource utilisation (HCRU), we would consider them to be similar whether non-drop seizures are accounted or not. The non-drop seizure types do not generally result in hospitalisation, and they would be managed as part of the

same set of specialist consultations already captured for drop-seizures. As such, we can assume costs for non-drop seizures are already captured in the model.

B7b. The current model accurately captures the most important clinical and patient benefits, even though it does not attempt to capture the contribution to QoL of the reduction in non-drop seizures. Drop-seizures are accepted as the most clinically relevant seizure type in LGS, driving the physical morbidity and complications of the disease over time. We acknowledged that excluding non-drop seizures is a potential benefit for patients on fenfluramine not captured in the model, and this can be considered a conservative approach.

B8. A semi-Markov cohort model was developed to represent the natural history of the disease, clinical pathway, and clinical outcomes reported for people with LGS. In a previous fenfluramine appraisal for Dravet Syndrome (TA808), however, an individual patient model was used. Although this model suffered from several validity issues, the rationale for using an individual patient simulation to more appropriately account for the heterogenous clinical presentation of the disease seems plausible and also applicable to LGS. Please justify why a cohort modelling approach was chosen over an individual patient modelling approach.

B8. Although the previous model in TA808 (fenfluramine for DS submission) implemented a patient-level approach, as specified by the EAG, the approach encountered some validity issues. The primary challenge in validating such a patient-level model stems from the fact that individual patient-level data (IPD) for comparators are often unavailable. Consequently, any estimates regarding the efficacy or safety of comparators carry significant uncertainty. For instance, in the TA808 submission, patient profiles from the fenfluramine trial were used in a bootstrapping algorithm along with the impact on seizure frequency estimated from ITCs to calculate patient profiles in the cannabidiol arm. This approach overlooks potential differences in patient heterogeneity between cannabidiol and fenfluramine and in the TA808 submission the ERG heavily criticised the bootstrapping algorithm.

Moreover, incorporating evidence from external RCTs into a patient-level model typically requires meta-regression to analyse changes in drop seizure frequency and seizure-free days at the patient level. However, this proves infeasible in the majority

of cases due to the lack of IPD for comparators. Calibrating the model is often necessary in a patient-level model to validate the outcomes, but this requires making assumptions without direct evidence.

On the other hand, alignment of the structure of the current Markov model with established clinical endpoints reported in pivotal trials (percentage reduction of drop seizures) lends credibility to the model. The structure is also in line with several previously published cost-effectiveness analysis in LGS, such as Clements et al. 2013, Verdian et al. 2010, and Neuberger et al. 2020, as well as the CBD TA615 submission (9, 34-36) . Furthermore, the current model translates the relative percentage reduction in drop seizure frequency into absolute seizure frequency, allowing for a link to cost calculation (and to QoL in scenario analysis).

Finally, the current model can simulate long-term follow-up efficacy outcomes and treatment waning based on the model states. As relative percentage reductions are clinically established endpoints, they are often captured in OLE and Real-World Evidence (RWE) studies. Incorporating these measures directly from observed data allows the straightforward implementation of waning and long-term discontinuation scenarios. Such an approach is mostly infeasible in patient-level models, such as that in fenfluramine in DS TA808, as there is a need for additional assumptions (or additional statistical models) regarding long-term waning without direct evidence from OLE data.

B9. A number of parameters in the economic model (i.e., costs) were informed based on the drop seizure frequencies. The number of drop seizures was calculated per 28 days while the model used a three-month cycle length. Please clarify how the 28 days results were modelled in cycles of three months.

B9. The fenfluramine trial, Study 1601, reports the 28-day median seizure frequency over a period of 12 weeks (3 months). The model cycle length is aligned with the phase III trial duration as well the assessment time interval available from the OLE study (3 months). The frequency of seizures is commonly/conventionally reported per 28 days in anti-epileptic drugs trials: "*Percentage change from baseline in seizure frequency (every 28 days) during the treatment period*", "*Patients with ≥50% reduction in seizure*

frequency (every 28 days) from baseline during the treatment period". The model aimed to be designed to reflect trial outcomes in the most straightforward way.

Intervention and comparator

B10. Priority question. As per NICE guideline NG17, third line treatments for LGS include: rufinamide, topiramate, clobazam, and cannabidiol with clobazam. Likewise, the final scope mentions the same treatments as comparators for people aged 2 and over with LGS whose seizures are inadequately controlled by established clinical management. However, these treatments are not included in the model as comparators. As mentioned before e.g., question A20, excluding these comparators provides an incomplete picture of the relative efficacy and cost effectiveness of fenfluramine. Likewise, non-pharmaceutical therapies such as ketogenic diet, vagus nerve stimulation, and invasive surgery can be recommended as additional treatment options for a proportion of patients with LGS in the UK (NG 217). Moreover, these therapies were included in the final scope issued by NICE as relevant comparators, and a significant proportion of patients in the studies included in the NMA and in the OLE studies received vagus nerve stimulation and were on a ketogenic diets. Nonetheless, these were not included in the economic model presented by the company.

a) **Please justify why rufinamide, topiramate, clobazam, and the non-pharmaceutical therapies were not included as individual comparators in the economic model.**

b) **Please elaborate on the position of non-pharmaceutical treatments in the care pathway of LGS patients in UK clinical practice.**

c) **Please provide an updated economic model and scenario analyses including pairwise comparisons and a fully incremental analysis of fenfluramine versus all (combinations of) relevant comparators (i.e., rufinamide, topiramate, clobazam, and the non-pharmaceutical therapies).**

d) **Topiramate is listed as one of the comparators (CS, Table 1) and as one of the ASMs (CS, Figure 5). Nonetheless, 0% of patients are taking**

topiramate in the SoC ASMs arm (CS, Table 60 and 61). Please justify the 0% of patients using topiramate and elaborate on how this reflects UK clinical practice, using UK data.

e) **Please update Tables 60 and 61 and provide an updated economic model and scenario analysis including a percentage of patients taking topiramate based on UK data.**

B10a. As mentioned in question A6a. which clarified the decision problem, the only possible comparators of fenfluramine + SoC are cannabidiol with clobazam + SoC or SoC alone. Indeed, as cannabidiol with clobazam is the only established clinical add-on therapy to have been formally appraised by NICE, and accepted as a clinically and cost-effective option, it is also the only therapy with sufficient trial data to permit a robust comparison. The other ASMs and the non-pharmaceutical treatments are not considered as comparators but constitute the SoC 'basket'.

Rufinamide, topiramate and clobazam are not considered as comparators but are part of the SoC. Indeed, in NICE evaluation of CBD in 2019 (TA615 – only treatment evaluated by NICE in LGS), the intervention "*cannabidiol with clobazam + SoC*" is compared to "*SoC*" alone which was defined as considered to be a 'basket' of choices of ASMs. As fenfluramine has the same positioning as cannabidiol with clobazam, and to be consistent with the previous NICE evaluation TA615, fenfluramine should be compared versus cannabidiol with clobazam + SoC or SoC alone. The company is therefore presenting results versus cannabidiol with clobazam + SoC and also provide an analysis to compare fenfluramine + SoC versus SoC alone.

B10b. As mentioned in Section B.1.3.3.2 - Current clinical pathway of care in England (pages 27 – 30 of the CS) and as presented in Figure 5 of the CS (figure based on NICE guideline 217 (39) and Cross et al. 2017 (40), non-pharmacological interventions may also be additional treatment options for some patients and can be considered alongside medication. Non-pharmaceutical treatments are an established part of the treatment pathway for LGS, and therefore part of the SoC mix into which fenfluramine would be added.

In Study 1601, non-pharmaceutical treatments were not prohibited, were considered necessary for the subject's welfare, and did not interfere with the response to the study

drug; overall 4.2% patients of Study 1601 received a ketogenic diet, 31.2% VNS, and 0.8% callosotomy.

In response to receiving the clarification questions, the company consulted three clinicians treating LGS in the UK to obtain clarity on the positioning and applicability of non-pharmaceutical treatments in the care pathway (8). Here it was confirmed that very few patients opt for surgical options. VNS and ketogenic diets are used as adjunctive treatment options and their use in practice reflects what was observed in patients within the fenfluramine clinical trial. The use of the non-pharmacological interventions is not set within any particular point on the current UK care pathway and the response to them is subject to significant variability , as such it is difficult to define how on average patients respond to each and when. It would therefore be most appropriate to consider them included as part of the existing SoC arm 'basket' opposed to forming conclusions in separate analysis. Overall observations of non-pharmacological treatments are that they can be effective as adjunctive therapies, but they are chosen on a very individualised basis, and LGS responds less well to these types of therapies compared to DS. These therapies are also less likely to be used in adults vs children.

B10c. Based on the above, it was not considered relevant to present cost-effectiveness pairwise comparison between all combinations of ASMs. The SoC varies due to the refractory nature of LGS. Given the orphan nature of the condition and the heterogeneous nature of the patients, it is not clinically or statistically meaningful to compare the intervention to individual or specific combinations of ASMs and non-pharmacological treatments (8). Clinicians also confirmed that in clinical practice, the choice of cannabidiol with clobazam + SoC is the most appropriate comparator opposed to comparing against one of the ASMs which are considered to be within the SoC 'basket' such as rufinamide. These drugs may have been considered prior to fenfluramine or cannabidiol as second line therapies and patients may still be on them or they would have been one of the previously failed ASMs.

B10d. The fact that topiramate was 0% appears to be a reporting mistake. It was corrected in the updated version of the model (13.8% has now been applied as reported in the CSR – please see below reported in Table 11). Please note the impact is almost null, as the percentage of use is the same in both comparative arms.

B10e. The model was updated using 13.8% as percentage of use of topiramate.

Table 11: Concomitant anti epileptic treatments - Safety Population

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B11. Priority question: Cannabidiol with clobazam has been recommended by NICE (TA615) only if the drop-seizure frequency is assessed every 6 months. If the drop-seizure frequency had not fallen by at least 30% compared with the 6 months prior to starting the treatment in TA615, cannabidiol was stopped. This decision was made by the committee following similar criteria for other antiepileptic drugs, despite that the marketing authorisation for cannabidiol did not specify a stopping rule.

a) **In the CS, two ways of treatment discontinuation are mentioned: 1) for patients with no or limited response to treatment in cycle 1 and 2, and 2) after cycle 2, where a stopping rule every 3 months was applied and all patients with a response of <25% discontinue treatment. Please provide supporting evidence with relevant external data and/or expert opinion that these routes of treatment discontinuation are consistent with similar ASMs.**

b) **Likewise, no stopping rule (or discontinuation due to lack of efficacy) was applied to SoC. Please, elaborate on the representativeness of this choice for the UK clinical practice and provide supporting evidence with relevant external data and/or expert opinion.**

c) **Please provide an updated economic model and scenario analysis in which cannabidiol with clobazam is used as recommended in NICE TA615 (i.e., applying a stopping rule when reduction in drop-seizure frequency is <30% compared to 6 months prior treatment).**

B11a. The above question relates to treatment discontinuation due to lack of efficacy and stopping rule. For cycle 1 and 2, cycle specific proportions of discontinuation were applied based on evidence collected from Study 1601 and fenfluramine OLE study (cycle 1: 0%; cycle 2: 7.3%, 12/164 patients in 6 months follow up). After cycle 2, discontinuation due to lack of efficacy is captured by a stopping rule and applied to patients with <25% response rate every 3 months. This approach was corroborated during an Advisory board meeting where clinicians advised that 25% response rate is considered an acceptable threshold. Please note, additional evidence from consulting UK clinical experts (conducted following receipt of these clarification questions) suggest that a stopping rule ranged between <25% to <30% from baseline would be clinically appropriate (see question A19) (11). Following the request by NICE to apply a stopping rule of 30% in the model, please refer to the additional analysis that will be provided on 21st September 2023 (question B11c).

B11b. LGS patients cannot be without the treatment of ASM (SoC) combinations due to the severity of the condition. The SoC represents the combination of ASMs that LGS patients are expected to be maintained on throughout treatment (including, clobazam, levetiracetam, valproate, lamotrigine, topiramate, and rufinamide). They are in line with

published evidence on current clinical practice and were validated by clinical experts to be appropriate and representative of current UK clinical practice (8). In the SoC arm discontinuation due to AE was applied from cycle 1 (1.1%) throughout the lifetime horizon. Similar to the other treatment arms, a stopping rule every 3 months was also applied and all patients with a response of <25% (health state 0) discontinue treatment and move on to subsequent treatment. However, since subsequent treatment was defined to be equal to SoC, the stopping rule in the SoC treatment arm has technically no effect on results. Discontinuation due to AEs however, can occur in any health state, and thus it impacts model outcomes, because the discontinuation health state is equivalent to health state 0.

B11c. Please note: an extension has been requested for this question by the company. Answers will be provided by 5pm on the 21st of September 2023.

B12. Priority question: In the CS page 133, cannabidiol dosage is determined as "The model assumed the maintenance dose of cannabidiol in the initial maintenance cycle to be 12 mg/kg/day to align with NICE TA615 submission. The maintenance dose after T+M for cannabidiol was based on real-world use of cannabidiol for Dravet Syndrome (DS) described in Silvennoinen, 2021 and expert opinion stating that the dose is not expected to exceed 14mg/kg/day, as patients are titrated up to their maximum tolerable dose".

a) Please elaborate on the comparability of the DS and LGS patient populations with regard to dosing of cannabidiol. Are DS patients expected to receive the same dosages of cannabidiol as LGS patients?

b) In TA615 Section 3.16, the following was concluded: "The committee noted that the company had not presented evidence that the doses used in clinical practice would be lower than those recommended in the summary of product characteristics. It concluded that it preferred the company's scenario analysis using an average dosage of 12 mg/kg/day". Please justify why the 14 mg/kg/day scenario was more appropriate as compared to the 12 mg/kg/day for the base case analysis.

B12a. In cannabidiol's marketing authorisation, the dosage indicated for DS is identical to dosage indicated for LGS (see cannabidiol SmPC(41)): *"Posology – For LGS and DS -The recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day)."* Therefore, DS patients are expected to receive the same dosages of cannabidiol as LGS patients. To note, this posology is different for the third indication of cannabidiol, for seizures associated with tuberous sclerosis complex (TSC).

B12b. UK clinical experts were consulted regarding the dose of cannabidiol used in clinical practice for LGS. Expert clinicians responded that they try to maintain low doses of cannabidiol to ensure tolerance. Paediatric dosing can go up to 20 mg/kg/day, lower doses ranging 15-20 mg/kg/day can be used in polypharmacy however this is very patient dependant. Another clinician mentioned that 10-15mg/kg/day is used in DS and it will be similar in LGS, however a different clinician mentioned that the dose of CBD is higher in LGS and goes up to 20 mg/kg/day. We can therefore see there is a large variability in dosing assumptions for cannabidiol in LGS, but there is the consensus that DS dosing should apply to LGS. Given that in the open-label extension of cannabidiol in LGS the mean modal dose per 12-week reporting interval ranged from 21-25 mg/kg/day and the mean modal dose in the last 12-weeks of treatment was 24 mg/kg/day, a maintenance dose of 14 mg/kg/day can be considered highly conservative, especially considering that the dose in the OLE is adjusted based on tolerability and efficacy, and considering the additional evidence we have received from UK clinical experts on the dose within UK clinical practice (42).

B13. As per NICE guidance documents (NICE 217), sodium valproate should not be offered as an add-on treatment for generalised tonic-clonic seizures to girls and women of childbearing potential, unless special circumstances.

a) Please provide a justification for not including this guidance in the model and elaborate on its impact for the final results.

b) Please provide an updated economic model and scenario analyses while including this exception for said subgroup.

B13a. The model simulates the UK LGS population with characteristics of Study 1601. According to the CSR (table 17), 15 (8+7) patients of the SoC + placebo arm receive sodium valproate as concomitant ASM. It is expected that patients who received sodium valproate in the trial did not present contraindications. UK clinical experts were consulted and confirmed that the vast majority of LGS patients have intellectual development problems and have a low probability of pregnancy. If there is a chance, patients would be taken off treatment after puberty; however, most females that are well maintained on the drug would continue due to the points raised above.

Based on the above information we can conclude that as most patients are expected to have a low probability of pregnancy and clinicians would use valproate as per clinical guidelines, the proportion of patients using sodium valproate within the cost-effectiveness model can be considered reflective of UK clinical practice.

B13b. The model simulates an average patient, without distinction of ASM depending on age or gender. Therefore, it is not possible to include exception for subgroups. As per above, on average the percentage and characteristics of patients taking sodium valproate is representative of the treated population.

Effectiveness

B14. **Priority question: In CS page 107 the calculation of number of drop seizures in each health state is discussed. Here, it is stated that *"As some seizure-related outcomes from the literature (e.g., resource use or mortality) relied on absolute number of drop seizure rather than rate of response to treatment (e.g., percentage reduction in seizures), the average number of drop seizures per 28 days was determined for each health state in the model. For health states 0 and 3, the mean drop seizures per 28 days were the observed median drop-seizure in Study 1601. For states 1 and 2, an approach described by Neuberger et al. (2020) (134) in LGS patients was used"*.**

a) **Please explain why the number of drop seizures at baseline is lower than in state 0 and validate this calculation with the study data.**

b) **Please justify why different approaches were used for health states 0 and 3 and health states 1 and 2.**

c) **The midpoint approach is explained as "The approach consisted of multiplying the baseline number of drop seizures by 1 minus the mid-point value in each health state. For example, the mid-point value of state 1: 25% to <50%, was 37.5%". This explanation is unclear to the EAG. Please provide a more detailed example and calculation of the midpoint approach.**

d) **Please provide an updated economic model using estimates for health states 1 and 3 using the same approach as for health states 0 and 3 i.e., using the observed median drop-seizure in Study 1601 or validate the results with study data.**

e) **Please provide an overview for which outcomes the midpoint approach was used.**

B14a. The number of drop seizures at baseline and state 0 were sourced from the Study 1601 data in the amendment analysis on the fenfluramine arm, which is 70.5 and 101.40, respectively – see Table 12 and Table 13 below. State 0 drop seizures (101.40) are based on the patients in the fenfluramine arm (43). The observed data for median drop-seizure frequency is indeed higher in state 0 compared to baseline. DSF at baseline is assessed across all patients, and since state 0 is the worse state it is considered logical to have the patients with more severe condition associated with higher seizure frequency compared to all patients at baseline. It does not mean patients will have more seizures after starting treatment. We would like to note that the baseline DSF has very minimal impact on the model results.

Table 12: Baseline DSF in Study 1601

Timepoint	Drop Seizures Median (IQR) 28-day	Drop Seizure total (N)
Baseline	70.50 (139.00)	30,944

**From Table 3.1 2022-FFA-01- Amendment analysis (43)*

Table 13: Drop seizure frequency of each state in Study 1601

Timepoint	Responder state (Treatment arm fenfluramine 0.7 mg/kg/day)	Drop Seizures Median (IQR) 28-day	Drop Seizure total (N)
T+M	0	101.40 (346.29)	35,691
	1	34.86 (60.11)	3,765
	2	38.16 (79.11)	5,583
	3	11.20 (17.61)	253

**From Table 3.3 2022-FFA-01- Amendment analysis (43)*

B14b. While we acknowledge the inconsistency between the approaches for calculating midpoints for states 1 and 2 versus states 0 and 3, utilising direct evidence for midpoints for all states reveals that the median number of DSF is higher in state 2 compared to state 1 (38.16 vs. 34.86), as indicated in Table 13 above. To align with the definition of health states and maintain consistency, we have employed different approaches in the base case for midpoint definition.

The states in the model were defined based on the percentage decline in DSF compared to baseline:

- State 0: No response (< 25% reduction)
- State 1: Response group 1: 25% to <50% reduction
- State 2: Response group 2: 50% to <75% reduction
- State 3: Response group 3: >=75% reduction

Please note that it was required to determine the absolute number of drop seizures for each state to link states to resource use input parameters. Furthermore, we needed to calculate reduction in SUDEP-related mortality in each state. For this reason, the approach used in Neuberger et al. (2020) was used to calculate the mid-point in percentage reduction in each state which results in absolute number of DSF:

- For State 1 and 2, for which the lower and upper bounds of reduction in DSF are known, we used the median of reduction and applied it to the baseline number of drop seizures:
    - For State 1, the median of percentage reduction between 25% and 50% is: 25% + (50% - 25%)/2 = 37.5%. This meant patients in this state experienced a median of 37.5% reduction in DSF compared to baseline, which is 44.06 DSF (using 70.5 as the median baseline DSF).

- For State 2, the median of percentage reduction is 50% + (75% - 50%)/2 = 62.5%. This meant that patients in this state experienced a median of 62.5% reduction in DSF compared to baseline, which is 26.44 DSF (using 70.5 as the median baseline DSF).

– For State 0 and 3, there were no lower and upper bounds on the percentage reduction of DSF; as such, we used the data from Study 1601 for the absolute number of drop seizures:
  - For State 0, there is no lower bound on the percentage reduction of DSF; as such, we used the data from Study 1601 for the absolute number of drop seizures, which is 101.40.
  - For State 3, there is no upper bound on the percentage reduction in DSF; as such, we used data from Study 1601 on the absolute number of drop seizures, which is 11.20.

B14c. The midpoint of each health state was used to calculate the absolute number of drop seizures and the reduction in SUDEP-related mortality according to the Equation 1 below:

Equation 1:

Absolute number of DSF for State i = Baseline DSF * (1- mid-point of State i)

In Equation 1 above, mid-point of state 1 (25% to 50%) is 37.5%. As a result, the absolute number of DSF for State 1 was = 70.50 (Baseline DSF) * (1-0.375) = 44.06. The description and calculation of the midpoint approach for each state has been provided in item b above.

Please note that reduction in SUDEP-related mortality was also calculated based on the midpoint of each health state (i.e., SUDEP-related mortality in a 25% to < 50% reduction state was the product of baseline SUDEP-related mortality multiplied by [1–0.375]).

B14d. ***We*** have provided in the updated model an option where users can choose the method for calculating the midpoint. Users can select between two approaches:

1. Calculated midpoints for state 1 and 2 (as described in item b above).

1. Median DSF (28 days) from Study 1601: Using data from Study 1601, which would change the midpoints for states 1 and 2 to be the same approach as that used in states 0 and 3.

As shown in the tables below, there was only a slight change in the model results, in favour of fenfluramine, when changing from the default midpoint to the fenfluramine Study 1601 method (New scenario) for midpoint calculations:

Table 14: Base case Scenario - Calculated midpoints for state 1 and 2

Comparator	Total Costs (£)	Total QALYs	Incremental Costs (£) FFA + SoC vs. comparator	Incremental QALYs FFA + SoC vs. comparator	ICER (£/QALY)
FFA + SoC	[redacted]	20.45	-	-	-
CBD + SoC	[redacted]	20.33	[redacted]	0.83	[redacted]
SoC	[redacted]	20.15	[redacted]	2.06	[redacted]

Table 15: New Scenario - Median DSF (28 days) from Study 1601

Comparator	Total Costs (£)	Total QALYs	Incremental Costs (£) FFA + SoC vs. comparator	Incremental QALYs FFA + SoC vs. comparator	ICER (£/QALY)
FFA + SoC	[redacted]	20.44	-	-	-
CBD + SoC	[redacted]	20.32	[redacted]	0.83	[redacted]
SoC	[redacted]	20.15	[redacted]	2.06	[redacted]

As described in detail in the following item B14e), midpoint approach was used in the model to determine mortality and disease management costs – routine care in the base case analysis.

Regarding disease management costs – routine care, DSF was used to determine the volume of health care resource utilisation required in each health state from the following average DSF per 28 days categories: seizure-free, ≤ 45, < 45 to ≤ 110, > 110. As can be seen in the table below, independently of the method used to estimate midpoints, the selection of seizure frequency category was the same. Thus, this modification had no impact on disease management costs – routine care.

Table 16: Selection of DSF per 28 days category according to health state median DSF per 28 days

Health state	Drop Seizures Frequency per 28 days		Selected drop seizure frequency per 28 days category
	Base case scenario (Calculated midpoints for state 1 and 2)	New scenario (Study 1601 - Treatment arm fenfluramine 0.7 mg/kg/day)	
0	101.40 (346.29)	101.40 (346.29)	< 45 to ≤ 110
1	44.06	34.86 (60.11)	≤ 45
2	26.44	38.16 (79.11)	≤ 45
3	11.20 (17.61)	11.20 (17.61)	≤ 45

Regarding mortality, the health state specific risk of SUDEP mortality was adjusted from baseline using the midpoint estimates which in turns impacts the calculation of accidental mortality. We can see the effect of the change of midpoint determination method on mortality in the QALYs and costs of all comparators and on the resulting ICERs. Mortality is thus impacted by the choice of midpoints method, however, was not a major driver of the model, and thus the effect on ICERs was limited.

Please note: an extension has been requested for some question by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B14e. Midpoint approach (either with data from trial or calculated midpoints) had an impact in the determination of the following model outcomes:

- Mortality, where data are used to calculate health state specific SUDEP risk, which in turn impacts the determination of accidental mortality (see question B20)
- Disease management cost – routine care, where data are used to determine the HCRU category of each health state (HCRU for LGS patients was defined within the following DSF (per 28 days) categories: seizure-free, ≤ 45, < 45 to ≤ 110, > 110)
- Patient and caregiver utilities in scenario analysis, where alternative sources of patient and caregivers' utilities were tested with utility values dependent on DSF per 28 days (categories: seizure-free, ≤ 45, < 45 to ≤ 110, > 110)

B15. Priority question: In the CS page 114 it is stated that "As shown in (Figure 27), cannabidiol state occupancy was stable after 12 months since T+M. On the other hand, fenfluramine state occupancy significantly

changed which justified the longer projection of efficacy period from cycle 5 to 9 (27 months)".

a) **Please explain how CS Figure 27 supports the longer projection period of efficacy from cycle 5 to 9.**

b) **Please explain how the model health states data correspond to the clinical trial data presented in CS Figure 27.**

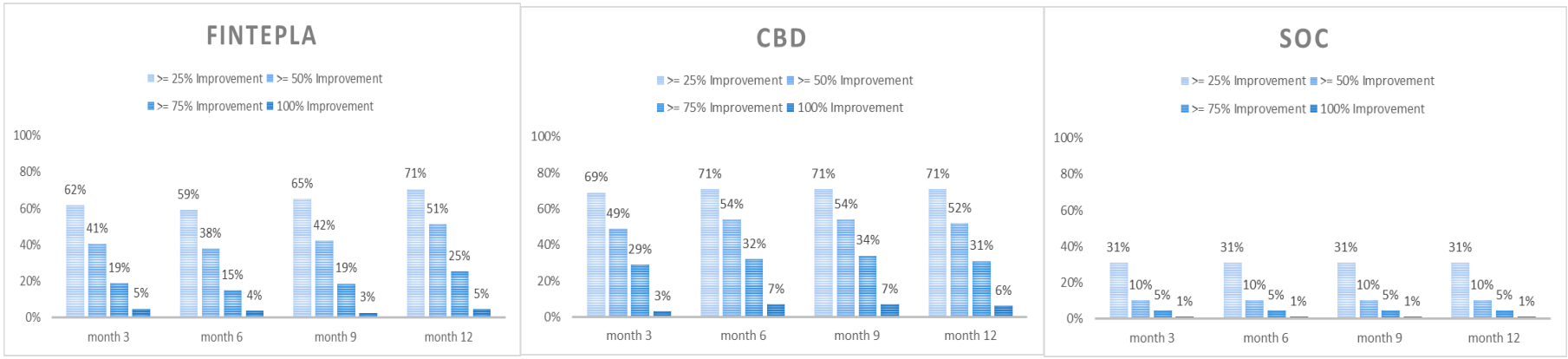
c) **Please explain why the model health states data from CS Figure 27 is different from the state occupancies in CS Table 39 and in the cost-effectiveness model for fenfluramine and cannabidiol.**

d) **Please provide an updated economic model and analysis with the alternative assumption of no efficacy for fenfluramine from cycle 5 to 9 i.e., patients remain in the same health state during this period (the same as cannabidiol).**

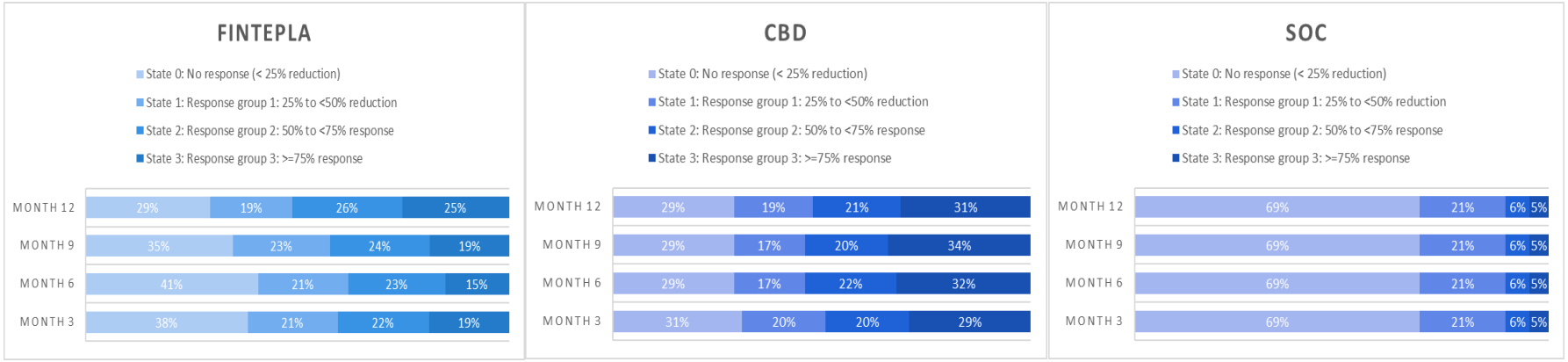
B15a. Figure 27 shows the state occupancy of treatment arms in the first year follow up after T+M (OLE study) for fenfluramine, cannabidiol, and SoC arms. The clinical trial data for fenfluramine (as shown in figure 27) state occupancy for >=25%, >=50%, >=75%, and 100% shows an increase in percentage of patients showing improvement from month 9 to month 12, from 65% to 71%, 42% to 51%, 19% to 25%, and 3% to 5% respectively (i.e., shows increased percentage of patients showing various improvement rates along the timeline). Based on this observation using data from the CSR statistical document (table 4.1 to 4.4) (43) , it was assumed that fenfluramine efficacy can be projected beyond cycle 5. Acknowledging the lack of long-term efficacy data, the last observed transition probability from FFA-OLE study (43) used in cycle 5 was used to support the projection of efficacy period in cycle 6-9 (27 months efficacy period used in the model). Please see below Figure 1 and Table 17 (extracted from CS document B figure 27 and Table 39).

Figure 1. State occupancy of treatment arms in the first-year follow-up after T+M (data from OLE studies)

Clinical trial data



Clinical trial data converted to the health states used in the economic model



Abbreviations: CBD, Cannabidiol; SoC, Standard of Care

Table 17. Transition probabilities after T+M

Variable		Value				Reference
Transition probabilities (from cycle 2)						
FFA						
TP matrices		S0	S1	S2	S3	
Cycle 2 (3-6 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	Transition probabilities from cycle 2 to cycle 5 were estimated from the fenfluramine OLE study (43).
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 3 (6-9 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 4 (9-12 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 5 (12-15 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 6-9 (up to 27 months)	State 0	[redacted]	[redacted]	[redacted]	[redacted]	Observed transition probability from OLE data in the last cycle (cycle 5) was applied from cycle 6 to cycle 9 (43).
	State 1	[redacted]	[redacted]	[redacted]	[redacted]	
	State 2	[redacted]	[redacted]	[redacted]	[redacted]	
	State 3	[redacted]	[redacted]	[redacted]	[redacted]	
Cycles 10+		Patients remain in the same health state				Assumption
CBD						
State occupancy		S0	S1	S2	S3	
Cycle 2 (3-6 months)		0.308	0.201	0.201	0.291	State occupancies from cycle 2 to cycle 5 were estimated from the CBD OLE study (44).
Cycle 3 (6-9 months)		0.291	0.170	0.220	0.319	
Cycle 4 (9-12 months)		0.291	0.170	0.201	0.338	
Cycle 5 (12-15 months)		0.291	0.190	0.209	0.310	
Cycles 6-9		Last observed data				State occupancies observed from NICE - cannabidiol submission (TA615) (2019) from cycle 4 to 5 shows stabilisation and, therefore, no change in state occupancy of cannabidiol was applied from cycle 6 to 9 (9)
Cycles 10+		Patients remain in the same health state				Assumption

Abbreviations: CI, confidence interval; S0, health state 0; S1, health state 1; S2, health state 2; S3, health state 3

B15b. and B15c. The clinical trial data shows the state occupancy per improvement category >=25%, >=50%, >=75%, and 100% seizure reduction. While the model health states are organized in four health states with mutually exclusive ranges (state 0: <25% reduction, state 1: 25% to <50% reduction, state 2: 50% to <75% reduction, and state 3: >=75% reduction). State occupancy from trial data were organised into corresponding health states in the model by calculating the corresponding number of patients based on the model health state categories for different time intervals.

The company recognises subtitles in Figure 27 were misleading. Figure 27 shows trial data in two distinct sets of categories: cumulative improvement categories (>=25%, >=50%, >=75%, and 100% seizure reduction) in the top row, and clinical trial data converted to the health states used in the economic model in the bottom row, i.e., health states with mutually exclusive ranges (state 0: <25% reduction, state 1: 25% to <50% reduction, state 2: 50% to <75% reduction, and state 3: >=75% reduction).

Please see in the following tables the state occupancy clinical trial data and model data for the OLE period.

Table 18:Comparators state occupancy – clinical 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%
Cannabidiol				
Clinical trial state occupancy				
Health State	**month 3**	**month 6**	**month 9**	**month 12**
State 0: < 25%	31%	29%	29%	29%
State 1: 25% to <50%	20%	17%	17%	19%
State 2: 50% to <75%	20%	22%	20%	21%
State 3: >=75%	29%	32%	34%	31%
Model state occupancy				
Health State	**month 3**	**month 6**	**month 9**	**month 12**
State 0: < 25%	31%	29%	29%	29%
State 1: 25% to <50%	20%	17%	17%	19%
State 2: 50% to <75%	20%	22%	20%	21%
State 3: >=75%	29%	32%	34%	31%
SoC				
Clinical trial state occupancy				

Health State	month 3	month 6	month 9	month 12
State 0: < 25%	69.0%	69.0%	69.0%	69.0%
State 1: 25% to <50%	20.7%	20.7%	20.7%	20.7%
State 2: 50% to <75%	5.7%	5.7%	5.7%	5.7%
State 3: >=75%	4.6%	4.6%	4.6%	4.6%
Model state occupancy				
Health State	**month 3**	**month 6**	**month 9**	**month 12**
State 0: < 25%	69.0%	69.0%	69.0%	69.0%
State 1: 25% to <50%	20.7%	20.7%	20.7%	20.7%
State 2: 50% to <75%	5.7%	5.7%	5.7%	5.7%
State 3: >=75%	4.6%	4.6%	4.6%	4.6%

Data from the clinical trials and data used in the model regarding state occupancy in the OLE period were the same for comparators cannabidiol and SoC, while slight differences were seen for fenfluramine. These differences were due in part to state occupancy in the model being determined from transition probabilities between states, and not based on state occupancies reported by clinical trial data (as was done for cannabidiol due to lack of transition probability data, and for SoC where it was assumed patients would remain in baseline health states). Additionally, clinical trial data encompasses ITT population, whereas the model health states (HS0, HS1, HS2 and HS3) are focused on treated population (the model holds a separate health state to accommodate patients that have discontinued treatment due to AE or lack of efficacy, including the stopping rule).

B15d. The company's base case analysis is considered to be highly conservative, particularly regarding assumptions on dosing for both fenfluramine and cannabidiol (see answer B12b). With regards to assumptions on efficacy, please see the answer to question 19, where it is stated that when comparing the first 12 months efficacy of fenfluramine versus cannabidiol's as shown in figure 27 (state occupancy of treatment arms in the first year follow up) in section B3.3.2.4 and in question B15, the evidence shows that treatment effect of fenfluramine is sustained and increasing, represented by increasing percentages of patients showing improvement in seizure outcomes of varying degrees over time. On the other hand, cannabidiol's efficacy plateaus with state occupancy remaining fixed for almost 6 months (from month 6 to 12). Therefore, although scenario analysis can be explored, it would not be plausible to make any conclusions that patients will remain in the same health states from cycles 5-9 for both interventions. Clinicians also support the notion that improved efficacy observed from

the long-term effects of fenfluramine in DS would also apply to LGS due to the synergies between both conditions. And although we do not have long-term OLE data for fenfluramine in LGS, the collative available evidence base suggests (form clinicians experience in DS, long-term data for DS and existing data within LGS) that efficacy continues to improve at least up until approximately month 25-30.

Please note: The company is looking further into this as continuous model adaptations are being implemented as per the EAGs request which will influence outcomes on different assumptions of efficacy. An extension has been requested for some related questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B16. The fenfluramine open label extension study data was used for estimating transition probabilities in cycle 2 to 5 and the cannabidiol open label extension study data was used for estimating transition probabilities in cycle 2 to 7. For approximately half of patients in these OLE studies, fenfluramine and cannabidiol treatments were new treatments as they received placebo during the initial trials.

a) Please explain why it was considered appropriate to use these OLE data starting from cycle 2 instead of cycle 1 as can be expected for patients new to these treatments.

b) Alternatively, the 6 month follow up data could have been used for cycle 2 instead of the 3 month follow up data. Please provide an updated economic model and a scenario analysis using this assumption.

c) Another option would be to include only the patients that actually continued treatment in the OLE study (i.e., the patients that were assigned to active fenfluramine or CBD treatment during the initial trials). Please provide an updated economic model and a scenario analysis with this assumption.

B16a. In the model, the efficacy data for cycle 1 (applied at the end of cycle 1 to determine the state occupancies of cycle 2) are based on the indirect treatment comparison using the phase III trial data. We acknowledge that the OLE studies (respectively for fenfluramine and cannabidiol) include patients who were on placebo in the phase 3 trial and start the intervention at the beginning of the OLE. There are two options available to account for this: using the 6 month follow up data for cycle 2

instead of the 3 month follow up data (this is addressed in B16.b) and include only the fenfluramine patients that continued treatment in the OLE study (this is addressed in B16.c). The data on cannabidiol patients continuing treatment are not publicly available.

B16b. We have updated the economic model to include a scenario analysis using the 6 month follow up data for cycle 2 instead of the 3 month follow up data.

Please note: an extension has been requested for some question by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B16c. The company has not been able to identify how many cannabidiol patients within their trial continued with cannabidiol in the OLE study vs those that started treatment in the OLE study, particularly for the cannabidiol with clobazam subgroup which is the approved sub-group for use in LGS. Without this data, updating the economic model and providing updated scenario analysis would bias one of the interventions as greater incremental efficacy is observed during the first few months of treatment. Only providing data for one treatment arm that has continued treatment within the OLE whilst data for all patients within another would not enable a plausible comparison to be made.

B17. Treatment could be discontinued due to treatment emergent adverse events (TEAEs) and lack of efficacy.

a) Treatment discontinuation due to TEAEs in cycle 1 was based on the NMA results, while for cycles 2 to 7 it was based on the crude study estimates of the fenfluramine OLE and cannabidiol OLE studies. Please justify this approach and elaborate on the comparability of the patient populations of both studies.

b) Please explain why it was deemed appropriate to assume no discontinuation due to TEAEs in the fenfluramine arm for cycle 6 and 7 (CS Table 44).

c) Please provide an updated economic model and alternative scenario with the same discontinuation rates due to TEAEs as the cannabidiol arm in cycle 6 and 7.

d) In the fenfluramine OLE study, 7.3% of the patients discontinue treatment due to a lack of efficacy in cycle 2. The same was assumed for cannabidiol. Please

explain why the results from Thiele et al. could not be used to obtain a lack of efficacy estimate.

e) If possible, provide an updated economic model and scenario analyses analysis using the lack of efficacy estimate for cannabidiol based on Thiele et al.

B17a. The discontinuation due to TEAEs at the first cycle (T+M) is based on NMA results, which is anchored using the SoC arm in both cannabidiol and fenfluramine Phase 3 trials. The NMA analysis, however, does not conduct any adjustment for the difference in characteristics of populations at baseline for these two studies. Due to the fact that the OLE studies are single cohort studies (no controls) in both fenfluramine and cannabidiol OLE trials, discontinuation data is directly extracted from these two studies.

Patient populations on treatment in both studies have been compared in terms of their baseline characteristics in the NMA analysis and show similar characteristics with regard to age and sex distribution (see Table 19 below).

Table 19: Baseline characteristics (age and sex) in both OLE studies

	N	Age at entry to OLE Mean (SD)	Male N (%)
FFA OLE	247	14.3 (7.6)	136 (55%)
CBD OLE*	366	15.9 (9.5)	198 (54%)

** Thiele E,et al. Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. Epilepsia. 2019 Mar;60(3):419-28.*

B17b. Discontinuation due to TEAEs occurring from cycle 2 to 5, i.e., up to 15 months were based on the OLE data for fenfluramine and cannabidiol. For fenfluramine, the AE rate was assumed to be 0% after cycle 5 throughout the time-horizon as the AE rate from OLE data turns to 0% at cycle 5 (15 months follow up), see table 44, p.119 in CS document B which is based on Table 2.1 from *UCB Data on File. statistical analysis Study 1601 and OLE data* (available in the reference pack). We extracted the data in Table 20 below.

Table 20: Discontinuation numbers by reason CSR part 2 analysis

For the cannabidiol arm, respective OLE data was also used. The proportion of patients with AE becomes 0 in cycle 7 (cannabidiol OLE study reports a 1.3% discontinuation rate at cycle 5, 1% at cycle 6, and then 0% at cycle 7) so we assumed no further discontinuation due to AE will occur after this cycle for cannabidiol arm, see table 44, p.119 in CS document B.

For SoC, AE rates from Study 1601 were used (1.1%) and were assumed to be the same at every cycle throughout the time-horizon.

B17c. We have updated the economic model to assume the same discontinuation rates due to TEAEs as the cannabidiol arm in cycle 6 and 7.

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B17d. Thiele et al 2019 publication presents the percentage of patients discontinuing due to AEs (**"***Thirty-five patients (9.6%) discontinued treatment due to AEs*").

However, it does not present the percentage of patients discontinuing due to lack of efficacy. Therefore, this publication could not be used to estimate this parameter.

B17e. Based on the above, no update of the model was performed.

B18. In the CS B.3.3.5, treatment waning is explained as: "After cycle 9 (month 27), treatment waning was applied as a proportion of patients assumed to undergo waning of efficacy. This was implemented using the last deteriorating transition probability observed from the OLE study from month 9 to 12 of follow-up and was applied to both fenfluramine and cannabidiol arms – due to lack of data for cannabidiol deterioration rates (12). Proportions of patients for treatment waning were calculated from the OLE study in the last 3 months of observation (5.2%). The same value was applied to patients receiving fenfluramine and cannabidiol (Table 46)".

a) Please explain in more detail how treatment waning was implemented in the model i.e., which transitions are subject to treatment waning and how was this implemented. Please justify this approach.

b) How was treatment discontinuation due to waning implemented in the model?

c) How is the stopping rule implemented in the model?

d) It is stated that 5.2% of patients experience treatment waning after cycle 9 (month 27). However, also the 12-15 month transition probabilities were used to inform transitions between states after cycle 9, see the values below from the Excel file 'Transition prob – data' tab, cells AJ31:AO35. Please explain in further detail the difference between deteriorating transition probabilities and treatment waning, and explain how the values in the table below were obtained and how they relate to the 5.2% of patients with treatment waning mentioned in CS Table 46.

12-15 months	State 0	State 1	State 2	State 3	Sum
State 0	1,000	0,000	0,000	0,000	1,000
State 1	0,013	0,987	0,000	0,000	1,000
State 2	0,000	0,015	0,985	0,000	1,000
State 3	0,000	0,003	0,008	0,989	1,000

B18a. Since treatment effect was applied only up to cycle 9 (up to 27 months efficacy period), from cycle 10 onwards patients were assumed to either stay in their

corresponding state, experience waning of efficacy or were subject to potential competing occurrences of discontinuation or death. This means that patients can not improve and can only transition to worse states. Treatment waning was implemented in the model by considering two main elements. First the proportion of patients that experience treatment waning. Second the deteriorating transition probabilities that describe the waning experienced by those patients.

Treatment waning was applied each cycle (starting on cycle 10) to 5.2% of patients on treatment. The 5.2% value was calculated from fenfluramine OLE study in the last 3 months of observation and was used for both fenfluramine and cannabidiol arms due to lack of data for cannabidiol. Specifically, it was calculated as the proportion of patients discontinuing due to lack of efficacy in the last cycle of the fenfluramine OLE study divided by total number of patients in this cycle which is 6/116 = 5.2% (from Table 2.1 and 1.3 of UCB statistical analysis) (43).

Table 21: Number of patients who discontinued due to lack of efficacy and number of total patients.

	Discontinued due to lack of efficacy	Total number of patients
Month 10-12 of FFA OLE	6	116

Source: Table 2.1 and table 1.3 of UCB statistical analysis (43)

The effect of waning of efficacy (applied to 5.2% of patients on treatment) is described by the deteriorating transition probabilities observed from the fenfluramine OLE study (from month 9 to 12 of follow up, which correspond to months 12 to 15 of the model). This was applied to both fenfluramine and cannabidiol arms due to lack of data for cannabidiol deterioration rates (45). These deteriorating transition probabilities represent the transition probabilities observed in the last 3 months of observation of the fenfluramine OLE study concerning only the transitions to maintain or worsen the health state (Table 4.4 UCB statistical analysis) (43).

Table 22: Transition probabilities (number of patients) applied in cycle 5 estimated from the fenfluramine OLE study (excel cells 'Transition prob – data'!B59:G63)

[redacted]

Table 23: Deteriorating transition probabilities (number of patients) determined from transition probabilities cycle 5 estimated from the fenfluramine OLE study (excel cells 'Transition prob – data'!AI59:AN63)

[redacted]

Table 24: Deteriorating transition probabilities (percentage of patients) calculated from deteriorating transition probabilities (number of patients) (excel cells 'Transition prob – data'!AO59:AT63):

[redacted]

Table 25: Deteriorating transition probabilities (percentage of patients) calculated to apply transition of state only to 5.2% of patients (state transition probabilities multiplied by 5.2% and the remaining patients to remain in the same health state) (excel cells 'Transition prob – data'!AJ31:AO35)

[redacted]

In summary, waning of treatment efficacy is implemented in the model by applying in each cycle, to a proportion of patients, deteriorating transition probabilities (transition probabilities without possibility of improving health state), simulating the overall decline of efficacy over time. Due to lack of cannabidiol specific treatment waning data, the same treatment waning was applied to both fenfluramine and cannabidiol.

B18b. There is no specific discontinuation due to waning implemented in the model. Waning leads to worsening health states, which leads to increased discontinuation due to lack of efficacy (stopping rule).

Discontinuation due to lack of efficacy was implemented for T+M period and cycle 2 based on data collected from Study 1601 (0%) and OLE study (7.3% 12/164) (see Table 45). After cycle 2, discontinuation was captured by a stopping rule for patients in health state 0 evaluated every 3 months. Applying this for Cycle 10 onwards meant that patients deteriorating and reaching health state 0 (<25% response) from respective health states have no possibility of improving and would therefore stay in health state 0 and stop treatment.

B18c. Stopping rule was considered for patients with no or limited reduction in drop seizures. This was implemented in the model by discontinuing patients that are in health state 0 (<25% response) and do not improve (transition to a better health state). In the base case the stopping rule is applied every 3 months at the end of each cycle.

B18d. Deteriorating transition probabilities were used in the model to implement/simulate treatment waning of efficacy (see item B18a for detailed explanation of treatment waning and deteriorating transition probabilities). While the deteriorating transition probabilities determine the effect of treatment waning on a patient, it was assumed only a portion of patients would experience waning each cycle (5.2% calculated from fenfluramine OLE study in the last 3 months of observation). The mentioned excel table ('Transition prob – data' tab, cells AJ31:AO35) represents the calculated deteriorating transition probabilities, already accounting for transitions to occur only in 5.2% of patients, used in the model.

B19. In TA615 for the cannabidiol submission, treatment effectiveness over time was discussed: "*The committee concluded that the effectiveness of cannabidiol was likely to diminish over time*". Please provide an updated economic model and scenario analyses exploring a scenario with no treatment effect after 27 weeks for all patients.

B19. No evidence demonstrating that fenfluramine effectiveness diminishes over time exists. In fact, when comparing the first 12 months efficacy of fenfluramine versus cannabidiol's as shown in figure 27 (state occupancy of treatment arms in the first year follow up) in section B3.3.2.4 and in question B15, the evidence shows that treatment effect of fenfluramine is sustained and increasing, represented by increasing percentages of patients showing improvement in seizure outcomes of varying degrees

over time. On the other hand, cannabidiol's efficacy plateaus with state occupancy remained fixed for almost 6 months (from month 6 to 12). Furthermore, in the CBD TA615 submission waning was not considered nor applied prior to this committee's conclusion. Nevertheless, the committee's conclusion that effectiveness was likely to diminish over time was already well-regarded and upheld in this CS as we have already factored in waning of treatment effects in the model as explained in section B.3.3.5 in CS document B and further elaborated in answer to question B18.

B20. Non- Sudden Unexpected Death in Epilepsy (SUDEP) mortality was assumed to be 21.40% based on a Dravet patient population (CS REF 138).

a) Please justify the use of DS mortality for LGS based on nature and clinical progression of both diseases.

b) In CS page 112 it is stated that "*experts highlighted during the advisory board that mortality remains low in practice and is not the primary outcome of interest*". How does this statement relate to the non-SUDEP mortality rate of 21.40% used for the modelling?

c) Please provide an updated economic model and scenario analyses exploring a non-SUDEP mortality that is more in line with the expert statements.

B20a. Mortality rates for both DS and LGS can be challenging to estimate precisely due to various factors, including the underlying causes, patient heterogeneity, and improvements in medical care over time. Due to the absence of LGS-specific data, evidence was sourced from Cooper et al. 2016 on DS patients (Table 26) (46). This was done in line with the TA615 cannabidiol submission where clinical experts considered this approach to be appropriate (47). Furthermore, UK clinical experts have been consulted and were asked to clarify how assumptions of mortality in DS can be applied in LGS. They highlighted that large heterogeneity exists between patients. They indicated that mortality is not thought to be as high in LGS as it is within DS, but comparably there is very poor data in LGS, and it is difficult to determine precise mortality rates that would apply to all patients.

B20b. Thank you for pointing this out. The statement on page 122 highlights clinical expert opinion on mortality. The accidental mortality was calculated in the model as a proportion (21.40%) of SUDEP and status epilepticus mortality not as a proportion of

the LGS patient population (see table 49 below extracted from CS), using the data provided in Cooper et al. 2016 (46), as follows: SUDEP deaths = 10, SE deaths = 4, Accidental deaths = 3

Probability of accidental death (given SUDEP + SE mortality) = accidental deaths / (SUDEP deaths + SE deaths) = 3 / (4+10) = 21.4%

With this approach, accidental mortality was calculated based on SUDEP and SE mortality. Considering that SUDEP mortality in the model is health state specific (worse health states have higher risk of SUDEP), accidental mortality ultimately used in the model was between 0.028% (state 3) and 0.070% (state 0). We considered these values to be in line with the statement mentioned in page 122.

B20c. Based on the above, no further update will be made.

Table 26: Non-SUDEP: SE and accidental mortality

Non SUDEP: SE and accidental mortality	Probability*	Reference
Probability of SE mortality for DS patient	0.093%	Cooper et al. 2016 (46)
Additional proportion of accidental mortality compared to SE + SUDEP mortality	21.40%	

*Notes: * Following the CBD NICE submission (2019), epilepsy-related rates for Dravet syndrome were used as a proxy.*

Abbreviations: DS, Dravet Syndrome; SE, Status Epilepticus.

Adverse events

B21. TEAEs that were most commonly reported in both the fenfluramine and cannabidiol trials, including rash, somnolence, fatigue, diarrhoea and decreased appetite were included in the economic model. AE rates for fenfluramine, SoC and cannabidiol were sourced directly from the safety data of their respective trials. The disutility for fatigue (-0.060) and an assumed cost of one visit to a specialized nurse was applied to all TEAEs.

a) Please justify how the TEAEs included in the economic model were selected from the trials and explain how "*most commonly reported*" was defined.

b) Please provide further justification for assuming the same disutility and cost irrespective of the TEAE that occurs.

c) The CS reported a unit cost of £57.00 for one visit to a specialized nurse, while £52.00 seems to be assumed in the economic model. Please confirm which value is correct and adjust the CS or economic model accordingly.

d) Please provide an updated economic model and scenario analyses exploring TEAE-specific disutilities and costs based on literature and/or expert opinion.

B21a. Please note that in the question it is stated that rash and fatigue are included in the economic model. This is inaccurate. The TEAEs reported across both cannabidiol and fenfluramine phase III trials are defined as those with an occurrence in at least 10% of patients, or those leading to withdrawals from treatment. The TEAEs used in the model were selected based on those reported in both published pivotal trials of fenfluramine (Knupp et al., 2022 (16)) and cannabidiol (Thiele et al., 2018 (17)). Fenfluramine study 1601 reported: somnolence, decreased appetite, diarrhoea, vomiting, pyrexia, and fatigue. CBD trial reported somnolence, decreased appetite, diarrhoea, vomiting, and pyrexia. As such, the final five selected AEs including: somnolence, diarrhoea and decreased appetite, pyrexia, and vomiting were the TEAEs that were most common in both published trials.

B21b. In line with NICE's CBD submission from 2019, the cost of managing AEs was assumed to be equivalent to that of a single visit to a specialised nurse. This approach was chosen because most common AEs were not classified as grade 3 or 4, which would require hospitalisation. Both cannabidiol and fenfluramine exhibit a consistent, well-defined, and manageable safety and tolerability profile. The majority of AEs, which were typically mild to moderate, occurred during the initiation of treatment (within 2-4 weeks), were transient, and resolved within 4 weeks of onset.

In the previous TA615 submission, the company initially employed a straightforward approach by considering only the cost of AEs and not their associated disutility. However, the ERG highlighted the potential importance of assessing the impact of TEAEs on QoL. Consequently, we included utility decrements in accordance with NICE's appraisal. However, due to the scarcity of evidence in LGS patients, we adopted utility decrement for patients on oral antiepileptic medications in general population from Matza et al. (2019) (48). Since the AEs reported with oral medication in Matza et al. (2019) (48) did not align with the TEAEs in our population, we assumed

TEAEs would have similar decrement in utility as those experiencing "*Fatigue*" in general population taking oral antileptic medications. As such, a disutility of (-0.060), which was associated with the AE of fatigue among the general population taking antiepileptic treatments, was applied to all TEAEs in LGS.

Additionally, it should be emphasised that according to the model results, TEAEs have a very negligible impact on both total cost and QALYs.

B21c. Thank you for pointing out this error. The correct value is £57.00 provided in the report, we have adjusted the economic model accordingly.

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B21d. No evidence was found on disutilities for specific adverse events in severe epilepsy. Therefore, it will not be possible to provide further analysis on this.

Quality of Life

B22. Priority question: Although health-related quality of life (HRQoL) data were collected in Study 1601 and the OLE study using QOLCE-16, these were not considered for inclusion in the cost-effectiveness analysis because the QOLCE-16 is a disease-specific measure and long-term data were not yet available. Instead, the company used utility scores from an abstract of Verdian et al. to inform health state utilities in the economic model. This involved a vignette study focussed on drop seizure frequency in which the rating of LGS health states using the VAS and EQ-5D was done by members of the general public.

a) If available, please provide the full publication of the study by Verdian et al.

b) Please justify whether the study of Verdian et al. incorporated all relevant domains of generic health related quality of life (i.e., not merely condition-related domains) and elaborate on the potential implications of this.

c) **Please elaborate on the limitations (and potential implication for the economic model) of vignette studies as compared to patient reported outcome studies and the implications of this for the utility scores obtained by Verdian et al.**

d) **Please provide a complete overview of the collected QOLCE-16 data in Study 1601 and the OLE study per (reduction in) drop seizure frequency category, per treatment arm and per time point.**

e) **Please elaborate on the feasibility of mapping QOLCE-16 data from Study 1601 and the OLE study to EQ-5D data to inform health state utilities in the economic model, and if feasible provide a scenario analysis with mapped EQ-5D utilities.**

f) **Please provide an updated economic model and scenario analysis in which utilities are informed by the QOLCE-16 data from Study 1601 and the OLE study by mapping these data to EQ-5D.**

B22a. Health utility data were derived from a 2008 conference abstract by Verdian *et al.* 2008 (49). Unfortunately, only the conference abstract is available. The utilities from this abstract were found to be used in several subsequent studies including Verdian *et al.* 2010 for a cost-effectiveness study (36), Clements et al. 2013 in a trial-based study (35), and it was also mentioned in the previous NICE TA615 submission (9). The PDF version of the conference abstract is provided in the reference pack material.

B22b. Verdian *et al.* 2008 study describes that all health states were piloted with 9 members of the UK general public. Time trade off interviews (TTO) were conducted with 119 members of the general public of whom 48% were caregivers/parents of children aged 4 to 18. A secondary analysis involved the participants rating each LGS health state on a visual analogue scale (VAS) and using the EQ5D tool. We have used in our base case model, the utility data gathered by the secondary analysis which utilised the EQ5D tool to ensure that all the relevant generic health related quality of domains (the five major domains (5D)): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are captured.

B22c. We have used the utility data gathered in Verdian *et al*. 2008 through secondary analysis which utilised the EQ5D tool to ensure that all the relevant generic health

related quality of domains are captured. Verdian *et al.* 2008 describes that Four health state descriptions of LGS outcomes were developed following literature review and extensive consultations with clinical experts. Health states were defined by tonic-clonic (drop attack) seizure frequency which is the salient feature of LGS. In a study that assessed usefulness of vignette-based utilities by Matza et al. 2021 (50), Matza argues that in situations where patients are difficult to access, for example when it is not possible to recruit a large enough representative sample, vignette studies may be the only feasible way to estimate utilities to represent these health states in a model. This justification applies to LGS patients because it is a rare disease and hence difficult to recruit representative sample of LGS patients. This also explains the rarity of utility studies on LGS disease in literature. In the TA615 NICE submission, vignette study was also used due to unavailable utility data from literature.

Although vignette studies may be rigorously developed, there is a limitation that utilities are not directly provided by patients living in the health states and therefore utilities may differ from the health status of actual patients with the condition. The common understanding is that patients tend to value health states higher than members of the general public (51). However, there is no conclusive suggestion on this point as none of these approaches are flawless as pointed out in a recent systematic literature review by Helgesson et al. 2020 (51). In the current NICE guide to the methods of technology appraisal in section 5.1.2 NICE notes the uncertainty on choices of value judgement perspectives and highlights that although the reference case specifies methods preferred by the institute (perspective of patients or when relevant carers), it does not preclude the Appraisal committee's consideration of non-reference case analysis (52).

B22d. QOLCE questionnaire is a low-burden parent/caregiver assessment that evaluates how epilepsy affects day-to-day functioning of patients 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 change from baseline in QOL using QOLCE was one of the exploratory objectives of Study 1601 and OLE.

Study 1601 and the OLE study used the original 76-item parent-rated questionnaire (QOLCE-76). There are 16 dimensions to the QOLCE. The QOLCE scores items have 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 worse possible response. Item scores are transformed to a 0-100 scale. A value of 0 represents the lowers or poorest score and 100 reflects the highest level of functioning.

QOLCE data was gathered at the randomisation visit (visit 3) and at the EOS/ET (visit 12) for study 1601. For OLE treatment period, QOLCE was gathered at visit 20 (month 6) and visit 22 (month 12) or at end of treatment procedures for withdrawn patients. However, exploratory end points including assessing quality of life using QOLCE can only be provided in the final analysis (i.e., not available for interim analysis for the OLE treatment period). Results obtained at visit 12 (after approximately 3 months) were provided as calculated change from baseline, as these are currently the only available data. Change from baseline in quality of life using QOLCE was calculated by subtracting the overall score at baseline from the overall score at visit 12 or at end of treatment procedures for withdrawn patients. Each treatment group was compared pairwise with others using pairwise Wilcoxon tests.

QOLCE is a disease specific (epilepsy specific) tool and does not convey accurate generic quality of life data, but rather clinical status of the patients (53). Results are provided in enclosed trial data UCB Data on File, Trial CSRs Part 1, Table 14.2.12.1.1, as change in baseline QOLCE scores at visit 12 (after approximately 3 months of study 1601 duration), which did not show consistent differences between treatment arms at this early time point in the trial.

B22e and B22f. Unfortunately, it is not feasible to map QOLCE data for several reasons. The lack of an appropriate mapping algorithm to convert the QOLCE scores to EQ-5D values make it impossible to obtain utilities through mapping approach. Moreover, at this point, data available (provided in the CSR data on file) are at visit 12 as change from baseline scores obtained at visit 3. This early data is unlikely to capture treatment effects for longer than 99 days. On the other hand, results of QOLCE from OLE trial treatment period will only be available in the final analysis, and response rate at the end of OLE is yet to be assessed since it is known that response rate are typically low in trials for severe refractory epilepsy, where most patients are unable to participate in surveys due to intellectual impairment and/or age.

B23. Priority question: In addition to patient utilities, caregiver utilities were included in the company's base-case. As no caregiver-specific utility scores were provided by Verdian et al., the same utility values were assumed for both patients and caregivers. In compliance with TA615, the company's base-case assumed 1.8 caregivers per LGS patient.

a) Please justify the appropriateness of including caregiver utilities in the economic model for all patients (i.e., all drop seizure frequency categories).

b) Please justify including caregiver utilities for both children and adults and elaborate on potential differences between younger and older patients (e.g., caregiver utilities may not be relevant for older patients that are institutionalised).

c) Please elaborate on the appropriateness of assuming 1.8 carers per patient over the whole patient's lifetime.

d) Please confirm that if a patient in the economic model died, the corresponding carer utility was also set to zero. If so, please elaborate on the implications of this assumption (i.e., overestimation of the impact on mortality, given that the caregiver does not die together with the patient).

e) Considering the relatively low utility values of LGS patients, please elaborate on the plausibility of assuming the same utility values for caregivers.

f) In the NICE Decision Support Unit document regarding the modelling of caregiver HRQoL, modelling a caregiver disutility is reported to be the most common approach. Please provide an updated economic model and scenario analyses exploring alternative approaches of implementing caregiver utilities. At least including, in line with TA614, applying a caregiver disutility to only the two worst health states in the model until a patient dies.

B23a. LGS is a rare, severe, highly complex developmental and epileptic encephalopathy (DEE) which begins in childhood and continues into adulthood. It

causes significant developmental delay or loss of developmental skills, leading to substantial social difficulties and costs (54). This disease significantly impacts the patient and subsequently caregiver's abilities to perform daily living activities and substantial detriment on their quality of life. Evidence from literature suggests that the nature of the disease imposes extremely demanding caregiver responsibilities as patients will need caregiver support for all aspects of daily life and because of the debilitating effect caused by the treatment resistant seizures (55).

Caregiver utilities were included for all patients in the model as it is not expected that caregivers of patient groups with better response health states would have a normal quality of life. Indeed, patients will still have seizures and caregivers would still contend with the inherent uncertainties surrounding seizure occurrences and the anxiety associated with the potential onset of SUDEP or *status epilepticus*.

This is further supported by evidence from the Study 1601 on caregiver levels of anxiety and depression that were assessed during the study using HADS and Zarit caregiver burden inventory. Changes in emotional distress in caregivers from baseline were not statistically significant in any of the treatment groups during the study suggesting that caregiver utility for all patient groups remains substantially affected. In addition, improvement in seizure response to treatment does not negate the fact that patients still remain dependent on caregivers for daily living activities due to cognitive and functional impairment effect of LGS that are irreversible (56). The impact on carer QoL is attributed to the need for continuous attention and vigilance of parents during the day and at night. In addition, the unpredictable nature of seizures adds a significant psychological burden for parents (57).

B23b. For many children with LGS, the need for carers remains the same after they reach adulthood. Cognitive impairment is noted in up to 95% of patients with LGS within 5 years of disease onset, and functional impairment renders 87% of patients with LGS unable to live independently, with 58% being completely dependent on others for all activities of daily living (56). Therefore, regardless of a patient's age, it is expected that LGS patients will require informal caregiver support.

B23c. The literature indicates that ≥1 carer for patients with severe epilepsy syndromes is not unusual. For example, in the large pan-European DISCUSS survey

of DS patients (Lagae, L. et al. Developmental Medicine & Child Neurology 2017), almost 80% of households had more than one adult caregiver. The need for > 1 carer remains the same for children even after they reach adulthood due to cognitive and functional impairment. We noted that for LGS patients during the NICE TA615, 1.8 caregivers was deemed suitable in line with Lagae et al., 2017. As such, 1.8 caregivers were assumed in the company submission in line with previous TA615 submission (9, 58).

B23d. We confirm that once a patient dies in the economic model, the corresponding carer utility was also set to zero. We acknowledge this may result in overestimation of treatment effects, especially due around mortality. The company will test this overestimation by modelling an alternative scenario applying a caregiver disutility, as requested in item B.23.f), instead of the current approach.

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B23e. Although utility values for LGS patients are relatively low, the impact of LGS on caregivers is considered substantial as caregivers have to provide round the clock care (see B23a for further info on how LGS heavily impacts caregivers), and evidence suggests that utility values for caregivers were also relatively low. Lo *et al* 2021 indicate that unlike DS, utility values for patients with LGS and LGS caregivers were highly consistent and highly correlated (0.81) (59). This implies that the impact of seizures in LGS and the considerable effects on the overall HRQL of patients and caregiver were closely aligned, with reported mean patients TTO (time trade off) utility ranging from -0.186 to 0.754 and the mean caregiver TTO utility values ranging from 0.032 to 0.810. Moreover, the assumption that caregiver utilities would be the same as patient utilities was made due to the scarcity of caregiver utility values available from literature. Most utility values for LGS are derived using vignette studies, and considering the cognitive impairment of patients with LGS, valuation tends to be provided from general population perspective, hence adding another layer of difficulty in estimating utility values for LGS patients accurately (49, 59). As such, this assumption which relies on the proven equivalent severe impact of LGS on caregivers HRQL was considered as a reasonable approach in absence of data. Finally, we

intend to explore modelling caregiver disutility as an additional scenario as requested in B23f.

B23f. Please note: an extension has been requested for this question by the company. Answers will be provided by 5pm on the 21st of September 2023.

We will implement in the next version of the model the disutility approach to capture the LGS caregiver utility rather than assuming same utilities as LGS patients.

Cost and resource use

B24. Priority question: In the CS, it was stated that " *outcomes for patients with LGS are typically very poor; the majority of patients will require home-care or institutionalisation*". However, the costs of institutionalisation and home care (e.g., specific home support, wheelchair) were not included in the economic model.

a) Please justify why costs of institutionalisation and home care were not included in the economic model.

b) Please provide an updated economic model and scenario analysis including costs of institutionalisation and home care based on previous appraisals (e.g., TA615), relevant literature and/or expert opinion.

B24a. Costs of institutionalisation were not included in this model as it was found difficult to differentiate the percentage of patients institutionalised according to the reduction of seizure frequency. In the cannabidiol submission TA615, 10% of the patients experiencing seizures were assumed to go to an institution when reaching the age of 18 years old versus 2% for the patients who were drop seizures free.

B24b. We will implement a function to add the cost of institutionalisation assuming it will be applied to 10% of all patients reaching 18 years old similarly to TA615.

Please note: an extension has been requested for this question by the company. Answers will be provided by 5pm on the 21st of September 2023.

B25. Health care resource utilization (HCRU) for primary care was based on the number of drop seizures in each health state.

a) Please justify why seizures other than drop seizures were not considered for the estimation of HCRU costs.

b) The mean number of drop seizures per health state were matched to seizure frequency categories (0, <45, 45-110 and >110) taken from the previous cannabidiol submission. Please justify this approach (i.e., why was categorisation of seizure frequency not based on Study 1601?).

c) Please justify why HCRU were estimated separately for two age groups of patients (<12y and ≥12y).

B25a. Reduction in drop seizures was the primary endpoint of the trial. Drop seizures are known to be more prominent in LGS compared to other epilepsies. The physical morbidity and complications are driven by falls due to drop attacks which impacts resource utilisation. HCRU levels would be similar whether non-drop seizures are considered or not. The non-drop seizure types do not generally result in hospitalisation, and they would be managed as part of the same set of specialist consultations already captured for drop-seizures. As such, costs for non-drop seizures are already captured in the model.

B25b. HCRU considered in the model include primary care (LGS routine care) and secondary care (seizure associated care). The HCRU inputs associated with the number of seizures were sourced from UK clinical experts and obtained from the NICE cannabidiol submission (TA615) (9). The HCRU were defined according to the health states defined in TA615, e.g. according to seizure frequency categories (0, <45, 45-110 and >110). To be able to use this dataset in our model (which was the most recent and accurate source), we had to match our HS based on percentage reduction with the above seizure frequency categories. This was done using a combination of Study 1601 data and the midpoint estimates method. A detailed description of the methods and calculations used in the model can be found in question B14.

B25c. The HCRU were defined for two age groups of patients (<12y and >12 year) to account for the frequency of utilisation of HCRU and some unit costs which are

expected to differ between childhood and adulthood patients (see Table 63, 64, and 68 in the CS document B).

With regards to frequency of utilisation, the debilitating impact of seizures are expected to require more HCRU utilisation during childhood because in that age patients are expected to be more vulnerable compared to adults and might require more medical care as they have not yet been on established treatment, especially because of heterogeneity of patients' needs for treatment. Furthermore, children with LGS are expected to initially need more medical care as they have not yet adapted to the condition compared to adults who were living with the disease for a relatively longer period of time. In addition, some cost items deviate between childhood and adulthood patients with LGS with regards to unit costs within resource utilisation. This includes for instance unit cost for specialist visit, and inpatient admissions and ICU (60).

B26. In the CS, it was assumed that patients who discontinued either fenfluramine or cannabidiol treatment were given a basket of treatments in subsequent lines. The distribution of treatments within this basket was assumed to be the same as the SoC arm of Study 1601.

a) Please justify the assumption that the type and distribution of subsequent treatments are similar regardless of the initial treatment (i.e., fenfluramine or cannabidiol). Please cross-validate this assumption with other TAs, provide evidence from clinical guidelines and compare with real-world data (preferably UK).

b) Please justify why cannabidiol was not modelled as a subsequent line of treatment for patients who discontinued from fenfluramine.

c) Please justify why non-pharmacological therapies (e.g., ketogenic diet, vagus nerve stimulation, surgery) were not included as subsequent treatments.

B26a. During the Advisory board, clinical experts emphasised the heterogeneity in patients and the fact that patients are usually on combinations of ASMs as stipulated by NICE guideline NG217. The SoC treatment included ASMs that were used according to the guideline and decision scope and were based on evidence from patient distributions among ASMs from Study 1601 (7). When patients discontinue the main treatment (fenfluramine + SoC or cannabidiol with clobazam + SoC) they are

expected to remain only on SoC which is why the subsequent treatments were set to be similar to the initial SoC treatment only. In the absence of specific representable data this approach was used in line with TA615 cannabidiol for LGS submission and TA808 fenfluramine for DS submissions (9, 33). This approach was corroborated by clinical experts during the advisory board meeting (8).

UK clinical experts further reiterate that returning to treatment would be very individualised, it depends on response and what each patients' issues are with treatment (11). Overall, there is a large variability between patients, they may re-start a previous ASM that was tried but not explored thoroughly, however, overall, they would continue with existing ASMs, and patients would not be expected to immediately start fenfluramine or cannabidiol when failing cannabidiol or fenfluramine respectively. Patients would go back to SoC if they fail on cannabidiol or fenfluramine.

B26b. Cannabidiol was not modelled as a subsequent line of treatment for patients who discontinued from fenfluramine as no data exist on the subject.

B26c. As mentioned for question B10b., non-pharmacological interventions may also be additional treatment options for some patients and can be considered alongside medication. Non-pharmaceutical treatments are an established part of the treatment pathway for LGS, and therefore part of the SoC mix into which fenfluramine would be added. This is why non-pharmacological therapies were not included as separate subsequent treatments.

Severity

B27. Priority question: the QALY shortfall calculation resulted in a severity modifier of x1.7. In the original CS, this modifier was applied to the willingness-to-pay threshold, whereas in the updated CS it was applied to the QALYs of both patients and caregivers. Note that the NICE health technology evaluations manual states that it should only apply to patients: *"The committee will consider the severity of the condition, defined as the future health lost by people living with the condition…" (p. 152)*

a) **Please justify why the x1.7 severity modifier in the updated CS was applied to both patient and caregiver QALYs, rather than patient QALYs only.**

b) **Please provide an updated economic model and scenario analysis applying the severity modifier to patient QALYs only.**

B27a. Indeed, NICE health technology evaluations manual states that*: "the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS" (61)*. We confirm that we did follow this guidance. In the case of LGS, both patients and caregivers are living with the condition as both are heavily impacted by the debilitating effects of the disease. The impact of LGS on caregivers is considered substantial as caregivers have to provide round the clock care (see B23a for further info on how LGS heavily impacts caregivers), and evidence suggests that utility values for caregivers were also relatively low. Lo *et al* 2021 indicate that unlike Dravet Syndrome, utility values for patients with LGS and LGS caregivers were highly consistent and highly correlated (0.81) (59). This would mean that patients and caregivers living with the condition are subjected to a QALY shortfall that we attempted to capture to reflect the severity of the disease.

B27b. Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023. This will incorporate applying the severity modifier to patient QALYs only.

B28. Please provide an updated QALY shortfall calculation for all requested scenario analyses and model updates in this clarification letter (at least including the scenario analyses requested in B20, B22 and B23) that impact the result of the QALY shortfall calculation.

B28. Please note: an extension has been requested for this question by the company. Answers will be provided by 5pm on the 21st of September 2023.

Sensitivity and scenario analyses

B29. Questions pertaining to the probabilistic sensitivity analysis (PSA):

a) Life years (LYs) are not included as an output in the PSA. Please provide an updated economic model including LYs as an output in the PSA.

b) LYs and QALYs for patients and caregivers are reported together in the deterministic and probabilistic results. Please provide QALYs and LYs (and costs, if relevant) separately for patients and caregivers.

c) Table 88 of the CS provides an overview of parameters included in the PSA. The table suggests that some baseline patient characteristics are included, whilst others are not (e.g., the proportion of the population that are male is included whilst age is not). Please provide an overview of baseline characteristics, specifying whether they are included in the PSA or not. Further, please provide justification as to why each characteristic was included or not.

d) CS Table 88 shows that the duration of the titration period was varied probabilistically in the PSA. Please justify this inclusion and elaborate on the impact that this has on subsequent model cycles.

e) According to the CS, PSA results deviated from deterministic base-case results due to a dose-cap being applied to the dose per day for fenfluramine, but not for cannabidiol. Please discuss the plausibility of, and provide justification for, not applying this dose cap to cannabidiol. If applicable, please provide a dose cap to cannabidiol and present the updated base-case results.

f) The PSA does not include a fixed random seed. For reproducibility purposes, please include a fixed random seed in the PSA and provide updated results.

B29a. We confirm LYs are now displayed as output of the PSA.

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B29b. We confirm LYs and QALYs are now presented separately for patients and caregivers.

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B29c. Please see Table 27 below showing an overview of baseline characteristics, specifying whether they are included in the PSA or not and justification where applicable.

Table 27: Justification for inclusion/exclusion of baseline characteristics in the PSA

Measures at baseline	Included in the PSA	Justification
Average age at model initiation and age distribution	**No**	Age at model initiation is used in the Markov engine and determines the time horizon. It is also correlated with age distribution, which is used to determine the proportion in each age group, subsequently employed in weight and dose calculations. Age is not included in the probabilistic sensitivity analysis (PSA) since it would define the model time horizon and necessitate correlation with age distribution.
Proportion male, % (n/N)	**Yes**	
Median number of drop seizures at baseline per 28 days, median (IQR)	**Yes**	
Proportion of GTC, % (n/N)	**Yes**	
Proportion of patients with each AED at baseline - FFA	**Yes**	
Proportion of patients with each AED at baseline - CBD	**Yes**	
Proportion of patients with each AED at baseline - SoC	**Yes**	
Rescue medications (Diazepam), % (n/N)^	**Yes**	
Distribution of seizure-free days % (n/N)	**Yes**	
Weight 2-5 years of age	**Yes**	
Weight 6-11 years of age	**Yes**	
Weight 12-17 years of age	**Yes**	
Weight 18-35 years of age	**Yes**	
Weight ≥35 years of age	**Yes**	

B29d. Thanks for pointing this out. There should not be uncertainty around the titration, it was included only for exhaustivity of the parameters in the sensitivity analysis. We have updated the economic model to exclude titration period from the PSA.

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B29e. The decision of applying or not a dose-cap is based on the approved posology of each treatment, especially the maximum recommended dose:

- For cannabidiol plus clobazam, in its marketing authorisation for LGS, the dosage is indicated as (see cannabidiol SmPC(41)): "*The recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day).*"
- For fenfluramine, in its marketing authorisation for LGS, the dosage is indicated as the following table (see fenfluramine SmPC(62)):

Table 28: Fenfluramine dosage recommendations for LGS

Starting dose – first week	0.1 mg/kg taken twice daily (0.2 mg/kg/day)
Day 7 - second week	0.2 mg/kg twice daily (0.4 mg/kg/day)
Day 14 - maintenance dose	0.35 mg/kg twice daily (0.7 mg/kg/day)
Maximal recommended dose	26 mg (13 mg twice daily i.e. 6.0 mL twice daily)

We can note that the maximum dose for fenfluramine has a fix dose-cap (26 mg) whereas the maximum dose of cannabidiol is weight-dependent (20 mg/kg/day), therefore, a dose-cap for cannabidiol is not applicable.

B29f. We confirm we added a fixed random seed in the PSA to provide fixed PSA results.

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

B30. Figure 31 of the CS provides a tornado plot to present results of the deterministic one-way sensitivity analyses. Two weight variables for the age brackets 12-17 and 18-35 years only show negative variation in the incremental cost-effectiveness ratio (ICER). Please justify the plausibility of the results and discuss the reason(s) for this one-way variation.

B30. Thank you for highlighting that the two weight variables for the age brackets 12-17 and 18-35 years only show negative variation in the tornado plot. In fact, this figure was misleading and has been corrected in the model, as can be seen in the figure below:

Please note: Figure 32 within the CS provides the tornado plot, Figure 31 provides the cost-effectiveness acceptability curve with severity modifier, we assume the EAG are referring to Figure 32 in the question above.

Figure 2: Updated tornado plot

The two weight variables show negative variation in the ICER for both lower and upper bounds tested, i.e., both ICER using lower and upper bound values are lower than the base case ICER.

When using lower bound instead of base case weight, the lower ICER was driven by the lower dosage required for both fenfluramine and the comparator cannabidiol, since for both drugs, dosage is weight dependent (0.5 mg/kg/day for fenfluramine and 14 mg/kg/day for cannabidiol). A lower daily dose resulted in lower acquisition costs for both treatment arms, however, since daily acquisition cost of fenfluramine is higher than cannabidiol when considering the same weight, savings on fenfluramine acquisition costs were greater, leading to a lower ICER than the base case.

When simulating weight upper bound values for these two age groups, the ICERs obtained were lower than the ICERs of lower bound values. In this case, since the weight is increased relatively to base case, daily dosage of fenfluramine and cannabidiol is greater. However, according to the SmPC for fenfluramine, patients cannot exceed the dose of 26 mg per day. Thus, fenfluramine's maximum dose has a fix dose-cap (26 mg) whereas the maximum dose of cannabidiol is weight-dependent (20 mg/kg/day). This means that fenfluramine daily dosage stops increasing with weight after daily dose-cap is reach, while cannabidiol daily dosage keeps increasing with weight. For weights resulting in fenfluramine dosages above dose-cap, as is the case with the upper bound values in this analysis, there is a stagnation of fenfluramine acquisition costs, whereas acquisition cost of the comparator cannabidiol keeps

increasing with weight. The difference between acquisition costs results in a lower ICER compared to base case and even with the lower bound values tested.

Please note: an extension has been requested for some questions by the company. An updated version of the model will be provided by 5pm on the 21st of September 2023.

Validation and transparency

B31. Due to a lack of data on LGS patients, DS data were used as a proxy to inform, among others, SUDEP and non-SUDEP rates. However, differences exist between LGS and DS regarding, for example, aetiology, presentation timing, and duration and type of seizures.

a) Please discuss the plausibility and appropriateness for using DS data as a proxy for LGS data and provide justification for assuming similarity.

b) Please discuss the likely impact that this similarity assumption will have on overall results.

B31a. Although differences exist between LGS and DS, there is evidence that epilepsy-related deaths may be associated with frequency of seizures rather than underling condition (63, 64). Furthermore, UK clinical experts have been consulted and were asked to clarify how assumptions of mortality in DS can be applied in LGS. They highlighted that large heterogeneity exists between patients. Mortality is not thought to be as high in LGS as it is within DS, but comparably there is very poor data in LGS and it is difficult to determine mortality rates that would apply to all patients. The SUDEP mortality used from DS data was in line with approach taken in TA615 cannabidiol NICE submission where it was validated by clinical experts as a valid alternative source in the absence of LGS SUDEP mortality (33, 46).

B31b. It is difficult to assess likely impact in light of lack of data on mortality rates for LGS, however, mortality is not a major driver of the model results since overall LGS mortality rates used in the analysis are noticeably low. This means that the uncertainty around mortality was not translated into uncertainty in the model analysis of cost effectiveness. We have tested this in the deterministic sensitivity analysis (DSA), were we varied parameters either by the upper and lower bounds of 95% confidence

intervals, or 20% variation if confidence intervals were unavailable. When we varied mortality parameters outlined in Table 29 below, the results had very limited impact on the ICER.

Table 29: DSA results – mortality related parameters

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Mortality_Baseline_SUDEP	[redacted]	[redacted]	[redacted]
proportion_mortality_accidental	[redacted]	[redacted]	[redacted]
Mortality_cost	[redacted]	[redacted]	[redacted]
proportion_mortality_SE	[redacted]	[redacted]	[redacted]

B32. Priority question: The results of the face validity and external validity assessment, and the quality control assessment conducted by an independent health economist, are not detailed in the validation exercises mentioned in the CS report.

a) Please provide a detailed description of the validity assessments and respective outcomes conducted for face validity and external validity, and for the quality control assessment.

b) Please provide a completed TECH-VER checklist with results (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/)

c) Face validity was assessed during an advisory board meeting with UK clinical experts. Please provide the full minutes from this meeting.

B32a.

-Face validity: Clinical validation

Face validity of the model was assessed by examining the problem formulation, model structure, clinical assumptions, and data sources by UK clinical experts (8). This was done to ensure that the model fully captures LGSs' clinical context and utilises data and assumptions that corresponds with real-world conditions. Overall, clinical experts agreed with the decision problem and the proposed positioning of fenfluramine as a direct comparator to cannabidiol with clobazam within the model. They indicated that

the model outcomes seem consistent with LGS disease natural history emphasising that drop seizures as a primary outcome is highly relevant and easiest to measure. In addition, SoC treatments and patient characteristics data from fenfluramine trial used within the model were considered representative of UK clinical practice. On the other hand, clinical experts noted that while the model captured main elements from the nature of LGS disease, several benefits of fenfluramine treatment and its impact on LGS patients were not fully captured, including for example benefits on cognitive performance, inclusion of family utilities, and benefits beyond seizure control such as early response, tolerability, and patient retention. They did however acknowledge that relative difficulty of including these benefits within the model due to the multiple variable factors affecting these benefits and potential lack of LGS specific data. The main advice from clinical experts, however, were to rely on DS data in light of limited availability of LGS specific data (8).

The model's structure went through several steps of validation by comparing it to assumptions of previously published models and NICE submissions. Regarding the model's state definition, the relative percentage reduction in seizure frequency has been used in many review submissions and CEM publications in LGS (34, 35). The main criticism of such models, however, was their lack of inclusion of seizure-free days and the absolute number of drop-seizure frequency that have shown to be determinant of health-related quality of life and cost. In our model, we incorporated absolute drop-seizure frequency by using a midpoint estimate for each state. Furthermore, the distribution of seizure-free days from the fenfluramine study within each state was used as a scenario in utility calculation.

Additionally, the duration of the efficacy period was assumed to be the same in both the NICE cannabidiol submission and the DS submission for fenfluramine (27 months since baseline). ERG noted in the CBD 615 submission that the model should account for a potential decrease of treatment effect. The fenfluramine model has the possibility of including treatment waning, from cycle 10 (month 30), using observed data from deteriorating transition probabilities for patients in fenfluramine OLE studies, and the proportion of patients discontinuing treatment due to a lack of efficacy in the long run. The same rate of waning was applied to all patients in all treatment arms (FFA+SoC, CBD with clobazam +SoC, SoC).

-External validity: Comparison with other published economic models

The current cost-effectiveness analysis was compared to the NICE cannabidiol submission (2019) results in terms of cost, LY and QALY estimates. Further, our model's state-based mortality estimates were validated against morality rates in LGS reported in the literature (Chin et al. 2016).

As detailed in the validation section of the submission dossier (ID1651_Fenfluramine_LGS_Document B – section B.3.14), overall, the results largely align with the NICE-CBD submission (2019) in terms of the cost of SoC and show a modest difference between the incremental estimated LYs and QALYs. The total LY and QALY of caregivers over 60 years in our model are comparable to those reported in the DS NICE fenfluramine submission (2022) as similar utility approach was used.

Furthermore, the mortality rates derived from our model were validated against literature on LGS mortality. The disease-specific mortality rate in the LGS has been reported in the literature at 6.12 per 1000 person-years (Chin et al. 2016). The estimated number of deaths in the SoC arm of the model is close to this number which shows the validity of our estimate (6.8 per 1000 person-years).

B32b. A completed TECH-VER checklist with results have been conducted and can be found in the attached document titled "ID1651_Fenfluramine_LGS_ Clarification Answers_TECH-VER checklist [noCON]"

B32c. The report produced from the meeting has been attached. Please note we did not commission for full meeting scripts or a recording from the meeting, the vendor was requested to provide an executive summary and provide recommendations based on this to support the submission and the assumptions within it.

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Single technology appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Clarification questions – Addendum to responses

September 2023

File name	Version	Contains confidential information	Date
ID1651_Fenfluramine_LGS_ Addendum_Clarification Answers [Redacted]	1.0	No	21st September 2023

[This addendum provides additional information in response to the clarification questions document titled 'ID1651_Fenfluramine_LGS_Clarification Answers' dated September 14, 2023. This document contains responses and supplementary information/data for the following questions: B10e, B11c, B14d, B15d, B16b, B17c, B17e, B21c, B23f, B24b, B27b, B28, B29a, B29b, B29d, and B29f. Please read this Addendum in conjunction with the original Response to EAG Clarification Questions document and the attachments accompanying this addendum, including the updated Excel model and the updated confidentiality checklist].

Section B: Clarification on cost effectiveness data

Intervention and comparator

B10. Priority question. As per NICE guideline NG17, third line treatments for LGS include: rufinamide, topiramate, clobazam, and cannabidiol with clobazam. Likewise, the final scope mentions the same treatments as comparators for people aged 2 and over with LGS whose seizures are inadequately controlled by established clinical management. However, these treatments are not included in the model as comparators. As mentioned before e.g., question A20, excluding these comparators provides an incomplete picture of the relative efficacy and cost effectiveness of fenfluramine. Likewise, non-pharmaceutical therapies such as ketogenic diet, vagus nerve stimulation, and invasive surgery can be recommended as additional treatment options for a proportion of patients with LGS in the UK (NG 217). Moreover, these therapies were included in the final scope issued by NICE as relevant comparators, and a significant proportion of patients in the studies included in the NMA and in the OLE studies received vagus nerve stimulation and were on a ketogenic diets. Nonetheless, these were not included in the economic model presented by the company.

a) **Please justify why rufinamide, topiramate, clobazam, and the non-pharmaceutical therapies were not included as individual comparators in the economic model.**

b) **Please elaborate on the position of non-pharmaceutical treatments in the care pathway of LGS patients in UK clinical practice.**

c) **Please provide an updated economic model and scenario analyses including pairwise comparisons and a fully incremental analysis of fenfluramine versus all (combinations of) relevant comparators (i.e., rufinamide, topiramate, clobazam, and the non-pharmaceutical therapies).**

d) **Topiramate is listed as one of the comparators (CS, Table 1) and as one of the ASMs (CS, Figure 5). Nonetheless, 0% of patients are taking topiramate in the SoC ASMs arm (CS, Table 60 and 61). Please justify the**

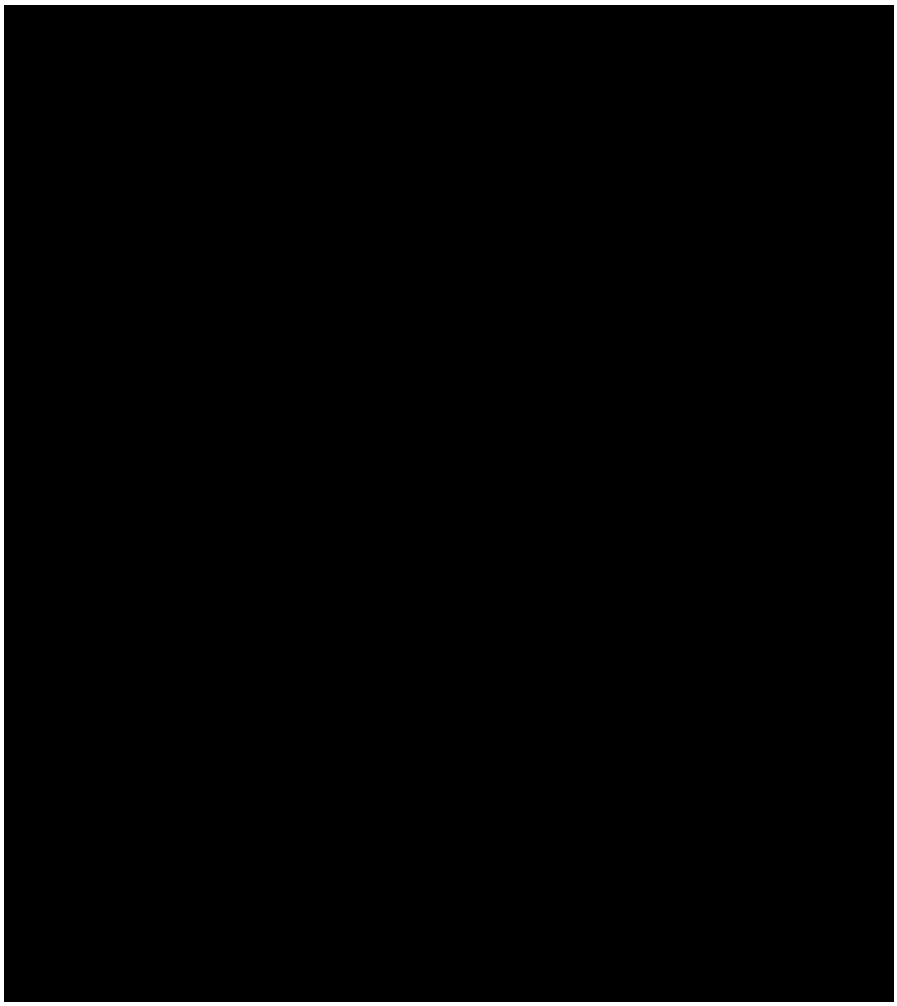
0% of patients using topiramate and elaborate on how this reflects UK clinical practice, using UK data.

e) **Please update Tables 60 and 61 and provide an updated economic model and scenario analysis including a percentage of patients taking topiramate based on UK data.**

B10a. to B10d. Answers to these questions have been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B10e. The model was updated using 13.8% as percentage of use of topiramate.

Table 1. Concomitant anti-epileptic treatments - Safety Population



Source: UCB Study 1601 CSR (1)

Concomitant anti-epileptic treatments baseline distribution observed in Study 1601 for patients on topiramate is 13.8% (Table 1) (1). As such, 13.8% of patients are

considered to be taking topiramate within the SoC ASMs and subsequent treatment in each arm within the model. Updated Table 60 and Table 61 from the CS document B submission are presented below in Table 2 and Table 3 respectively.

Table 2. Distribution of patients taking SoC ASMs in each arm

Technology	FFA +.SoC	CBD w CLB + SoC	SoC only	Reference
Clobazam	44%	100%	44%	Study 1601 (2) ASM distribution at baseline in the SoC arm.
Levetiracetam	23%	23%	23%	
Valproate	56%	56%	56%	
Lamotrigine	33%	33%	33%	
Topiramate	**14%**	**14%**	**14%**	CBD SmPC for 100% concomitant clobazam (3)
Rufinamide	21%	21%	21%	

Table 3. Patient distribution in subsequent treatment applied to all patients

Technology	Patient distribution (%)	Reference
Clobazam	44%	Study 1601 (2) ASM distribution at baseline in the SoC arm.
Levetiracetam	23%	
Valproate	56%	
Lamotrigine	33%	
Topiramate	**14%**	
Rufinamide	21%	

Results of the updated economic model and changes requested in the base case in this question and in question B21c are presented at the end of this document under section New base case results.

B11. Priority question: Cannabidiol with clobazam has been recommended by NICE (TA615) only if the drop-seizure frequency is assessed every 6 months. If the drop-seizure frequency had not fallen by at least 30% compared with the 6 months prior to starting the treatment in TA615, cannabidiol was stopped. This decision was made by the committee following similar criteria for other antiepileptic drugs, despite that the marketing authorisation for cannabidiol did not specify a stopping rule.

a) In the CS, two ways of treatment discontinuation are mentioned: 1) for patients with no or limited response to treatment in cycle 1 and 2, and

2) after cycle 2, where a stopping rule every 3 months was applied and all patients with a response of <25% discontinue treatment. Please provide supporting evidence with relevant external data and/or expert opinion that these routes of treatment discontinuation are consistent with similar ASMs.

b) **Likewise, no stopping rule (or discontinuation due to lack of efficacy) was applied to SoC. Please, elaborate on the representativeness of this choice for the UK clinical practice and provide supporting evidence with relevant external data and/or expert opinion.**

c) **Please provide an updated economic model and scenario analysis in which cannabidiol with clobazam is used as recommended in NICE TA615 (i.e., applying a stopping rule when reduction in drop-seizure frequency is <30% compared to 6 months prior treatment).**

B11a. to B11b. Answers to these questions have been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B11c. The economic model was updated to include a scenario applying a stopping rule when patients' response is below the 30% reduction in drop seizure frequency. after 6 months on treatment. Considering that the 30% threshold does not correspond to a model health state boundary (HS0: <25%, HS1: 25%-50%, HS2: 50%-75%, HS3: >75%), there was a need to assess the percentage of patients between 25% and 30% reduction inside HS1 in order to implement this scenario. As presented in Table 4 it was calculated through post-hoc analyses following the reception of these questions, that 20.4% patients of Study 1601 inside HS1 had a response below 30%. Therefore, for this scenario, the model applies the stopping for patients in HS0 and 20.4% of HS1 every other cycle (every 6 months).

The results of this scenario (B11c) are presented in Table 15 within New results for scenarios section at the end of this document.

Table 4. Patients with <30% reduction in drop seizure frequency during T+M (mITT population with 25-50% reduction in drop seizure frequency during T+M)

Effectiveness

B14. **Priority question: In CS page 107 the calculation of number of drop seizures in each health state is discussed. Here, it is stated that *"As some seizure-related outcomes from the literature (e.g., resource use or mortality) relied on absolute number of drop seizure rather than rate of response to treatment (e.g., percentage reduction in seizures), the average number of drop seizures per 28 days was determined for each health state in the model. For health states 0 and 3, the mean drop seizures per 28 days were the observed median drop-seizure in Study 1601. For states 1 and 2, an approach described by Neuberger et al. (2020) (134) in LGS patients was used"*.**

a) **Please explain why the number of drop seizures at baseline is lower than in state 0 and validate this calculation with the study data.**

b) **Please justify why different approaches were used for health states 0 and 3 and health states 1 and 2.**

c) **The midpoint approach is explained as "The approach consisted of multiplying the baseline number of drop seizures by 1 minus the mid-point value in each health state. For example, the mid-point value of state 1: 25% to <50%, was 37.5%". This explanation is unclear to the EAG.**

Please provide a more detailed example and calculation of the midpoint approach.

d) **Please provide an updated economic model using estimates for health states 1 and 3 using the same approach as for health states 0 and 3 i.e., using the observed median drop-seizure in Study 1601 or validate the results with study data.**

e) **Please provide an overview for which outcomes the midpoint approach was used.**

B14a, b, c & e. Answers to these questions have been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B14d. We have provided in the updated model an option where users can choose the alternative method for calculating the midpoint. Users can select between two approaches:

1. Calculated midpoints for HS1 and HS2.
2. Median DSF (28 days) from Study 1601: using the same approach for HS1 and HS2 as the one used in HS0 and HS3. See Table 5 below for inputs used in this scenario.

Table 5. Number of drop seizure per health state

Median points (T+M)	Calculated mid-point (number of drop-seizures per last 28 days)	Reference
state 0: No response (< 25% reduction)	101.40	Using FFA registration trial data (median % change in state 0 for FFA 0.7 mg)
state 1: Response group 1: 25% to <50% reduction	34.86	Using FFA registration trial data (median % change in state 1 for FFA 0.7 mg)
state 2: Response group 2: 50% to <75% reduction	38.16	Using FFA registration trial data (median % change in state 2 for FFA 0.7 mg)
state 3: Response group 3: >=75% response	11.20	Using FFA registration trial data (median % change in state 3 0 for FFA 0.7 mg)

We have provided a scenario to reflect the effect of changing health state 1 and 2 to be using median DSF from study 1601 following same approach used in states 0

and 3. The results of this scenario (B14d) are presented in Table 15 within New results for scenarios section at the end of this document.

B16. The fenfluramine open label extension study data was used for estimating transition probabilities in cycle 2 to 5 and the cannabidiol open label extension study data was used for estimating transition probabilities in cycle 2 to 7. For approximately half of patients in these OLE studies, fenfluramine and cannabidiol treatments were new treatments as they received placebo during the initial trials.

a) Please explain why it was considered appropriate to use these OLE data starting from cycle 2 instead of cycle 1 as can be expected for patients new to these treatments.

b) Alternatively, the 6 month follow up data could have been used for cycle 2 instead of the 3 month follow up data. Please provide an updated economic model and a scenario analysis using this assumption.

c) Another option would be to include only the patients that actually continued treatment in the OLE study (i.e., the patients that were assigned to active fenfluramine or CBD treatment during the initial trials). Please provide an updated economic model and a scenario analysis with this assumption.

B16a. to B16c. Answers to these questions have been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B16b. We have updated the economic model to include a scenario analysis using the 6 month follow up data for cycle 2 instead of the 3 month follow up data. Please see transition probability using 6 months follow up data in Table 6 below.

Table 6. Transition probabilities based on six months follow up data from fenfluramine OLE study

[redacted]

Results of the scenario analysis using 6 months follow up data for cycle 2 are provided in Table 15 (B16b) in the New results for scenarios section.

B17. Treatment could be discontinued due to treatment emergent adverse events (TEAEs) and lack of efficacy.

a) Treatment discontinuation due to TEAEs in cycle 1 was based on the NMA results, while for cycles 2 to 7 it was based on the crude study estimates of the fenfluramine OLE and cannabidiol OLE studies. Please justify this approach and elaborate on the comparability of the patient populations of both studies.

b) Please explain why it was deemed appropriate to assume no discontinuation due to TEAEs in the fenfluramine arm for cycle 6 and 7 (CS Table 44).

c) Please provide an updated economic model and alternative scenario with the same discontinuation rates due to TEAEs as the cannabidiol arm in cycle 6 and 7.

d) In the fenfluramine OLE study, 7.3% of the patients discontinue treatment due to a lack of efficacy in cycle 2. The same was assumed for cannabidiol. Please explain why the results from Thiele et al. could not be used to obtain a lack of efficacy estimate.

e) If possible, provide an updated economic model and scenario analyses analysis using the lack of efficacy estimate for cannabidiol based on Thiele et al.

B17a., B17b. and B17d. Answers to these questions have been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B17c. We have updated the economic model to assume the same discontinuation rates due to TEAEs as the cannabidiol arm in cycle 5 and 6. Please see updated inputs in Table 7 below.

Table 7. Discontinuation due to TEAE at follow up

Time point	FFA Proportion % (n/N)	CBD Proportion % (n/N)	SoC proportion % (n/N)
Cycle 2 (6-month follow-up)	3.7% (6/164)	6.8% (25/366)	1.1% (1/87)
Cycle 3 (9-month follow-up)	4.1% (6/146)	5.9% (20/341)	1.1% (1/87)
Cycle 4 (12-month follow-up)	1.6% (2/128)	4.7% (15/321)	1.1% (1/87)
Cycle 5 (15-months follow-up)	1.3% (4/116)	1.3% (4/306)	1.1% (1/87)
Cycle 6 (18-months follow-up)	1.0% (3/116)	1.0% (3/302)	1.1% (1/87)
Cycle> 7 (>21-months follow-up)	0.0% (0/116)	0.0% (0/299)	1.1% (1/87)
Reference	FFA-OLE study (4), assuming same discontinuation rate as CBD for cycle 5 and 6.	CBD-OLE study(5)	Assumption - SoC discontinuation from Study 1601(2)

Abbreviation: CBD, Cannabidiol, FFA, Fenfluramine; n, Sample Size, N, Population Size

We have provided a scenario to reflect the effect of changing the model to assume same discontinuation due to TEAEs as cannabidiol in cycle 5 and 6. The results of this scenario (B17c) are presented in Table 15 within New results for scenarios section at the end of this document.

B17e. Based on answers already provided in submitted clarification document part I (14 September), no update of the model was performed.

Adverse events

B21. TEAEs that were most commonly reported in both the fenfluramine and cannabidiol trials, including rash, somnolence, fatigue, diarrhoea and decreased appetite were included in the economic model. AE rates for fenfluramine, SoC

and cannabidiol were sourced directly from the safety data of their respective trials. The disutility for fatigue (-0.060) and an assumed cost of one visit to a specialized nurse was applied to all TEAEs.

a) Please justify how the TEAEs included in the economic model were selected from the trials and explain how "*most commonly reported*" was defined.

b) Please provide further justification for assuming the same disutility and cost irrespective of the TEAE that occurs.

c) The CS reported a unit cost of £57.00 for one visit to a specialized nurse, while £52.00 seems to be assumed in the economic model. Please confirm which value is correct and adjust the CS or economic model accordingly.

d) Please provide an updated economic model and scenario analyses exploring TEAE-specific disutilities and costs based on literature and/or expert opinion.

B21a., B21b. and B21d. Answers to these questions have been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B21c. Thank you for pointing out this error. The correct value is £57.00 provided in the report, we have adjusted the economic model accordingly.

Results of the updated economic model and changes requested in the base case in this question and in question B10e are presented at the end of this document within the New base case results section.

Quality of Life

B23. Priority question: In addition to patient utilities, caregiver utilities were included in the company's base-case. As no caregiver-specific utility scores were provided by Verdian et al., the same utility values were assumed for both patients and caregivers. In compliance with TA615, the company's base-case assumed 1.8 caregivers per LGS patient.

a) Please justify the appropriateness of including caregiver utilities in the economic model for all patients (i.e., all drop seizure frequency categories).

b) **Please justify including caregiver utilities for both children and adults and elaborate on potential differences between younger and older patients (e.g., caregiver utilities may not be relevant for older patients that are institutionalised).**

c) **Please elaborate on the appropriateness of assuming 1.8 carers per patient over the whole patient's lifetime.**

d) **Please confirm that if a patient in the economic model died, the corresponding carer utility was also set to zero. If so, please elaborate on the implications of this assumption (i.e., overestimation of the impact on mortality, given that the caregiver does not die together with the patient).**

e) **Considering the relatively low utility values of LGS patients, please elaborate on the plausibility of assuming the same utility values for caregivers.**

f) **In the NICE Decision Support Unit document regarding the modelling of caregiver HRQoL, modelling a caregiver disutility is reported to be the most common approach. Please provide an updated economic model and scenario analyses exploring alternative approaches of implementing caregiver utilities. At least including, in line with TA614, applying a caregiver disutility to only the two worst health states in the model until a patient dies.**

B21a. to B21e. Answers to these questions have been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B23f. As requested, a scenario has been added to test caregiver disutility. In TA614, caregiver disutilities were calculated relative to the UK VAS norm of 0.828 (from Szende et al. 2014) (6, 7). Using the same method, we calculated the disutilities of caregivers by finding the difference between the UK caregiver utility scores for LGS estimated in the Auvin et al. 2021 study and the UK VAS norm (6, 8) . In Auvin et al. 2021, LGS caregivers had utility scores of: 0.78 in the least severe health state (30 seizure-free days in a month and 0 drop seizures in a month), 0.52 in the intermediate

health state (15 seizure-free days in a month and 80 drop seizures in a month), and 0.38 in the most severe health state (3 seizure-free days in a month and 130 drop seizures in a month) (8). Therefore, when compared to the 0.828 UK utility norm, the decrements in utility were -0.048 for the least severe health state, -0.308 for the intermediate health state, and -0.448 for the most severe health state. Values of caregiver disutilities applied in the model for this scenario are presented in Table 8.

Table 8. Caregivers decrements of utility (disutility approach)

Number of Seizures	No. of Seizure-Free Days		
	≤ 3 days	> 3 - ≤ 15 days	> 15 days
Seizure-Free	-0.048	-0.048	-0.048
≤ 45 seizures	-0.048	-0.048	-0.048
>45 - ≤ 110 seizures	-0.308	-0.308	-0.308
> 110 seizures	-0.448	-0.448	-0.448

Results of this scenario (B23f) can be found at the end of this document in section "New results for scenarios" in Table 15.

Cost and resource use

B24. Priority question: In the CS, it was stated that "*outcomes for patients with LGS are typically very poor; the majority of patients will require home-care or institutionalisation*". However, the costs of institutionalisation and home care (e.g., specific home support, wheelchair) were not included in the economic model.

a) Please justify why costs of institutionalisation and home care were not included in the economic model.

b) Please provide an updated economic model and scenario analysis including costs of institutionalisation and home care based on previous appraisals (e.g., TA615), relevant literature and/or expert opinion.

B24a. Answer to this question has been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B24b. From the Personal Social Services Research Unit 2022, the cost per institutionalisation is £1,594.(9) Institutionalisation is assumed to be applied to 10% of all patients reaching 18 years old, similarly to TA615.(7) As requested, we are providing as a scenario the inclusion of this costs in the model.

Results of this scenario (B24b) can be found at the end of this document in section "New results for scenarios" in Table 15.

Severity

B27. Priority question: the QALY shortfall calculation resulted in a severity modifier of x1.7. In the original CS, this modifier was applied to the willingness-to-pay threshold, whereas in the updated CS it was applied to the QALYs of both patients and caregivers. Note that the NICE health technology evaluations manual states that it should only apply to patients: *"The committee will consider the severity of the condition, defined as the future health lost by people living with the condition…" (p. 152)*

a) Please justify why the x1.7 severity modifier in the updated CS was applied to both patient and caregiver QALYs, rather than patient QALYs only.

b) Please provide an updated economic model and scenario analysis applying the severity modifier to patient QALYs only.

B27a. Answer to this question has been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B27b. As requested, the economic model has been updated to include a scenario analysis with severity modifier applied to patients QALYs only.

Please see Table 15 in the New results for scenarios section for the results of the scenario analysis (B27b).

B28. Please provide an updated QALY shortfall calculation for all requested scenario analyses and model updates in this clarification letter (at least including the scenario analyses requested in B20, B22 and B23) that impact the result of the QALY shortfall calculation.

B28. Please note that for question B20 and B22, no model update was undertaken based on responses and explanation provided for these questions and submitted with clarification document part I (on 14th September). An updated QALY shortfall calculation for all remaining requested scenario analyses including B23 are provided in Table 15 within **New results for scenarios** section towards the end of this document. For each scenario, an ICER was presented as well as an ICER with severity modifier applied. Please note the ICER with severity modifier remains applied to patients and carers. An additional scenario with it being applied to patients only was provided as per the request in question B27b.

Sensitivity and scenario analyses

B29. Questions pertaining to the probabilistic sensitivity analysis (PSA):

a) Life years (LYs) are not included as an output in the PSA. Please provide an updated economic model including LYs as an output in the PSA.

b) LYs and QALYs for patients and caregivers are reported together in the deterministic and probabilistic results. Please provide QALYs and LYs (and costs, if relevant) separately for patients and caregivers.

c) Table 88 of the CS provides an overview of parameters included in the PSA. The table suggests that some baseline patient characteristics are included, whilst others are not (e.g., the proportion of the population that are male is included whilst age is not). Please provide an overview of baseline characteristics, specifying whether they are included in the PSA or not. Further, please provide justification as to why each characteristic was included or not.

d) CS Table 88 shows that the duration of the titration period was varied probabilistically in the PSA. Please justify this inclusion and elaborate on the impact that this has on subsequent model cycles.

e) According to the CS, PSA results deviated from deterministic base-case results due to a dose-cap being applied to the dose per day for fenfluramine, but not for cannabidiol. Please discuss the plausibility of, and provide justification for, not applying this dose cap to cannabidiol. If applicable, please provide a dose cap to cannabidiol and present the updated base-case results.

f) The PSA does not include a fixed random seed. For reproducibility purposes, please include a fixed random seed in the PSA and provide updated results.

B29c. to B29e. Answers to these questions have been provided by the company to NICE in the document "ID1651_Fenfluramine_LGS_ Clarification Answers" submitted on Thursday 14th September 2023.

B29a. We confirm LYs are now displayed as output of the PSA tab of the model.

B29b. We confirm LYs and QALYs are now presented separately for patients and caregivers.

B29d. Thanks for pointing this out. There should not be uncertainty around the titration, it was included only for exhaustivity of the parameters in the sensitivity analysis. We have updated the economic model to exclude titration period from the PSA.

B29f. We confirm we added a fixed random seed in the PSA to provide fixed PSA results.

Drug doses

Fenfluramine dose

Based on new internal evidence on the average mean daily dose for fenfluramine for all subjects in the OLE study, we would like to use a maintenance dose of [redacted] mg/kg/day within the base case of the model instead of 0.5mg/kg/day assumed in the original CS base case. The change in the modelled fenfluramine dose is based on real world data and expert clinical opinion. According to the fenfluramine OLE study, efficacy continued to improve at lower average doses of fenfluramine than what was used in study 1601, which justifies the use of a lower dose within the model. Furthermore, in the fenfluramine OLE study, doses were titrated based on tolerability and safety, which is more reflective of clinical practice (1). Finally, the company sought further insight from UK clinical experts, , they advised that the dosing and efficacy seen within Dravet Syndrome is likely to be reflected the LGS indication (10). A dose of 0.413 mg/kg/day is comparable to the average dose of patients in Dravet Syndrome that are not on stiripentol (0.44mg/kg/day) (11). Therefore, the dose of [redacted] **mg/kg/day** was used in the new base case to closely reflect the dose that is expected to be utilised in practice. Please note: average doses from the fenfluramine OLE study were accepted for use within the economic model within NICE's appraisal of Fenfluramine for use in Dravet Syndrome (TA808) (12).

Cannabidiol dose

Following the EAG highlighting that the dose of cannabidiol within the model needs to be reconsidered, the company re-evaluated the evidence surrounding the cannabidiol OLE study and gained further UK expert clinical opinion on what the dose of cannabidiol in clinical practice is likely to be (10). It was indicated that cannabidiol dose is plausibly closer to 20mg/kg/day, particularly given that the mean modal dose within the OLE is 24mg/kg/day, which was generally consistent across each 12-week period as well as in the last 12 weeks of data for each patient (5). Although we are aware that some clinicians dose their patients between 10-12mg/kg/day, if a patient is tolerating cannabidiol, many titrate higher until a response is achieved. Adequate reductions in drop seizure frequency are rarely seen at lower doses of cannabidiol, patients are either up titrated or treatment is discontinued. Furthermore, cannabidiol

has an uncapped dosing regimen, and as observed in the OLE study, some patients are dosed up to 30mg/kg/day (13). Finally, in the OLE study doses were titrated based on tolerability and safety, which is considered more reflective of clinical practice. Therefore, an average dose of **16 mg/kg/day**, which can still be considered as highly conservative, was used in the new base case. Please note: within the NICE appraisal of cannabidiol for Lennox-Gastaut syndrome (TA615) an average dose of 12mg/kg/day was considered appropriate based on an assumption that 20% of patients reach a higher dose of 20mg/kg/day. However, there is very high uncertainty around this estimate. UCB has discovered that the assumption is highly conservative given data observed within the OLE and having interviewed clinicians on dosing within current practice in 2023.

New base case results

Adjustments made to base case analysis

Based on question **B11e** and **B21c** we have made some changes to the base case analysis to consider corrections requested in the abovementioned questions. As such, topiramate percentage was adjusted in the model from 0% to 13.8% and the unit cost of £57.00 for one visit to a specialised nurse was corrected in the model. In addition, changes to base case inputs included changes specified in the preceding section drug doses, which is using an average maintenance dose of [redacted] **mg/kg/day** for fenfluramine, and **16mg/kg/day** for cannabidiol.

In summary, with the exception of changing patient distribution of ASM with regards to topiramate, correcting the cost of nurse visit, and changing the average maintenance daily dosage used for fenfluramine and cannabidiol, all other inputs were kept the same as inputs in the original base case analysis provided in the CS document section B.3.9.1.

Base-case incremental cost-effectiveness analysis results

Deterministic results

The aggregated base case results for the cost-effectiveness of fenfluramine + SoC compared with cannabidiol (with clobazam) + SoC are presented in Table 9.

Over the lifetime time horizon, treatment with fenfluramine + SoC was associated with a total of 3.68 QALYs at a total cost of [redacted]. Treatment with cannabidiol (with clobazam) + SoC was associated with a total of 2.86 QALYs at a total cost of [redacted]. Compared with cannabidiol, treatment with fenfluramine has resulted in an incremental gain of 0.82 QALYs and an incremental cost of [redacted], yielding an ICER of [redacted] and therefore within the decision-making cost-effectiveness threshold. Moreover, when the x1.7 severity modifier is applied as a QALY weight, the resulting ICER is below £10,000/QALY (Table 10).

Table 9. Base-case results: FFA + SoC versus CBD w CLB + SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
CBD w CLB + SoC	[redacted]	20.33	2.86	-	-	-	-
FFA + SoC	[redacted]	20.45	3.68	[redacted]	0.12	0.82	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Fenfluramine meets the criteria for a severity weight of x 1.7, as mentioned in Section **Error! Reference source not found.**. in the CS document B. Incorporating the s everity modifier on QALYs for evaluating the cost-effectiveness of fenfluramine + SoC versus cannabidiol (with clobazam) + SoC, are presented in Table 10. Over the lifetime time horizon, fenfluramine + SoC provides 6.31 QALYs at a cost of [redacted], while cannabidiol (with clobazam) + SoC offers 4.88 QALYs at a cost of [redacted]. When compared to cannabidiol, fenfluramine has produced an additional gain of 1.43 QALYs at an added cost of [redacted]. This leads to an ICER of [redacted], which is below the NICE threshold for cost-effective treatments.

Table 10. Base-case results with severity modifier applied: FFA + SoC versus CBD w CLB + SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
CBD w CLB + SoC	[redacted]	20.33	4.88	-	-	-	-
FFA + SoC	[redacted]	20.45	6.31	[redacted]	0.12	1.43	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard Of Care.

Although treatment and monitoring costs of fenfluramine are higher than cannabidiol, the introduction of fenfluramine resulted in lower disease management costs (routine care and seizure associated), ASMs cost, subsequent treatment costs, and mortality costs. This yields a total of [redacted] when doing the sum over the time horizon as per the Table 11below.

Table 11. Total costs by category of cost: FFA + SoC versus CBD w CLB + SoC

Item	Intervention cost (FFA + SoC)	Comparator cost (CBD w CLB + SoC)	Increment	Absolute increment	% absolute increment
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	£507	£0	£507	£507	[redacted]
Disease management cost routine care	£38,431	£38,816	-£385	£385	[redacted]
Disease management cost seizure associated care	£29,323	£30,308	-£986	£986	[redacted]
ASM cost	£1,773	£2,306	-£533	£533	[redacted]
Subsequent treatment cost	£11,551	£11,852	-£301	£301	[redacted]
Adverse event cost	£46	£24	£21	£21	[redacted]
Mortality costs	£885	£897	-£12	£12	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Adapted from Pharmaceutical Benefits Advisory Committee (2008).
Abbreviations: ASM, Antiseizure Medication; FFA, Fenfluramine; CBD w CLB, Cannabidiol with Clobazam; SoC, Standard of Care.

Complementary analysis: cost-effectiveness in comparison of SoC

The aggregated base case results for the cost-effectiveness of fenfluramine + SoC compared with SoC are presented in Table 12.

The incremental analysis for fenfluramine + SoC was also presented versus SoC alone. Compared to SoC, fenfluramine has resulted in an incremental gain of 2.05 QALYs and incremental cost of [redacted], yielding an ICER of [redacted] (Table 12). However, when the x1.7 severity modifier is applied as a QALY weight, the resulting ICER is [redacted] (Table 13).

Table 12. Base-case complementary results: FFA + SoC versus SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
SoC	[redacted]	20.15	1.63	[redacted]	-	-	-
FFA + SoC	[redacted]	20.45	3.68	[redacted]	0.30	2.05	[redacted]

Abbreviations: FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; Incr., Incremental; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Table 13. Base-case complementary results with severity modifier applied: FFA + SoC versus SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
SoC	[redacted]	20.15	2.80	[redacted]	-	-	-
FFA + SoC	[redacted]	20.45	6.30	[redacted]	0.30	3.50	[redacted]

Abbreviations: FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; Incr., Incremental; LYG, Life Years Gained; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Exploring uncertainty

New probabilistic sensitivity analysis

Cost-effectiveness plane

Results from the PSA are presented in Figure 1.

The cost-effectiveness plane of FFA + SoC versus CBD w CLB + SoC shows that [redacted] of the simulations are located in the North-East quadrant where FFA + SoC is associated with higher costs but also higher QALYs; [redacted] of the simulations are located in the South-East quadrant where FFA + SoC is associated with higher QALYs, and lower costs compared to CBD + SoC.

The probabilistic mean ICER was [redacted] per QALY gained (Table 14) which is lower than the base case ICER [redacted]. The difference is explained by the incremental costs. While the weight of the patients in each age group is varied in the PSA, there is a cap applied on the dose per day for fenfluramine (26 mg/day), but there is no maximum dose per day for cannabidiol, leading to lower incremental costs of fenfluramine and therefore a lower probabilistic ICER value. Nevertheless, this suggest that the results of the cost effectiveness analysis are robust and consistent when considering inherent uncertainty in input parameters, with the ICER likely to fall within the cost-effectiveness threshold.

Figure 1. Cost-effectiveness plane FFA + SoC versus CBD w CLB + SoC

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; QALYs, Quality-Adjusted Life Years; SoC, Standard Of Care.

Table 14. Average results from the probabilistic sensitivity analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
CBD w CLB + SoC	[redacted]	3.68	-	-	-
FFA + SoC	[redacted]	2.86	[redacted]	0.82	[redacted]

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; FFA, Fenfluramine; ICER, Incremental Cost-Effectiveness Ratio; QALYs, Quality-Adjusted Life Years; SoC, Standard of Care.

Cost-effectiveness acceptability curves

The results from the cost-effectiveness acceptability curve are presented in Figure 2 below. The cost-effectiveness acceptability curve (CEAC) plots the probability that the intervention is cost-effective at a range of decision thresholds. The probability of being cost-effective at a threshold of £30,000 is [redacted].

Figure 2. Cost-effectiveness acceptability curve

Abbreviations: CBD, Cannabidiol; FFA, Fenfluramine.

New deterministic sensitivity analysis

Figure 3 presents a tornado diagram showing the twenty parameters with the greatest impact on the ICER, with descending ICER sensitivity.

Figure 3: Tornado plot: deterministic sensitivity analyses: FFA + SoC versus CBD w CLB + SoC

Abbreviations: CBD w CLB, Cannabidiol with Clobazam; EQ-5D, EuroQol 5 Dimension; FFA, Fenfluramine; GTC, Generalised Tonic-Clonic; HCRU, Healthcare Resource Use; SoC, Standard of Care; T+M, Titration and Maintenance.

New results for scenarios

Results of all updated scenario analysis and new scenarios (with and without severity modifier x 1.7 weighting applied to QALYs of patients and caregivers) are presented in Table 15. The original scenarios were presented page 179-180 of document "ID1651_Fenfluramine_LGS_Document B v2 [CON]".

Table 15. Summary of the scenario analyses explored and comparison to the base case

Parameter	Base case	Scenario analyses	FFA+SoC vs CBD w CLB SoC			ICER	ICER (severity modifier applied to patients & caregivers)
			Incremental costs	Incremental QALYs	Incremental QALYs (with severity modifier)		
Base case	**N/A**	**N/A**	[redacted]	**0.82**	**1.4**	[redacted]	[redacted]
Original scenarios updated (based on the new base case)							
	Varying the time horizon						
Time horizon	Lifetime	15 years	[redacted]	0.71	1.21	[redacted]	[redacted]
	Varying NMA dataset						
NMA dataset	GBA	EMA	[redacted]	0.85	1.44	[redacted]	[redacted]
	Varying the stopping rule						
Discontinuation (all treatment)	Applied if response <25%	Applied if response <50%	[redacted]	0.33	0.56	[redacted]	[redacted]
	Varying the discontinuation due to lack of efficacy for CBD (cycle 2)						
Discontinuation rate (CBD)	7.30%	19.60%	[redacted]	0.9	1.53	[redacted]	[redacted]
	Removing waning of efficacy						
Treatment efficacy (all treatment)	Waning	No waning	[redacted]	1.38	2.34	[redacted]	[redacted]
	Varying the waning for CBD (from cycle 10)						
% of patients undergoing waning	5.20%	19.60%	[redacted]	1.1	1.87	[redacted]	[redacted]

Parameter	Base case	Scenario analyses	FFA+SoC vs CBD w CLB SoC			ICER	ICER (severity modifier applied to patients & caregivers)
			Incremental costs	Incremental QALYs	Incremental QALYs (with severity modifier)		
	Varying the drug maintenance dosage						
CBD dosage	16 mg/kg/day	12 mg/kg/day	[redacted]	0.82	1.4	[redacted]	[redacted]
FFA dosage	0.413 mg/kg/day	0.7 mg/kg/day	[redacted]	0.82	1.4	[redacted]	[redacted]
CBD and FFA dosages	16 mg/kg/day (CBD) and 0.5 mg/kg/day (FFA)	12 mg/kg/day (CBD) and 0.7 mg/kg/day (FFA)	[redacted]	0.82	1.4	[redacted]	[redacted]
	Varying the utilities						
Utilities for patients and caregivers	Verdian EQ-5D	Verdian TTO	[redacted]	0.55	0.93	[redacted]	[redacted]
		Verdian VAS	[redacted]	1.08	1.84	[redacted]	[redacted]
		Lo TTO	[redacted]	0.71	1.21	[redacted]	[redacted]
		Lo VAS	[redacted]	0.46	0.79	[redacted]	[redacted]
		Auvin VAS	[redacted]	0.41	0.7	[redacted]	[redacted]
	Varying the mortality						
Mortality	Dependent of seizure frequency	Independent of seizure frequency	[redacted]	0.83	1.41	[redacted]	[redacted]
New scenarios added after reception of the clarification questions							
	Results for question B11c						
Stopping rule	Discontinue if <25% response at 3 months	Discontinue if <30% response at 6 months	[redacted]	1.13	1.93	[redacted]	[redacted]
	Results for question B14d						
Source of drop seizures per 28 days	Median point	Study 1601	[redacted]	0.82	1.4	[redacted]	[redacted]
	Results for question B16b						
FFA OLE data used for Cycle 2	3 month follow up data	6 month follow up data	[redacted]	0.82	1.39	[redacted]	[redacted]
	Results for question B17c						
Discontinuing patients due to AE	Cycle 5: 0.00% Cycle 6: 0.00%	Cycle 5: 1.31% Cycle 6: 0.99%	[redacted]	0.81	1.37	[redacted]	[redacted]

Parameter	Base case	Scenario analyses	FFA+SoC vs CBD w CLB SoC			ICER	ICER (severity modifier applied to patients & caregivers)
			Incremental costs	Incremental QALYs	Incremental QALYs (with severity modifier)		
	Results for question B23f						
Caregiver utility approach	Verdian et al. (2008) - EQ-5D	Disutilities using Auvin et al. (2021) applied to UK VAS norm	[redacted]	0.55	0.94	[redacted]	[redacted]
	Results for question B24b						
Cost of institutionalisation	Excluded	Included	[redacted]	0.82	1.4	[redacted]	[redacted]
	Results for question B27b						
Severity modifier	Not applied	Applied to patients only	[redacted]	1.03	N/A	[redacted]	[redacted]
Number of caregivers	1.8	2	[redacted]	0.88	1.5	[redacted]	[redacted]

Abbreviations: CBD w CBL, Cannabidiol with Clobazam; EMA, European Medicine Agency; EQ-5D, EuroQol 5 Dimension; FFA, Fenfluramine; GBA, Federal Joint Committee of Germany (Gemeinsamer Bundesausschuss); ICER, Incremental Cost-Effectiveness Ratio; kg, Kilogram; mg, Milligram; N/A, Not Applicable; SoC, Standard of Care; TTO, Time Trade-Off; VAS, Visual Analog Scale; QALYs, Quality-Adjusted Life Years.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Tuberous Sclerosis Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Tuberous Sclerosis Association (TSA) is the only UK charity focused on improving the lives of people affected by rare genetic disorder Tuberous Sclerosis Complex (TSC). We provide help for today and hope for tomorrow by: • Providing direction or a listening ear through our support and information services for the TSC community, including through our UK-wide TSA Support Line. • Organising events and opportunities across the UK and virtually for those affected by TSC, allowing the TSC community to come together and feel less alone. • Funding internationally-significant research into the causes, diagnosis, management and treatment of TSC that has the greatest impact on those affected by the condition. • Campaigning on behalf of the TSC community to ensure that the TSC community has consistent and meaningful access to social support and healthcare provision. You can find more about our charity at www.tuberous-sclerosis.org. The TSA does not have members, but we support over 4,000 people across the UK who are in contact with the charity including individuals living with TSC, their family, carers and friends.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	The TSA has a policy on working with the medicines industry which you can find here: https://tuberous-sclerosis.org/working-with-the-medicines-industry/ The TSA has received the following funding from the comparator company Jazz Pharma Ltd in the last 12 months: • £22,000 funding to support TSC Clinics Network secretariat and the TSC Clinics Education meeting 2023 • £577 involvement fee for TSA Joint Chief Executive to take part in a Europe-wide Patient Advisory Group on Epidyolex

<table>
<tr><td>If so, please state the name of the company, amount, and purpose of funding.</td><td></td></tr>
<tr><td>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</td><td>No</td></tr>
<tr><td>5. How did you gather information about the experiences of patients and carers to include in your submission?</td><td>We spoke with four families in the UK who care for someone living with TSC and Lennox-Gastaut seizures to inform this submission. All four patients had refractory epilepsy with only a partial response to treatment with anti-epileptic drugs.

Details of the families:
<table>
<tr><th></th><th>Age of patient (as of Sept 2021)</th><th>Sex of patient</th><th>Co-diagnosis of Lennox-Gastaut Syndrome</th><th>Participated in clinical trial</th></tr>
<tr><td>Family A</td><td>16 years</td><td>Male</td><td>Yes</td><td></td></tr>
<tr><td>Family C</td><td>37 Years</td><td>Female</td><td>Yes</td><td></td></tr>
<tr><td>Family F</td><td>7 years</td><td>Male</td><td>Yes</td><td></td></tr>
<tr><td>Family G</td><td>15 Years</td><td>Male</td><td>Yes</td><td></td></tr>
</table>
</td></tr>
</table>

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Tuberous Sclerosis Complex (TSC) is a rare genetic condition. Every month around 10 babies are born with TSC in the UK. TSC causes growths to develop in different organs around the body, such as the brain, lungs, kidneys, eyes, heart and skin. These growths are sometimes referred to as benign (non-cancerous) tumours. When they cause problems, it is mainly because of their size and where they are growing in the body. Eight out of ten people with TSC have epilepsy that typically starts in infancy and is difficult to control using epilepsy medication. Five out of every ten people with TSC have learning disabilities. Around three in ten people have profound learning disabilities and need round-the-clock care and life-long support from their families or move into residential care to receive this high level of support. Nine out of ten people with TSC develop TSC-associated neuro-psychiatric disorders (TAND) which can include autism spectrum disorders, attention deficit hyperactivity disorders, aggression, depression, anxiety and sleep disorders which have a serious impact on family life. Different types of epilepsy - called the 'epilepsy syndrome' - can occur in children with TSC. The two most common epilepsy syndromes are: (1) West syndrome: this is diagnosed on the basis of infantile spasms, the age at onset of spasms (under 12 months of age) and a typical EEG appearance - called hypsarrhythmia. (2) Lennox-Gastaut syndrome (LGS): this is diagnosed on the basis of different seizure types that occur in a child (particularly tonic, tonic-clonic and partial seizures), the age at onset of the different types of seizures (between 1 and 6 years of age) and a typical EEG appearance (called slow spike and slow wave activity). It is important to understand that a child with TSC may start with West syndrome in the first year of life and then evolve (change) into Lennox-Gastaut syndrome in the second or third year of life. When a TSC diagnosis is made, the whole family is affected both physically and mentally. A secondary diagnosis of LGS can have even deeper impact on families' quality of life and on their ability to cope with the disease and support the child's ability to reach an acceptable level of well-being. Families and carers have reported the experience of losing control and feelings of despair and helplessness. They have shared their day-to-day struggles with their children's behaviour including what it's like to manage the rage, anger and mood swings. It not only affects their relationship with their child who has TSC but also their relationship with each other and the wider family circle including siblings who feel left-out and neglected as the parents focus on the needs of their child with TSC. In many instances, parents have had to give up work to become full time carers. There are additional costs for home improvements associated with TSC: the TSA Support Line receives regular calls from parents wishing to access our small family grants to purchase fridges to store medication or batches of ketogenic food, replace washing machines, tumble dryers, beds and bedding urgently needed to cope with the impact of urinary and faecal incontinence, and invest in improvements to make back gardens secure and safe for children with no sense of danger to play in.

	One family with a young child who has co-diagnosis of TSC and LGS told us (family F): “Our lives changed completely when our son who is now seven years old was diagnosed with TSC as it impacts on every member of the family. We are never in a stable situation. Our son is unable to speak, he is unbalanced physically, he has brain damage to the left side, which impacts the right side of body, he has a buggy and can’t do long walks. He can’t eat, he can’t drink out of a straw. He has subclinical seizures and shows signs when they are coming on. He has tired moments and attends a special needs classroom in a mainstream school. He has one to one care and can’t be left alone – he must be with an adult at all times. He is a lovely boy, with strong emotional intelligence, and the intellectual intelligence of a 3 to 4 year-old. I gave up my job as a CEO 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 as our son has autistic traits. We are unable to attend events such as weddings, and organising day care for him is hard work. We have lots of support from aunts, uncles and grandparents. Our son disrupts social events, screaming to go home after a few minutes. This affects my and my husband’s time with his younger sister. We are always looking for an easy escape route at social events and when out and about. His behaviour can upset his sister. He is spoon fed and eats blended foods.” A mother shared the impact of TSC and LGS on her 16 years-old son (family A): “He was diagnosed at 12 months old and seemed to be developing normally until about 5-years old. He has behaviour issues. He gets cross and throws things across the room, he has anger issues and can be aggressive. Our son goes to respite, he is very full on and challenging for me. He shouts a lot, so we avoid outings. When younger cousins come to stay over, he has to be watched at all times – he sometimes throws things across the room, and if he wants to run across the room he does so. He has no concept of danger. He is very vulnerable. I can’t remember the last time I slept through the night or had more than eight hours of sleep. I can’t take him out on my own - he is too big to control when a seizure hits. He relies on his family for thinking as he doesn’t understand danger.” One mother with an adult daughter living with TSC and LGS (37 years old) told us (family C): "She has to have two people with her 24 hours a day because of seizures and behaviour. She has no idea of danger, so she could just walk into the road and be hit by a car and she wouldn’t know what to do. You have to keep everything out of her way as she will drink whatever is in the cupboard, she would pick up and eat whatever is lying around so she has to be monitored. She has had problems with breathing as she doesn’t chew properly so it becomes a choking hazard. She has to be fed to make sure she has swallowed properly otherwise she’ll continue eating even whilst choking. You cannot leave her with food, she would choke, she would die. Food has to be cut up or mashed.”

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	LGS can be difficult to treat with anti-epileptic medicines, with most children and adults with LGS requiring a combination of medicines and other therapies. TSC patients, including those with LGS, often try between 15 and 20 anti-epileptic drugs. Most of them state that there tends to be a "honeymoon period" where the prescribed drug works for a short duration, then it stops working and they move to next medication. Family C told us that their adult daughter has tried every medication available for epilepsy: "Some of them seem to work, but then she gets used to it and they stop. They go through cycles and we have gone through all of the drugs and been told there is nothing new on the horizon. With some drugs she got very aggressive and bad tempered, so we took her off these as we didn't think they were doing her any good". Others have tried non-interventional treatments like vagal nerve stimulation, ketogenic diet or surgery with varying degrees of success. Three patients went through vagal nerve stimulation (families A, C and G). It had to be removed in one patient (family G) due to post-surgery complications. Two parents told us that the vagal nerve stimulation has had a positive impact on their children's epilepsy and reduced the severity of seizures in both cases (families A and C). Family A told us that their daughter had undergone corpus callosotomy but it didn't work.

8. Is there an unmet need for patients with this condition?	When we asked people living with TSC and LGS, and their families and carers to share the aspects of living with TSC that are not met by currently available treatments, majority of families said that their child's seizures, epilepsy and behaviour problems are the areas that need addressing urgently. These areas impact the most on their day-to-day lives and they would welcome help and support in addressing these unmet needs. Family A told us that the aspect of TSC that they struggle most with their 16 years-old son are: "His rages, his temper, his shouting. His mood changes very suddenly. He still has seizures during the night." The statement above is in line with typical manifestations of TSC. Epilepsy is the most common neurological feature of TSC, affecting approximately 84 per cent of people living with the condition (Kingswood et al, 2017). More than 50 per cent of people with TSC who have epilepsy will not respond to standard anti-epilepsy medicines and may need an alternative form of treatment (Wylie et al. 1993, Pellock et al. 2001). One in every two people living with TSC have learning disabilities such as intellectual impairment and problems with attention and memory (Gillberg et al. 1994; Harrison & Bolton, 1997; Joinson et al. 2003, Bolton et al. 2015). Around 30 per cent of these individuals have profound learning disabilities, and around 20 per cent have an IQ slightly below the normal range (De Vries et al. 2015). Fifty per cent of people living with TSC have an IQ in the same range as the general population (De Vries et al. 2015). Uncontrolled epilepsy is believed to be a contributing factor to learning disabilities in people living with TSC (Bolton et al. 2015).

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The people living with TSC who will benefit most are those with co-diagnosis of LGS. It is possible that younger patients will derive extra benefits from getting their epilepsy under control at an early age, because uncontrolled epilepsy is believed to be a contributing factor to learning disabilities in people living with TSC (Bolton et al. 2015). Epilepsy is generally more difficult to control for individuals living with TSC who have moderate or severe learning disabilities. There is a wide range of severity in TSC. Some people living with TSC are so mildly affected that they experience few problems. Five out of every ten people with TSC have learning disabilities. Around three in ten people have profound learning disabilities and need round-the-clock care and life-long support from their families or move into residential care to receive this high level of support. Early onset of epilepsy has been associated with a higher frequency and severity of intellectual disability (Gupta at al, 2020) and a slower gain in intellectual ability, which has also been linked to seizure severity (Tye et al, 2020). People with TSC who have epilepsy have been shown to have lower health-related quality of life (HRQL) compared with those without epilepsy (Vergeer et al, 2019). All age groups will have a better quality of life and a lower risk of serious co-morbidity and mortality (such as SUDEP) if fenfluramine hydrochloride can provide better seizure control.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes. One in every two people living with TSC have learning disabilities such as intellectual impairment and problems with attention and memory (Gillberg et al. 1994; Harrison & Bolton, 1997; Joinson et al. 2003, Bolton et al. 2015). Around 30 per cent of these individuals have profound learning disabilities, and around 20 per cent have an IQ slightly below the normal range (De Vries et al. 2015). Fifty per cent of people living with TSC have an IQ in the same range as the general population (De Vries et al. 2015). Uncontrolled seizures are believed be a contributing factor to learning disabilities in people living with TSC (Bolton et al. 2015).

Other issues

13. Are there any other issues that you would like the committee to consider?	Carers of people with TSC have significantly lower quality of life and higher anxiety and depressive symptoms (Rentz et al, 2015). Parents and carers have also reported anxiety regarding the unknown future for the person with TSC that they care for and the possibility of medical emergencies, new symptoms, repeated surgeries and side effects of treatments. The need for supervision and monitoring of patients with TSC due to LGS seizures and TAND manifestations also contributes to the burden on carers and wider family members (MacDonald 2019). TSC can impact on the life of the whole family, with activities centred around the patient's needs and siblings consequently missing out on family time.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Epilepsy is the most common neurological feature of TSC, affecting eight out of ten of people living with the condition, some with co-diagnosis of Lennox-Gastaut seizures. Over half of people with TSC who have epilepsy will not respond to standard anti-epilepsy medicines and may need an alternative form of treatment. • Early onset of seizures and epilepsy have been associated with a higher frequency and severity of intellectual disability and a slower gain in intellectual ability, which has also been linked to seizure severity. • When we asked people living with TSC and their families and carers to share the aspects of living with TSC that are not met by currently available treatments, all seven families said that their child's seizures, epilepsy and behaviour problems are the areas that need addressing urgently. These areas impact the most on their day-to-day lives and they would welcome help and support in addressing these unmet needs.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	Medicines Value and Access Pharmacist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? No A specialist in the clinical evidence base for this condition or technology? No Other (please specify): Medicines Value and Access team
5a. Brief description of the organisation (including who funds it).	NHS England
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	n/a
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	n/a
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	n/a

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	n/a
9a. Are any clinical guidelines used in the	n/a

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	n/a
9c. What impact would the technology have on the current pathway of care?	n/a
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	n/a
10a. How does healthcare resource use differ between the technology and current care?	n/a
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	n/a
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	n/a

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	n/a
11a. Do you expect the technology to increase length of life more than current care?	n/a
11b. Do you expect the technology to increase health-related quality of life more than current care?	n/a
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	n/a

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	n/a

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	n/a
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	n/a
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	n/a
16a. Is the technology a 'step-change' in the management of the condition?	n/a

16b. Does the use of the technology address any particular unmet need of the patient population?	n/a
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	n/a

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	n/a
18a. If not, how could the results be extrapolated to the UK setting?	n/a
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	n/a
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical	n/a

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	n/a
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA615?	n/a
21. How do data on real-world experience compare with the trial data?	n/a

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	n/a
22b. Consider whether these issues are different from issues with current care and why.	n/a

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• At triage meeting with NICE and NHS England – there was discussion around comparators. • Cannabidiol should be considered as a comparator as fenfluramine would be offered in the same position within the treatment pathway of LGS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating Lennox-Gastaut seizures and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	J Helen Cross
2. Name of organisation	UCL Great Ormond Street Institute of Child Health
3. Job title or position	The Prince of Wales's Chair of Childhood Epilepsy, & Director
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Lennox-Gastaut syndrome? ☐ A specialist in the clinical evidence base for Lennox-Gastaut syndrome or fenfluramine? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for Lennox-Gastaut syndrome? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Lennox Gastaut syndrome is an early onset developmental and epileptic encephalopathy, characterised by multiple seizure types, and neurocognitive delay. Seizures are generally resistant to medication. IN the longer term 7% become seizure free. Aims of treatment are to have seizures under optimal

	control, minimise injury from drop attacks, and minimise side effects, particularly behavioural side effects.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction in seizures by >30%, particularly drop attacks, with no deterioration in behaviour.
10. In your view, is there an unmet need for patients and healthcare professionals in Lennox-Gastaut syndrome?	Despite newer treatments becoming available, this remains one of the most difficult epilepsy to treat – with multiple seizure types, including drop attacks and non convulsive episodes remaining troublesome. There is therefore a real unmet need for new treatments
11. How is Lennox-Gastaut syndrome currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Lennox Gastaut syndrome may evolve from another epilepsy type (eg infantile spasms) or occur de novo age 3-5 years with no previous history. This is an electroclinical syndrome – the diagnosis is based on the seizure types and EEG findings. There are many different causes The treatment pathway will likely be valproate as first line, with addition of lamotrigine if incomplete benefit. (NICE guidelines 217). Subsequent treatments considered are cannabidiol, clobazam, rufinamide and topiramate. Ketogenic diet is also utilised. It is not unusual for combination therapy to be required; monotherapy is unlikely to be of benefit alone
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	This should be specialist prescription (paediatric neurologist/neurologist); these children/adults should already be under specialist care. Adults may be under Learning disability consultants. There will be a need for cardiac monitoring (echocardiograms); access to this investigation will be required

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	This is a medication that has demonstrated benefit in children resistant to existing treatments for seizures associated with Lennox Gastaut syndrome. By reduction of seizures (and the most effect seen in trial was to generalised tonoc clonic seizures) I do expect an increase in health related quality of life in those where useful. It is difficult to comment on length of life, although reduction in generalised tonic clonic seizures reduces the risk of Sudden Unexplained Death in Epilepsy
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The need for regular cardiac monitoring, namely echocardiogram would be an additional burden for the families – in older individuals with significant behaviour disorder this may be challenging.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would suggest this medication is trialled as third line treatment, should treatment with older medications has failed to improve seizures, or significant
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Within the trial caregiver global impression of change showed significant improvement – it is difficult to otherwise accurately assess QOL in this population. If convulsive seizures reduce, without adverse effects particularly on behaviour this is likely to result in substantial benefit
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The benefit from fenfluramine in Lennox Gastaut syndrome does not appear to be as dramatic as that seen in Dravet syndrome, but still provides a further treatment option in an extremely complex disease.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most side effects reported are decreased appetite or somnolence – both of which respond to adjustments in dose. An adverse effect on behaviour has not been common, which is a distinct advantage in this population.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	The trial reflects current UK practice. The measurable effects on seizures were documented- drop attacks particularly. Furthe the global impression of change.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No – but only limited clinical trials in this population
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA615?	N/A
23. How do data on real-world experience compare with the trial data?	Not available
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	Adult population with Lennox Gastaut syndrome may not be under the care of a specialist and therefore may not have access to new treatments.

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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

There are few treatment options; few lead to significant benefit in seizure control

Fenfluramine provides a further treatment option in resistant cases

Click or tap here to enter text.

Thank you for your time.

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Single Technology Appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Clinical expert statement

Information on completing this form

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Treating Lennox-Gastaut seizures and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Rhys Thomas
2. Name of organisation	Newcastle University, Royal Victoria Infirmary Newcastle
3. Job title or position	Reader in Epilepsy, Honorary Consultant in Epilepsy
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Lennox-Gastaut syndrome? ☒ A specialist in the clinical evidence base for Lennox-Gastaut syndrome or fenfluramine? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for Lennox-Gastaut syndrome? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	It is important that you really understand the impact of seizures for people with Lennox Gastaut syndrome (LGS).

	Everyone with LGS has an intellectual disability. It always has a childhood onset and there are many structural, genetic and cryptogenic causes. These may be considered to be 'fixed' features. In contrast seizures are dynamic meaning that they are variable. These can be aggravated by illness, poor sleep or stress, they can be improved by appropriately chosen antiseizure medications (ASM). What is singular about LGS is that a) Injudicious ASM prescription can aggravate seizures b) ASMs that sedate can aggravate the impact of the intellectual disability and produce challenging behaviour c) ASMs that sedate can mimic the triggers of seizures such as illness and sleep depravation. Furthermore the seizures in LGS are particularly cruel. They are not just convulsive (generlaiused tonic clonic seizures) but they may not stop by themselves (status epilepticus). They can be injurious such as drop seizures (atonic seizures). They can be hard to identify and disturb waking hours (atypical absence), and sleep (tonic seizures). Seizures are the most important *modifiable* feature of LGS.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Significance may be a) Fewer emergency admissions, or fewer intensive care admissions b) More seizure free days, or days without the need for rescue medication c) More 'on days' or good days – fewer drowsy or challenging days d) A reduction of a third or more for dangerous seizures (atonic, convulsive)

10. In your view, is there an unmet need for patients and healthcare professionals in Lennox-Gastaut syndrome?	Yes; particularly for drugs that have a moderate seizure impact with a minor likelihood to sedate
11. How is Lennox-Gastaut syndrome currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Paediatricians will be able to diagnose LGS as it occurs and take advantaghe of the new ILAE (2022) definitions and new (2022) NICE guidance. There are expert guides (Cross et al 2017, Front Neurol). Chin et al Frontiers in Neurol 2021 identified 34 guidelines for LGS. Paediatric pathways are laid out in the NICE guidance and are supported by regional networks, and the joint working of paediatric neurologists and community paediatricians. For adults there are also expert guides (Montouris E&B et al 2020) but the treatment pathways are less distinct. There are epilepsy experts at neuroscience centres, most neurology centres and few district general hospitals. Most LGS care will be in secondary or tertiary care, with some support in some regions from intellectual disability psychiatrists where competence allows. The technology would initially consolidate LGS care in secondary and tertiary centres as the expertise in prescription learned in Dravet syndrome (such as Blueteq) and the requirement for echos best suits this environment. The critical support that these teams have is an epilepsy specialist nurse.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	The technology is current being used for another rare childhood onset epilepsy, Dravet syndrome.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The drug will be used in a similar way to existing drugs - in some much as it will be initiated by specialists and titrated to effect. Fenfluramine titration is rapid compared to similar drugs and the clinical impact can be seen rapidly. Unlike cannabidiol there is no need to co-prescribe clobazam. The drug-drug interactions of fenfluramine appear less clinically significant than cannabidiol's.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. My experience of introducing cannabidiol to my region and then fenfluramine for Dravet syndrome leads me to expect there to be clinical benefits. Namely improved seizure control and improved alertness, less sedation.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Fenfluramine has a side effect in some people of weight loss. Patients who are already underweight may not tolerate this (conversely this side effect is a boon for others).
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The need for echocardiogram surveillance will be challenging in some regions. I predict that centres where patients travel large distances and cross IT systems will have the greatest challenges here. (IT systems for ordering and reviewing results).
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It would be reasonable to use a general rule of 'last drug in first one out' if there is no reduction in seizure control after a typical observational period of approximately six months, and to withdraw the drug. We do not think it is truly disease modifying and so if there is no seizure benefit it should be withdrawn.

	A seizure improvement of 30% or more would normally be sufficient for the drug to continue – or in special circumstances, less than this but – for example, the seizures are shorter /less intense.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. It is hard to measure the impact on parents/care givers, siblings accurately. The importance to a family of seizure free days means that the family may be able to leave the house. The importance of seizure free nights is that a parent may be able to sleep and sleep is a critical fuel for emotional and cognitive resilience. The importance of seizures being less intense and less often on paid carers is that they may stay long term to support this young adult, rather than seek employment in another less draining care setting. Weight loss may well extend life – we know that people with intellectual disability and epilepsy die much earlier and are prone to metabolic syndrome and its complications. There may be unintended benefits of the enhanced cardiac surveillance.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Fenfluramine two really attractive qualities 1) The time to maximum dose and maximum seizure benefit is comparatively short, which means the time of exposing a young person/adult to a new therapy is reduced. You not only get to where you're going quickly, but you know if you're going to succeed. If successful this also allows for more rapid de-prescription of other ASMs. 2) It is a minimally sedating ASM and so much less likely to trigger seizures, such as tonic seizures, in LGS.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Only weight loss in a minority, as above.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Broadly yes. This is a complex cohort in which to recruit and so it perversely more representative than other RCTs and trials. This is a not only because LGS is a rare condition, with multiple causes, but also that if you started to draw up major exclusions, you'd decimate your possible patient pool. More work in older adults with LGS would be nice to see, but not necessarily needed.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Fenfluramine for LGS is available in other territories so colleagues may have their own private databases, be performing local and regional audits.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA615?	No
23. How do data on real-world experience compare with the trial data?	In epilepsy, surprisingly well. Short-term seizure control can invariably be extrapolated to longer term control. Tolerability less so – but this is less of an issue here as fenfluramine is a well-tolerated drug with few late emergent side effects. Clinicians tend to be more cautious in the real world, using smaller doses and titrating up more slowly.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	Some systemic inequalities exist It is easier to contact your clinical team and particularly your specialist nurse if you speak English. You always need an advocate to support you if you have an intellectual disability, such as in LGS.

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Regulation around ASMs in pregnancy is poor and so we have insignificant safety data for our drugs when they come to market, which means that we are less likely to start new drugs in women of child-baring potential. This is not an issue in LGS.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Lennox Gastaut is difficult to treat and seizure aggravation, sedation limits current therapies

Fenfluramine is rapidly titrated and the clinical effect is evident rapidly – which improves safety

Fenfluramine is less sedating than some other anti seizure medicines and has few drug-drug interactions

Weight loss is measurable and is not a dangerous side effect

Seizure severity and seizure free days are as important an impact for some people as absolute seizure reduction

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Clinical expert statement

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send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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NICE National Institute for Health and Care Excellence

Part 1: Treating Lennox-Gastaut seizures and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Victoria Tsang
2. Name of organisation	Neonatal and Paediatric Pharmacy Group
3. Job title or position	Highly Specialised Paediatric Pharmacist – Neurology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with Lennox-Gastaut syndrome? ☐ A specialist in the clinical evidence base for Lennox-Gastaut syndrome or fenfluramine? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links
8. What is the main aim of treatment for Lennox-Gastaut syndrome? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Help with seizure control and symptom control.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in frequency of drop or convulsive seizures
10. In your view, is there an unmet need for patients and healthcare professionals in Lennox-Gastaut syndrome?	For patients whom fail on all current treatment, fenfluramine could provide another final treatment option to help control symptoms and improve quality of life
11. How is Lennox-Gastaut syndrome currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently they will try conventional anti-seizure medications as mono-therapy and as a combination therapy. As per current epilepsy in children guideline found via: Epilepsies in children, young people and adults (nice.org.uk) If anti-seizure medications fails, and patients are eligible they will be started on cannabidiol under the care of a tertiary centre in combination with clobazam (Overview | Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome | Guidance | NICE) Fenfluramine could be a fourth treatment option if all the above fails. However there would be extra resources needed to ensure patient safety prior to starting fenfluramine.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Fenfluramine is currently used for dravet syndrome (Fenfluramine for treating seizures associated with Dravet syndrome (nice.org.uk)). It could be used in a similar way for patients with LGS. Providing another treatment option for this patient cohort. Fenfluramine should only be used under the care of a specialist (i.e tertiary centre) with a specialised multi disciplinary team whom care provide expert advice and care for the patient. To ensure fenfluramine can be provided safely for the patients extra resources would be required to ensure patients can be safely initiated and monitored whilst

	on fenfluramine. Currently it is recommended to have a baseline echocardiogram and to monitor every 6 months for 2 years. This will have a significant impact on local cardiologists' workload and will need to be taken into account. Furthermore more specialist teams' time will be required to discuss potential cases in MDTs, to write up prescriptions and monitor patient's progress. Furthermore more administrative time will be spent (e.g. completing blueteq, ordering monitoring parameters etc).
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	It may add and improve quality of life for patient cohort whom have failed all current treatment options.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Nil comment
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	See answer to question 12. Not expected that fenfluramine will be easier or more difficult to use for patients.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients must be discussed at an MDT in a specialise centre prior to starting treatment
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	-
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	-
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	-
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	-

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	-
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA615?	No
23. How do data on real-world experience compare with the trial data?	-
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	-

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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Single Technology Appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Lennox-Gastaut syndrome or caring for a patient with Lennox-Gastaut syndrome. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

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Patient expert statement

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with Lennox-Gastaut syndrome

Table 1 About you, Lennox-Gastaut syndrome, current treatments and equality

1. Your name	Lisa Suchet
2. Are you (please tick all that apply)	☐ A patient with Lennox-Gastaut syndrome? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with Lennox-Gastaut syndrome? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Lennox-Gastaut syndrome? **If you are a carer (for someone with Lennox-Gastaut syndrome) please share your experience of caring for them**	My husband and I have a 9yrs old son with Tuberous Sclerosis Complex (TSC) and a secondary diagnosis of atypical LG.
7a. What do you think of the current treatments and care available for Lennox-Gastaut syndrome on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**a) Treatments are limited and tend to work on the same pathways in the brain as I understand, so once you have tried a handful of drugs and failed to gain seizure control, you probably won't be able to. It then becomes a battle of combinining different drugs for the best control possible and balancing those with side effects and toxicity.** **b) Identically.**
8. If there are disadvantages for patients of current NHS treatments for Lennox-Gastaut syndrome (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Well, firstly, they 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. At one point he used to repeatedly wretch over the loo. At another time he lost his apetite to such an extent he lost a third of his body weight and was anorexic. LG for my son includes regular seizures (weekly), subclinical seizures (invisilble ones), but where he displays pre and post seizure behaviour (fatigue, meltdowns, feeling unwell), learning disabilities and sensory processing disorder. This makes regular blood tests required for exisiting drugs very traumatic for him, especially if he has just had a seizure; it makes certain flavours and textures difficult for him to swallow. He was on a granular medication but started to reject taking it (I tried putting it in my own mouth and it was literally like eating a mouthful of sand, how he coped for as long as he did with this I do not know), so we had to move to a liquid solution which now requires 26mls syringed into his mouth every day which is a lot. Other meds cause terrible mouth ulcers. We have to mix others with powdered multivits, so we can syringe them into his mouth as they taste so bad. Todd also

	has to do regular urine tests which he handles well, but its all due to the drugs he is on.
9a. If there are advantages of Fenfluramine over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Fenfluramine help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**I am sorry but I am not familiar with the drug, only the condition it aims to treat.** **However, I would say that providing a new option for LG patients would be very welcome. It might be tolerable (fewer side effects) and more effective than others available.**
10. If there are disadvantages of Fenfluramine over current treatments on the NHS please describe these. For example, are there any risks with Fenfluramine? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I am unaware due to being unfamiliar with this drug
11. Are there any groups of patients who might benefit more from Fenfluramine or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I am unaware due to being unfamiliar with this drug
12. Are there any potential equality issues that should be taken into account when considering Lennox-Gastaut syndrome and Fenfluramine? Please explain	Just be aware that if certain tests are required to be on it, prescribers need to take in to account the needs of patient e.g. regular blood tests are hugely traumatic for sensory people, understanding the need to take drugs and new drugs can be difficult for LG patients who are learning disabled. They might refuse to take them

if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	so taste and texture need to be considered. Side effects can be very difficult for them to communicate if they have speech and language disabilities, including for positive side effects. Its often a guessing game for carers as to how they are being affected by a drug, its not just a case of waiting to see if the seizures stop or change, which can often take weeks anyway. Contraindications are always a consideration as LG patients are usually on a myriad of AEDs. I would also add that where a patient might be having therapy e.g. speech and language, physio, OT; it is unhelpful when drug side effects cause any progress achieved with the therapies to regress.
13. Are there any other issues that you would like the committee to consider?	This drug should be considered as something that could be a life line to LG patients who have tried every other drug available and still have seizures which limited their own quality of life and that of their carers.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- LG is hugely debilitating for patients and their families/carers – issues include learning diabilities, meltdowns and challenging behaviour, seizures at any moment, risk of injury from seizures. My son complains he feels ill a dozen times a day, every single day.
- Most LG patients have tried a myriad of drugs, without success and suffer various side effects
- This drug should be considered as something that could be a life line to LG patients who have tried every other drug available and still have seizures which limited their own quality of life and that of their carers.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Patient expert statement

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Produced by Kleijnen Systematic Reviews (KSR) Ltd in collaboration with Maastricht University Medical Center+ (UMC+)

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Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AR	Aortic regurgitation
AS	Atonic seizure
ASM	Anti-seizure medication
BMI	Body mass index
BNF	British National Formulary
BRIEF®-2	Behaviour Rating Inventory of Executive Function® – Second Edition
CADTH	Canadian Agency for Drugs and Technologies in Health
CBD	Cannabidiol
CBZ	Carbamazepine
CBD + CLB	Cannabidiol with clobazam
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CGI-I	Clinical global impression-improvement
CI	Confidence interval
CiC	Commercial in confidence
CLB	Clobazam
CM-DBS	Centromedian deep brain stimulation
CMH	Cochran-Mantel-Haenszel
CMZ	Carbamazapine
COVID-19	Coronavirus disease 2019
CrI	Credible interval
CRD	Centre for Reviews and Dissemination
CRI	Cognitive Regulation Index
CS	Company submission
CSR	Clinical Study Report
CUA	Cost-utility analysis
CVD	Cardiovascular disease
CZP	Clonazapam
DARE	Database of Abstracts of Reviews of Effects
DIC	Deviance information criterion
DS	Dravet syndrome
DSA	Deterministic sensitivity analysis
DSF	Drop seizure frequency
E2080	Rufinamide
EAG	Evidence Assessment Group
EBM	Evidence-based medicine
ECG	Electrocardiogram
ECHO	Echocardiogram
ECM	Established clinical management
ED	Emergency Department
EEG	Electroencephalogram

EMA	European Medicine Agency
EMD	Estimated median difference
EOS	End of Study
EQ-5D	EuroQoL-5 Dimensions
ESC	Epilepsy Study Consortium
FDA	Food and Drug Administration
FE	Fixing errors
FEL	Felbamate
FFA	Fenfluramine
FV	Fixing violations
GBA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GEC	Global Executive Composite
GP	General Practitioner
GTC	Generalised tonic-clonic
HADS	Hospital Anxiety and Depression Scale
HAS	Haute Autorité de Santé
HCRU	Health care resource use
HL	Hodges-Lehmann
HRQoL	Health-related quality of life
HS	Health State
HS	Hemiclonic seizure
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Unit
ICUR	Incremental cost-utility ratio
INAHTA	International HTA Database
IQR	Interquartile range
IQWiG	Institute for Quality and Efficiency in Health Care
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KD	Ketogenic diet
kg	Kilogram
KSR	Kleijnen Systematic Reviews Ltd
LAM	Lamotrigine
LEV	Levetiracetam
LGS	Lennox-Gastaut syndrome
LTG	Lamotrigine
LYs	Life years
MA	Marketing authorisation
MD	Mean difference
mg	Milligram
mITT	Modified intention-to-treat
MJ	Matters of judgement
MS	Myoclonic seizure
N	Sample size
N/A	Not applicable
NG	National Guideline
NHB	Net health benefit

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NL	Netherlands
NMA	Network meta-analysis
NR	Not reported
NS	Not significant
OLE	Open label extension
OR	Odds ratio
PAH	Pulmonary arterial hypertension
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PCA	Prescription cost analysis
PHT	Phenytoin
PICOS	Population, intervention, comparison, outcomes and study type
PP	Per protocol
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
QOLCE	Quality-of-life in childhood epilepsy
RCI	Reliable Change Index
RCT	Randomised controlled trial
RFM	Rufinamide
RoB	Risk of Bias
RR	Risk ratio
RUF	Rufinamide
RWE	Real world evidence
SAE	Serious adverse event
SAF	Safety
SD	Standard deviation
SE	Standard error
SGTC	Secondarily generalised tonic-clonic
SLR	Systematic literature review
SM	Severity modifier
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single Technology Appraisal
SUCRA	Surface under the cumulative ranking
SUDEP	Sudden unexpected death in epilepsy
TA	Tonic atonic
TA	Technology Appraisal
TAK-935	Soticlestat
T+M	Titration and Maintenance

tDCS	Transcranial deep cortical stimulation
TEAE	Treatment emergent adverse event
TOP	Topiramate
TPM	Topiramate
TRAE	Treatment-related adverse event
TTO	Time trade-off
TS	Tonic seizure
UK	United Kingdom
UMC+	University Medical Center+
US	United States
USA	United States of America
VAS	Visual analogue scale
VGS	Valgus nerve stimulation
VHD	Valvular heart disease
VNS	Valgus nerve stimulation
VPA	Valproate
WTP	Willingness-to-pay
WHO	World Health Organization

Table of Contents

Abbreviations **3**

Table of Tables **9**

Table of Figures **12**

1. EXECUTIVE SUMMARY **13**

1.1 Overview of the EAG's key issues 13
1.2 Overview of key model outcomes 14
1.3 The decision problem: summary of the EAG's key issues 14
1.4 The clinical effectiveness evidence: summary of the EAG's key issues 16
1.5 The cost effectiveness evidence : summary of the EAG's key issues 20
1.6 Other key issues 23
1.7 Summary of the EAG's view 24

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM **26**

2.1 Population 29
2.2 Intervention 29
2.3 Comparators 30
2.4 Outcomes 31
2.5 Other relevant factors 33

3. CLINICAL EFFECTIVENESS **37**

3.1 Critique of the methods of review(s) 37
3.1.1 Searches 37
3.1.2 Inclusion criteria 39
3.1.3 Critique of data extraction 41
3.1.4 Quality assessment 42
3.1.5 Evidence synthesis 45
3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these) 69
3.2.1 Details of the included trials 69
3.2.2 Statistical analysis of the included trials 79
3.2.3 Baseline characteristics in the included trials 83
3.2.4 Risk of bias in the included trials 88
3.2.5 Efficacy results in the included trials 89
3.2.6 AEs in the included trials 97
3.2.7 Ongoing studies 101
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison 101
3.4 Critique of the indirect comparison and/or multiple treatment comparison 114
3.4.1 Results of the NMA of fenfluramine versus cannabidiol 114
3.4.2 Methodology of the NMA 123
3.5 Additional work on clinical effectiveness undertaken by the EAG 125
3.6 Conclusions of the clinical effectiveness section 125

4. COST EFFECTIVENESS **128**

4.1 EAG comment on company's review of cost effectiveness evidence 128

4.1.1 Searches performed for cost effectiveness section 128
4.1.2 Inclusion/exclusion criteria 131
4.1.3 Conclusions of the cost effectiveness review 133
4.2 Summary and critique of company's submitted economic evaluation by the EAG. 133
4.2.1 NICE reference case checklist 133
4.2.2 Model structure 134
4.2.3 Population 137
4.2.4 Interventions and comparators 138
4.2.5 Perspective, time horizon and discounting 141
4.2.6 Treatment effectiveness and extrapolation 141
4.2.7 AEs 147
4.2.8 HRQoL 147
4.2.9 Resources and costs 151
4.2.10 Severity 154
4.2.11 Uncertainty 155

5. COST EFFECTIVENESS RESULTS 157

5.1 Company's cost effectiveness results 157
5.2 Company's sensitivity analyses 159
5.3 Model validation and face validity check 159
5.3.1 Face validity assessment 159
5.3.2 Technical verification 159
5.3.3 Comparisons with other technology appraisals 160
5.3.4 Comparison with external data used to develop the economic model 160
5.3.5 Comparison with external data not used to develop the economic model 160

6. EAGs ADDITIONAL ANALYSES 162

6.1 Exploratory and sensitivity analyses undertaken by the EAG 162
6.1.1 EAG base-case 162
6.1.2 EAG exploratory scenario analyses 163
6.1.3 EAG subgroup analyses 163
6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG 166
6.3 EAG's preferred assumptions 174
6.4 Conclusions of the cost effectiveness section 174

7. REFERENCES 176

Table of Tables

Table 1.1: Summary of key issues 13

Table 1.2: Key issue 1: The comparator definition in the decision problem is too narrow 15

Table 1.3: Key issue 2: The outcomes of 'seizure frequency' is restricted to drop seizures in the decision problem, and seizure severity is not included in the decision problem..... 15

Table 1.4: Key issue 3: Measurement validity of the eDiary not demonstrated 16

Table 1.5: Key issue 4: Internal validity of the trial in terms of the between-arm similarity in the numbers of patients using specific combinations of concomitant medications is unclear 16

Table 1.6: Key issue 5: External validity of the trial in terms of the between-arm similarity in the numbers of patients using specific combinations of concomitant medications unclear..... 17

Table 1.7: Key issue 6: External validity of the trial in terms of age, gender or ethnicity unclear..... 18

Table 1.8: Key issue 7: Not all relevant comparisons in the ITC 19

Table 1.9: Key issue 8: Model structure based on relative reductions in drop-seizures instead of absolute seizure frequency 20

Table 1.10: Key issue 9: Intervention and comparators: Uncertainty regarding the maintenance dose of fenfluramine and cannabidiol..... 20

Table 1.11: Key issue 10: Treatment effectiveness and extrapolation: Uncertainty regarding the extrapolation of the fenfluramine plus SoC treatment effect 21

Table 1.12: Key issue 11: Treatment effectiveness and extrapolation: Discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC..... 21

Table 1.13: Key issue12: HRQoL: Uncertainty in the modelling of patient HRQoL..... 22

Table 1.14: Key issue 13: HRQoL: Plausibility of the approach for the modelling of caregiver HRQoL 22

Table 1.15: Key issue 14: HRQoL and resources and costs: Uncertainty in the proportion of institutionalised patients and the lack of modelling its impact on caregiver HRQoL..... 23

Table 1.16: Key issue 15: Application of severity modifier to caregiver QALYs..... 23

Table 2.1: Statement of the decision problem (as presented by the company) 26

Table 2.2: Differences between the NICE scope and the decision problem in terms of outcomes 31

Table 2.3: The decision problem (amended after clarification) 35

Table 3.1: Data sources for Appendix D: Identification, selection and synthesis of clinical evidence (as reported in CS) 37

Table 3.2: Eligibility criteria used in the systematic review 39

Table 3.3: Risk of bias in the included RCTs 43

Table 3.4: Primary and secondary publications for LGS efficacy studies included in the SLR 46

Table 3.5: Percentage of patients achieving ≥25%, ≥50%, ≥75% reduction in drop attacks from baseline and seizure freedom 52

Table 3.6: Change from baseline in total and DSF 55

Table 3.7: Change from baseline in GTC and TCT seizure frequency 59

Table 3.8: Safety outcomes and treatment discontinuation 63

Table 3.9: AESI 66

Table 3.10: Clinical evidence 70

Table 3.11: Summary of trial methodology 73

Table 3.12: Statistical methodology used 82

Table 3.13: Baseline characteristics of patients included in Study 1601 83

Table 3.14: Baseline characteristics of patients included in OLE study 87

Table 3.15: Summary of quality assessment of Study 1601 89

Table 3.16: Key effectiveness endpoint: Change from Baseline in DSF per 28 days during the OLE Treatment Period Responder analysis (mITT) 90

Table 3.17: CGI-I in Study 1601 95

Table 3.18: QOLCE in Study 1601 95

Table 3.19: HADS in Study 1601 96

Table 3.20: Most common TEAE (Study 1601) 97

Table 3.21: Serious TEAEs and treatment discontinuation (Study 1601) 98

Table 3.22: AESI in Study 1601 98

Table 3.23: Most common TEAEs OLE study 99

Table 3.24: Summary of the trials used to carry out the indirect or mixed treatment comparison 101

Table 3.25: NMA outcomes breakdown by treatment, studied population, and NMA network 105

Table 3.26: Patient baseline characteristics 108

Table 3.27: ASM-related inclusion/exclusion criteria and baseline concomitant medications usage (%) in each trial (Table 30 of Appendix D of the CS) 111

Table 3.28: Median number of previous ASMs and concomitant therapies 113

Table 3.29: Summary of the efficacy and safety outcomes available 114

Table 3.30: NMA selected outcomes with their corresponding trial network 115

Table 3.31: MD, probability of being the best, and SUCRA for median percent reductions in frequency of GTC seizures, fixed effects (FFA-PBO-CBD) 117

Table 3.32: RRs, probability of being the best, and SUCRA for ≥25%, 50% and 75% reduction in DSF, fixed effects FFA-PBO-CBD + CLB (GBA)) 120

Table 3.33: RRs, probability of being the best, and SUCRA for discontinuation due to AEs, fixed effects (FFA-PBO-CBD) 122

Table 3.34: Summary of ITT scenario results 123

Table 3.35: Summary of results for (FFA-PBO-CBD + CLB (GBA)) network 123

Table 3.36: Selected outcomes of interest from the NMA 123

Table 3.37: NMA models for continuous and binary outcomes 125

Table 4.1: Data sources searched for Appendix G: Published cost effectiveness studies (as reported in CS) 129

Table 4.2: Data sources searched for Appendix H: HRQoL-life studies (as reported in CS) 130

Table 4.3: Data sources searched for Appendix I: Cost and healthcare resource identification, measurement and valuation (as reported in CS) 131

Table 4.4: Eligibility criteria for the SLRs 132

Table 4.5: NICE reference case checklist 133

Table 4.6: Observed and estimated absolute number of drop seizures per 28 days 135

Table 4.7: Key baseline patient characteristics used in the economic model 138

Table 4.8: SoC distribution per arm (CS, Table 60) *In the original CS, topiramate had a 0% distribution; this was corrected by the company in the clarification response B10 139

Table 4.9: State occupancy for the fenfluramine + SoC, cannabidiol + clobazam + SoC and SoC arm from cycle 2 to 9. 141

Table 4.10: Treatment waning probabilities for fenfluramine + SoC, cannabidiol + clobazam + SoC and SoC 144

Table 4.11: Health state utility values 148

Table 4.12: Health state costs 153

Table 4.13: QALY shortfall analysis 155

Table 5.1: Probabilistic company base-case results, following clarification response 157

Table 5.2: Observed versus extrapolated QALYs (excluding severity modifier) 158

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on FE highlighted in Section 5.1) 164

Table 6.2: Deterministic EAG base-case – pairwise results 166

Table of Figures

Figure 3.1: PRISMA flow diagram 51

Figure 3.2: Study 1601 trial design 76

Figure 3.3: OLE trial design 77

Figure 3.4: Patient flow in Study 1601 and OLE study 79

Figure 3.5: Number of subjects taking combination of five concomitant ASMs in Study 1601 – Safety population 85

Figure 3.6: Primary and key secondary efficacy endpoint – Study 1601 90

Figure 3.7: Proportion of patients achieving ≥25%, ≥50% and ≥75% reductions from baseline in DSF during the Titration and Maintenance period 91

Figure 3.8: Responder rates for drop seizures after 1 year of fenfluramine treatment 92

Figure 3.9: Percentage reduction from baseline of GTC seizures in Study 1601 93

Figure 3.10: Clinically meaningful improvement (RCI ≥95% certainty) in BRIEF®-2 indexes/composite (pooled analysis including 0.2 and 0.7 mg/kg dose of fenfluramine) 99

Figure 3.11: Network diagram for median percent reductions in frequency of GTC seizures (FFA-PBO-CBD) 116

Figure 3.12: Forest plot for median percent reductions in frequency of GTC seizures, fixed effects (FFA-PBO-CBD) 117

Figure 3.13: Network diagram for ≥25%, ≥50% and ≥75% reduction in DSF (FFA-PBO-CBD + CLB (GBA)) 118

Figure 3.14: Forest plot for ≥25% reduction in DSF, fixed effects (FFA-PBO-CBD + CLB (GBA)) 118

Figure 3.15: Forest plot for ≥50% reduction in DSF, fixed effects (FFA-PBO-CBD + CLB (GBA)) 119

Figure 3.16: Forest plot for ≥75% reduction in DSF, fixed effects (FFA-PBO-CBD + CLB (GBA)) 119

Figure 3.17: Network diagram for discontinuation due to AEs (FFA-PBO-CBD) 121

Figure 3.18: Forest plot for discontinuation due to AEs, fixed effects (FFA-PBO-CBD) 122

Figure 4.1: Model structure* 136

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 relates to the clinical effectiveness, and Section 1.5 relates to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1651	Summary of issue	Report Section
1	The comparator definition in the decision problem is too narrow.	2.3
2	The outcomes of 'seizure frequency' is restricted to drop seizures in the decision problem, and seizure severity is not included in the decision problem.	2.4
3	Measurement validity of the eDiary not demonstrated.	3.2.1
4	The internal validity of the trial in terms of the between-arm similarity in the numbers of patients using particular treatments in each arm is unclear.	3.2.3.1
5	The external validity of the trial in terms of the exact combinations of concomitant medications used is unclear.	3.2.3.1
6	The external validity of the trial in terms of age, gender or ethnicity is unclear.	2.5
7	Not all relevant comparisons have been included in the ITC.	3.3, 3.4
8	Model structure based on relative reductions in drop-seizures instead of absolute seizure frequency.	4.2.2
9	Uncertainty regarding the maintenance dose of fenfluramine and cannabidiol.	4.2.4
10	Uncertainty regarding the extrapolation of the fenfluramine + SoC treatment effect.	4.2.6
11	Discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC.	4.2.6
12	Uncertainty in the modelling of patient HRQoL.	4.2.8
13	Plausibility of the approach for the modelling of caregiver HRQoL.	4.2.8
14	Uncertainty in the proportion of institutionalised patients and the lack of modelling its impact on caregiver HRQoL.	4.2.8 and 4.2.9
15	Application of severity modifier to caregiver QALYs.	4.2.10

HRQoL = health-related quality of life; ITC = indirect treatment comparison; QALY = quality adjusted life year; SoC = standard of care

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs (including the severity modifier) by:

- Reduction in the frequency of drop seizures. Incremental QALYs for fenfluramine + standard of care (SoC) (total for patients and caregivers [proportion of total incremental QALYs]) in health states 2 and 3 were 0.64 (45%) and 0.74 (53%) compared with cannabidiol + clobazam and SoC and 1.33 (38%) and 2.13 (61%) compared to SoC alone.
- Reduction in caregiver burden. The incremental caregiver QALYs (proportion of total QALY increment) for fenfluramine plus SoC were 0.91 (65%) compared with cannabidiol + clobazam + SoC, and 2.25 (65%) compared with SoC alone.

Overall, the technology is modelled to affect costs by:

- The higher treatment costs for fenfluramine. Incremental treatment costs (proportion of total incremental costs) for fenfluramine + SoC were [redacted] ([redacted]) compared to cannabidiol + clobazam + SoC and [redacted] ([redacted]) compared to SoC alone.

The parameters that have the greatest effect on the ICER (based on the company's deterministic sensitivity analyses (DSAs]) are:

- Fenfluramine cost per milligram (mg)
- Cannabidiol cost per mg
- The relative risk of treatment discontinuation for fenfluramine + SoC in the Titration and Maintenance period
- Weight (12-17 years and 18-35 years)
- Discount rate (benefits and costs)
- Number of caregivers
- The relative risk of treatment discontinuation for cannabidiol + clobazam + SoC in the Titration and Maintenance period

Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following company submission (CS) scenarios that have a substantial impact on the ICER:

- Varying the stopping rule (discontinuation if response is <50%, compared with <25% in the base-case)
- Increasing the percentage of cannabidiol + clobazam + SoC patients that undergo treatment waning (from 5.2% to 19.60% of patients)
- Drug Maintenance dosage (varying fenfluramine and cannabidiol dose both separately and simultaneously)
- Utility source

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the CS is broadly in line with the final scope issued by NICE. However, the intervention definition in the decision problem is inaccurate (Table 1.2) and the outcome of 'drop seizures' may be too restrictive (Table 1.3).

Table 1.2: Key issue 1: The comparator definition in the decision problem is too narrow

Report Section	2.3
Description of issue and why the EAG has identified it as important	After the clarification process, the company amended the decision problem comparators from SoC treatment (or ECM) to the more specific CBD + CLB + SoC, or SoC. The company restricted their specific comparator to CBD + CLB + SoC on the premise that only CBD + CLB + SoC has been evaluated in an STA by NICE as a 3rd line therapy. This is true, but in addition to CBD + CLB, NG217 recommends three alternative 3rd line therapies: clobazam, rufinamide and topiramate.
What alternative approach has the EAG suggested?	Add in three alternative 3rd line therapies: clobazam, rufinamide and topiramate. All these should also be considered as specific comparators alongside CBD + CLB (i.e., clobazam + SoC, rufinamide + SoC and topiramate + SoC).
What is the expected effect on the cost effectiveness estimates?	If these additional comparators are added into the model, the cost effectiveness estimate for fenfluramine may reduce, as the extended NMA demonstrated that some of these alternative treatments may have greater efficacy than fenfluramine.
What additional evidence or analyses might help to resolve this key issue?	Further analyses involving the alternative 3rd line therapies. These will not be able to be compared directly to fenfluramine but should be introduced into the NMA to permit indirect comparisons. An alternative might be to conduct subgroup analysis of Study 1601, identifying fenfluramine and placebo patients who were taking the same concomitant therapy, i.e., clobazam or rufinamide (topiramate not used in the trial). Indeed, this was done to inform the NMA with CBD + CLB. This would increase the risk of bias, given that randomisation was not stratified i.e., patients were not randomised within these subgroups. However, it might be that difference between fenfluramine and placebo in baseline characteristics was reduced by patients on the same concomitant therapy being similar in other ways.
CBD + CLB = cannabidiol + clobazam; EAG = Evidence Assessment Group; ECM = Established clinical management; NG = National Guideline; NICE = National Institute of Health and Care Excellence; NMA = network meta-analysis; SoC = standard of care; STA = Single Technology Appraisal	

Table 1.3: Key issue 2: The outcomes of 'seizure frequency' is restricted to drop seizures in the decision problem, and seizure severity is not included in the decision problem

Report Section	2.4
Description of issue and why the EAG has identified it as important	The outcome of seizure frequency is restricted to drop seizures in the decision problem, and to drop seizures and tonic-clonic seizures in the CS clinical efficacy report, but other seizure types are not included, despite the population comprising people with a variety of seizure presentations. The company clarified this by explaining that "*since drop seizures result in physical events such as falls and injuries, the data collection for these seizures is considered more easily identifiable, and the accuracy of measurement can be better compared to other seizures*". The EAG accepts the logic of using the most easily measured and verified seizure outcome available, but also notes that this prevents any evaluation of the effects of fenfluramine on less severe seizures, which are also of importance to patients. The assumption that efficacy in reducing severe seizures automatically implies efficacy

Report Section	2.4
	in reducing less severe seizures may not necessarily hold, because less severe types of seizures may differ from drop seizures in more ways than just severity. For example, they may differ in terms of pathophysiology, which might lead to different responses to treatment.
What alternative approach has the EAG suggested?	Add in all available seizure outcomes if available. If not, the effect of the absence of these outcomes on estimates of cost effectiveness should be considered.
What is the expected effect on the cost effectiveness estimates?	Possible reduction in cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Add in all available seizure outcomes, if available.
CS = company submission; EAG = Evidence Assessment Group	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified several concerns with the evidence presented on the clinical effectiveness, namely the measurement validity (Table 1.4), internal validity (Table 1.5), external validity of trial results (Tables 1.6 and 1.7), and an incomplete indirect treatment comparison (ITC) in terms of included comparisons (Table 1.8).

Table 1.4: Key issue 3: Measurement validity of the eDiary not demonstrated

Report Section	3.2.1
Description of issue and why the EAG has identified it as important	The validity of the efficacy measures depends on the measurement validity of the eDiary, an electronic, homebased handheld device provided to every subject, and used for recording of seizures. The company were asked to provide information of the measurement validity of these devices in the request for clarification. The company did not provide any convincing evidence of the validity of the eDiary as a measurement device. Therefore, the validity of much of the trial evidence is unclear.
What alternative approach has the EAG suggested?	More data supporting the measurement validity of the eDiary need to be provided.
What is the expected effect on the cost effectiveness estimates?	The cost effectiveness may be reduced.
What additional evidence or analyses might help to resolve this key issue?	More data supporting the measurement validity of the eDiary needs to be provided.
EAG = Evidence Assessment Group	

Table 1.5: Key issue 4: Internal validity of the trial in terms of the between-arm similarity in the numbers of patients using specific combinations of concomitant medications is unclear

Report Section	3.2.3.1
Description of issue and why the EAG has identified it as important	The internal validity of the trial in terms of the between-arm similarity in the numbers of patients using particular treatments in each arm is unclear. The data provided by the company after clarification suggest that there may be some between-arm

Report Section	3.2.3.1
	differences in the numbers of patients using specific combinations of concomitant medications (for example, the numbers of people in each arm receiving precisely fenfluramine + rufinamide + clobazam) that could influence outcome. However, it is very unclear which way any bias from this would act for each specific combination of concomitant medications. Given the wide array of permutations, some of these effects may cancel out across arms leaving a relatively small residual bias. A more important source of internal validity is likely to concern the non-pharmacological treatments. The overall prevalence of these treatments was given in the clarification response, but not per arm, so it is not possible to exclude differences in these treatments across arms.
What alternative approach has the EAG suggested?	The EAG would like information on the non-pharmacological treatments per arm.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	The EAG would like information on the non-pharmacological treatments per arm.
EAG = Evidence Assessment Group	

Table 1.6: Key issue 5: External validity of the trial in terms of the between-arm similarity in the numbers of patients using specific combinations of concomitant medications unclear

Report Section	3.2.3.1
Description of issue and why the EAG has identified it as important	The external validity of the trial in terms of the exact combinations of concomitant medications used is unclear. To understand the external validity more clearly, more information is required from sub-group analyses investigating whether particular combinations of concomitant medications used affect outcome. For example, would the comparison *fenfluramine + rufinamide + clobazam* versus *placebo + rufinamide + clobazam* have a different outcome to *fenfluramine + rufinamide + topiramate* versus *placebo + rufinamide + topiramate?* Superficially, the two comparisons might initially be expected to have very similar outcomes as a result of the identical ECM components across arms *within* each comparison cancelling each other out (effectively leaving both comparisons as simply fenfluramine versus placebo, and therefore the same as each other). This is perhaps rather naive as it assumes a purely additive effect on outcome from the additional treatments. More realistically, specific interactions between fenfluramine and the other anti-seizure medications might well create differences in outcome between the two different comparisons (given that equivalent and therefore potentially counterbalancing interactions between fenfluramine and placebo in the placebo arm of each comparison would not be expected). If particular combinations of concomitant medications *are* indeed shown to affect outcome, then it would be relevant to know about the similarity of such particular combinations of concomitant medications used in the trial and the UK target population. The company was unable to provide sub-group analyses because of the combination of a relatively small

Report Section	3.2.3.1
	sample size and a large number of different ASM combinations used in the trial. The company was also unable to provide objective data on the combinations of ASMs used in UK practice. Altogether, this means that it is not possible to confirm the external validity of trial results to the population in England and Wales.
What alternative approach has the EAG suggested?	Provision of data relating to 1) the effects of various combinations of concomitant medications on outcome and 2) the combinations of ASMs used in England and Wales.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Provision of data relating to 1) the effects of various combinations of concomitant medications on outcome and 2) the combinations of ASMs used in practice in England and Wales.
ASM = anti-seizure medications; EAG = Evidence Assessment Group; ECM = Established clinical management; UK = United Kingdom	

Table 1.7: Key issue 6: External validity of the trial in terms of age, gender or ethnicity unclear

Report Section	2.5
Description of issue and why the EAG has identified it as important	The external validity of the trial in terms of age, gender or ethnicity is also unclear. To understand the external validity more clearly, more information is required from sub-group analyses investigating whether age, gender or ethnicity affect outcome. If any of age, gender or ethnicity are shown to affect outcome, then it would also be important to know about the similarity of age, gender or ethnicity in the trial and the UK target population. However, the company did not provide sub-group analyses, nor any information on the characteristics of the UK population. The EAG would have liked to have seen the data for the exploratory sub-group analyses, so that the EAG could have made a judgement on the validity of the company's decision to not present sub-group analyses in the CS. In addition, it would have been very helpful if objective data on the UK target population, in terms of plausible confounding variables such as age or ethnicity, had been provided. It is therefore not possible to confirm the external validity of the trial to the target population.
What alternative approach has the EAG suggested?	Provision of data relating to 1) the effects of age, gender or ethnicity on outcome and 2) age, gender and ethnicity in practice in England and Wales.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Provision of data relating to 1) the effects of age, gender or ethnicity on outcome and 2) age, gender and ethnicity in practice in England and Wales.
CS = company submission; EAG = Evidence Assessment Group; UK =United Kingdom	

Table 1.8: Key issue 7: Not all relevant comparisons in the ITC

Report Section	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The ITC excluded six RCTs out of the nine RCTs originally declared by the company to be eligible. This meant that rufinamide, topiramate and clobazam (recommended as 3rd line medications by NICE, which is the line of therapy for which fenfluramine is also positioned) were excluded from the ITC. Given the importance of including such comparators, the rationale for these exclusions was not sufficiently convincing, and at clarification the company were asked to provide a fuller NMA. After clarification, the company directed the EAG to the fuller NMA results contained in the "UCB data on file NMA report [Appendix F]". The results from this extended NMA (including all nine RCTs) show that [redacted], rufinamide and lamotrigine were [redacted] to fenfluramine. Similarly, [redacted], clobazam (1 mg/kg), rufinamide, cannabidiol (20 mg/kg) and topiramate [redacted] fenfluramine to be [redacted], lamotrigine, felbamate, clobazam (1 mg/kg), clobazam (0.5 mg/kg), clobazam (0.25 mg/kg) and cannabidiol (10 mg/kg) were [redacted]. A similar picture was seen for discontinuation due to AEs and SAEs. [redacted]. For [redacted], fenfluramine was [redacted], but only lamotrigine and cannabidiol (20 mg/kg) were included alongside fenfluramine and placebo in that NMA. Overall, the fuller (nine RCTs) NMA provides information suggesting that the clinical benefits of other 3rd line ASMs may be superior to those of fenfluramine. The EAG notes the arguments provided by the company explaining why these fuller NMA results are not considered in the CS. These focus on potential intransitivity, but the EAG note that there is no evidence provided by the company that the excluded studies were actually different in terms of any of the factors described, only that data on these factors were absent. The EAG therefore remains unconvinced about the validity of the complete exclusion of these full NMA results from the CS, particularly given that they conflict with the conclusions made in the more limited NMA presented in the CS.
What alternative approach has the EAG suggested?	Inclusion of all nine RCTs in the NMA.
What is the expected effect on the cost effectiveness estimates?	Likely reduction of cost effectiveness of fenfluramine.
What additional evidence or analyses might help to resolve this key issue?	Inclusion of all nine RCTs in the NMA.

Report Section	3.3 and 3.4
AE = adverse events; ASM = anti-seizure medication; CS = company submission; EAG = Evidence Assessment Group; GTC = generalised tonic-clonic; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; RCT = randomised controlled trial; SAE = serious adverse events	

1.5 The cost effectiveness evidence : summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the issue Tables below.

Table 1.9: Key issue 8: Model structure based on relative reductions in drop-seizures instead of absolute seizure frequency

Report Section	4.2.2
Description of issue and why the EAG has identified it as important	The company's model structure was based on relative reductions in drop seizure frequency rather than absolute drop-seizure frequency, which potentially resulted in patients with varying absolute number of drop seizures in the same health state.
What alternative approach has the EAG suggested?	A model structure based on absolute seizure frequencies.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Provide an updated economic model and scenario analysis using health states which are categorized by absolute seizure frequency instead of relative reduction in seizure frequency.
EAG = Evidence Assessment Group	

Table 1.10: Key issue 9: Intervention and comparators: Uncertainty regarding the maintenance dose of fenfluramine and cannabidiol

Report Section	4.2.4
Description of issue and why the EAG has identified it as important	The initially modelled maintenance doses for fenfluramine and cannabidiol were 0.5 and 14 mg/kg/day, respectively. These were increased in the clarification response addendum with insufficient supporting evidence. Moreover, the initial maintenance dose for cannabidiol was higher than the recommended dose in NICE TA615 (12 mg/kg/day).
What alternative approach has the EAG suggested?	Maintenance doses of 0.5 and 12 mg/kg/day for fenfluramine and cannabidiol, respectively.
What is the expected effect on the cost effectiveness estimates?	This substantially increased the treatment costs of fenfluramine + SoC relative to CBD + CLB + SoC and hence increased the ICER.
What additional evidence or analyses	Supporting clinical evidence and expert opinion on the appropriate recommended dose for LGS patients in the UK.

Report Section	4.2.4
might help to resolve this key issue?	
CBD + CLB = cannabidiol + clobazam; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LGS = Lennox-Gastaut syndrome; SoC = standard of care; UK = United Kingdom	

Table 1.11: Key issue 10: Treatment effectiveness and extrapolation: Uncertainty regarding the extrapolation of the fenfluramine plus SoC treatment effect

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The treatment effectiveness for fenfluramine + SoC was assumed to increase after the study period (i.e., from cycle 5 to 9), while the treatment effectiveness for CBD + CLB + SoC was assumed to be stable. The EAG is uncertain about the prolongation of this treatment effect after the observed period.
What alternative approach has the EAG suggested?	The EAG prefers to use a stable treatment effectiveness after the observed period (the same assumption as for CBD + CLB + SoC).
What is the expected effect on the cost effectiveness estimates?	Using a stable treatment effectiveness after the observed period for fenfluramine + SoC substantially increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	To resolve this issue the treatment effect of fenfluramine + SoC should be observed over a longer time period.
CBD + CLB = cannabidiol + clobazam; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; SoC = standard of care	

Table 1.12: Key issue 11: Treatment effectiveness and extrapolation: Discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC in the first year of the economic model, resulting in an overestimation of patients in health states with better relative response in the fenfluramine + SoC arm.
What alternative approach has the EAG suggested?	Use state occupancies for fenfluramine + SoC directly derived from clinical trial state occupancies in the first year of the economic model, which is in line with the approach taken for the CBD + CLB +SoC and SoC arms.
What is the expected effect on the cost effectiveness estimates?	The effect depends on the assumed treatment dosages, but in the company base-case it decreased the ICER.
What additional evidence or analyses might help to resolve this key issue?	Provide exact patient numbers per health state to accurately model probabilistic outcomes.
CBD + CLB = cannabidiol + clobazam; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; SoC = standard of care	

Table 1.13: Key issue12: HRQoL: Uncertainty in the modelling of patient HRQoL

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	All utility values presented in the CS are suboptimal to inform patient HRQoL. The company used utility scores from a conference abstract of Verdian et al. to inform health state utilities in the economic model. The EAG was concerned about 1) the use of vignette studies to estimate patient utility values and 2) the face validity of the resulting utility values in this source.
What alternative approach has the EAG suggested?	Further justification on whether the study of Verdian et al. incorporated all relevant domains of generic HRQoL (i.e., not merely condition-related domains). Mapping QOLCE-16 data from Study 1601 and the OLE study to EQ-5D-3L to inform health state utilities.
What is the expected effect on the cost effectiveness estimates?	Expected effect on the cost effectiveness estimates depends on the selected source (Verdian et al., Auvin et al. Lo et al.) and method of eliciting patient utility values.
What additional evidence or analyses might help to resolve this key issue?	Further justification regarding the face validity of the seemingly relatively low health state utilities currently used compared to the scores from the QOLCE-16 instrument.
CS = company submission; EAG = Evidence Assessment Group; ED-5D-3L = EuropQol-5 Dimensions 3rd line; HRQoL = health-related quality of life; OLE study = open label extension study; QOLCE-16 = Quality of Life in Childhood Epilepsy-16	

Table 1.14: Key issue 13: HRQoL: Plausibility of the approach for the modelling of caregiver HRQoL

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The company modelled caregiver utilities by applying the same health utility values to 1.8 caregivers per patient. The EAG considers the assumption that the HRQoL of the caregivers equals the HRQoL of the LGS patient to be unrealistic. In addition, it overestimates the impact of mortality in the economic model, as the caregiver utility was set to 0 when a patient died (while in reality the caregivers do not die together with the patient).
What alternative approach has the EAG suggested?	A caregiver disutility approach, in line with TA614, to model caregiver HRQoL.
What is the expected effect on the cost effectiveness estimates?	Applying a caregiver disutility approach resulted in an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	Further justification regarding why the study of Auvin et al. was used for the calculation of the caregiver disutilities in the company's scenario analysis.
EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LGS = Lennox-Gastaut syndrome; TA614 = Technology Appraisal 614	

Table 1.15: Key issue 14: HRQoL and resources and costs: Uncertainty in the proportion of institutionalised patients and the lack of modelling its impact on caregiver HRQoL

Report Section	4.2.8 and 4.2.9
Description of issue and why the EAG has identified it as important	The company provided a scenario analysis including a per cycle institutionalisation cost of £1,594 that was applied to an assumed 10% of LGS patients being institutionalised when reaching the age of 18 years old. It was unclear to the EAG whether this percentage is representative of UK clinical practice. In addition, the impact of institutionalisation on caregiver HRQoL was not modelled.
What alternative approach has the EAG suggested?	Further justification and evidence to support the assumption that 10% of LGS patients would be institutionalised when reaching the age of 18 years. The EAG assumed 1.8 caregivers for the 90% of patients not institutionalised and 0.7 caregivers for the 10 % of institutionalised patients.
What is the expected effect on the cost effectiveness estimates?	The analysis assuming fewer caregivers for institutionalised patients resulted in an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	Further justification and evidence to support the assumption that 10% of LGS patients would be institutionalised when reaching the age of 18 years.
EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LGS = Lennox-Gastaut syndrome; UK = United Kingdom	

Table 1.16: Key issue 15: Application of severity modifier to caregiver QALYs

Report Section	4.2.10
Description of issue and why the EAG has identified it as important	NICE guidance defines severity as the "future health lost by people living with the condition with standard care in the NHS". Whilst the company derive the QALY shortfall using patient QALYs, the severity modifier was applied to both patient and caregiver QALYs, considering caregivers to also fall under this definition. The EAG believes the severity modifier application should be limited to patient QALYs only.
What alternative approach has the EAG suggested?	Apply severity modifier to patient QALYs only.
What is the expected effect on the cost effectiveness estimates?	Applying the severity modifier to patient QALYs only resulted in an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	N/A.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; N/A = not applicable; QALY = quality-adjusted life year	

1.6 Other key issues

There were no other key issues.

1.7 Summary of the EAG's view

The randomised controlled trial (RCT) evidence provided in the CS was suggestive of clinical benefits of fenfluramine over placebo (+ SoC), particularly for the 0.7 mg/kg/day dose of fenfluramine (+ SoC), but these were not observed for all outcomes, and the greater risk of adverse events compared to the lower dose or placebo needs to be considered. In addition, there were some unresolved questions about the quality of the trial evidence, concerning the measurement validity of the eDiaries, and the failure to collect data on the variety of seizure types that patients would have experienced. There were also questions about the internal validity of the trial data, largely because of ambiguity about the balanced use of non-pharmacological treatments across arms. Finally, external validity of the trial data to the UK target population was uncertain.

Even if these caveats are ignored or downplayed, valid comparators were omitted from the decision problem. National Guideline 217 (NG217) recommends three alternative 3rd line add-on therapies: clobazam, rufinamide and topiramate. All these could also have been considered as specific comparators alongside cannabidiol + clobazam (i.e., clobazam + SoC, rufinamide + SoC and topiramate + SoC). Head-to-head studies comparing these do not as yet exist, but indirect comparisons might be estimated in a network meta-analysis (NMA).

The company correctly developed an NMA and found nine relevant RCTs covering most of the relevant active comparators. Unfortunately, the company did not present this full NMA in the clinical submission, instead presenting a heavily annotated NMA that only included three RCTs, with cannabidiol + clobazam (+SoC) as the only active comparator. The reduced NMA demonstrated greater efficacy for fenfluramine (+ SoC) over cannabidiol + clobazam (+SoC) but the full NMA containing all nine RCTs, which was made available to the EAG after the clarification process, did not demonstrate that fenfluramine was superior to all other 3rd line comparators. For example, the results from this extended NMA (including all nine RCTs) show that [redacted], rufinamide and lamotrigine were [redacted] to fenfluramine. Similarly, [redacted], clobazam (1 mg/kg), rufinamide, cannabidiol (20 mg/kg) and topiramate [redacted] fenfluramine to be [redacted]The company's arguments why these fuller NMA results were not considered in the CS[1] focus on *potential* intransitivity, but the EAG note that there is no evidence provided by the company that the excluded studies were actually different in terms of any of the factors described, only that data on these factors were absent.

The CS base-case ICERs (probabilistic) were [redacted] (versus cannabidiol + clobazam + SoC) and [redacted] (versus SoC). The estimated EAG base-case ICERs (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, were [redacted] (versus cannabidiol + clobazam + SoC) and [redacted] (versus SoC) per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities for fenfluramine + SoC versus cannabidiol + clobazam + SoC of [redacted] at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were assuming a maintained instead of increasing fenfluramine treatment effect after the observed period, and assuming different average Maintenance doses for fenfluramine and cannabidiol. The ICER increased most in the scenario analysis with alternative assumptions regarding the proportion of patients experiencing waning of the fenfluramine treatment effect.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of fenfluramine + SoC, which can be partly resolved by the company by conducting further analyses. This includes providing a model structure based on absolute seizure frequencies, supporting clinical evidence on the appropriate average fenfluramine and cannabidiol Maintenance doses for Lennox-Gastaut syndrome (LGS) patients in the UK, clinical evidence of the fenfluramine + SoC treatment effect over a longer observed time period, further justification regarding the face validity of the health state utilities

currently used compared to the scores from the Quality-of-Life in Childhood Epilepsy (QOLCE)-16 instrument, and further justification and evidence to support the assumption that 10% of LGS patients would be institutionalised when reaching the age of 18 years. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of fenfluramine + SoC compared with the relevant comparators.

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	People aged 2 and over with LGS whose seizures are inadequately controlled by ECM.	People aged 2 and over with LGS whose seizures are inadequately controlled by ECM.	As per final NICE scope.	The positioning of fenfluramine in the CS[1] is presented more specifically as where cannabidiol is currently recommended i.e., at 3rd line.
Intervention	Fenfluramine hydrochloride	Fenfluramine hydrochloride	As per final NICE scope.	Fenfluramine would not be given alone, as suggested by the decision problem. It is a 3rd line add-on therapy thus should be defined as fenfluramine + SoC. After the clarification process the company correctly amended the intervention to fenfluramine + SoC. No justification is currently given of the dosages chosen for RCT evaluation.
Comparator(s)	ECM without fenfluramine hydrochloride, which may include combinations of: 1) ASMs, including but not limited to: • CBD + CLB • sodium valproate • lamotrigine • rufinamide • topiramate	ECM without fenfluramine hydrochloride, which may include combinations of: 1) ASMs, including but not limited to: • CBD + CLB • sodium valproate • lamotrigine • rufinamide • topiramate • felbamate • clobazam • levetiracetam	As per final NICE scope.	After the clarification process, the company amended the decision problem comparators from SoC treatment (or ECM) to the more specific CBD + CLB + SoC, or SoC. The company restricted their specific comparator to CBD + CLB + SoC on the premise that only CBD + CLB + SoC is endorsed by NICE as a 3rd line therapy. However, 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

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	• felbamate • clobazam • levetiracetam 2) ketogenic diet 3) vagus nerve stimulation 4) surgery	2) ketogenic diet 3) vagus nerve stimulation 4) surgery		alongside CBD + CLB (i.e., clobazam + SoC, rufinamide + SoC and topiramate + SoC).
Outcomes	The outcome 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)	The outcome measures to be considered include: • seizure frequency (drop seizure) • Response rate (percentage of reduction of drop seizures within these categories: <25%; 25-50%; 50-75%; >75%) • mortality (SUDEP and non-SUDEP including status epilepticus) • adverse events of treatment • HRQoL (patients and carers)	Only drop seizures, characteristic seizures of LGS and primary and key secondary endpoints in the RCT (Study 1601[2]) for fenfluramine, are considered in the CS.[1] Proportion of people seizure-free is not considered in the model as the proportion of patients who are (drop) seizure-free was very low in the Phase 3 trials of fenfluramine and cannabidiol (either 0 or 1 patient per treatment arm). The severity of seizures was captured through the types of seizures: GTC seizures leading to drops are associated with higher healthcare resource use, and this was captured in the model. Incidence of status epilepticus is not a model outcome *per se* but non-SUDEP was considered	Seizure severity and mortality are not included as outcomes in the decision problem, despite being included in the NICE scope. The outcome of seizure frequency is restricted to drop seizures in the decision problem, and to drop seizures and tonic-clonic seizures in the CS[1] clinical efficacy report, but other seizure types are not included.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			including status epilepticus deaths	
Economic analysis	No data provided.	No data provided.	No data provided.	No comments
Subgroups to be considered				No sub-groups were considered by the company. This appears to be a weakness of the submission. Sub-grouping for characteristics that are agreed (pre-hoc) to have a plausible effect on outcome can demonstrate differential effects across population strata. This may be important if the target UK population are found to have different population characteristics to the trial population. If these differing characteristics have been shown to influence outcome in a sub-group analysis, reasonable assumptions about the external validity of the trial data to the target population can be made.
Special considerations including issues related to equity or equality				The Comment provided by the company noted that there were no issues to highlight regarding special considerations related to equity or equality

Based on Table 1 in CS[1]

CBD + CLB = cannabidiol + clobazam; CS = company submission; EAG = Evidence Assessment Group; ECM = Established clinical management; GTC = generalised tonic-clonic; HRQoL = health-related quality of life; LGS = Lennox Gastaut syndrome; NICE = National Institute for Health and Care Excellence; NG = National Guideline; NMA = network meta-analysis; RCT = randomised controlled trial; SoC = standard of care; STA = single technology appraisal; SUDEP = sudden unexpected death in epilepsy; UK = United Kingdom

2.1 Population

The National Institute for Health and Care Excellence (NICE) scope originally defined the population as people aged 2 and over with Lennox-Gastaut syndrome (LGS) whose seizures are inadequately controlled by Established clinical management (ECM). The decision problem in the company submission (CS[1]) describes exactly the same population. However, the CS[1] indicates that the populations is more specific i.e., 3rd line.

EAG comment: No comments.

2.2 Intervention

The NICE scope originally defined the intervention as fenfluramine hydrochloride. The decision problem in the CS[1] describes exactly the same intervention.

EAG comment:

- Although the original decision problem agreed with the NICE scope in terms of the intervention, it was not in line with the trial evidence. The decision problem and NICE scope defined the intervention as fenfluramine alone. However, the trial evaluated fenfluramine + standard of care (SoC). The intervention in the trial makes more clinical sense as fenfluramine is envisaged as a 3rd line add-on therapy. One option, therefore, was for the company to redefine the decision problem as fenfluramine + SoC versus SoC, which was requested in the request for clarification. The company agreed, stating that, "*The intervention in the decision problem is reframed in Table 4 below. Indeed, fenfluramine is not given alone as it is indicated for the treatment of seizures associated with LGS as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older. Therefore, the intervention in the decision problem is fenfluramine + SoC. This is aligned with fenfluramine clinical trial, Study 1601, where the intervention was fenfluramine in addition to SoC compared to SoC alone (i.e., SoC plus placebo)".*[3] The Evidence Assessment Group (EAG) is happy with this response, although there is then the question as to what constitutes SoC onto which fenfluramine would be added. According to the NICE scope and the CS[1] care pathway (Figure 6), 2nd line pharmacotherapy would be either lamotrigine monotherapy or lamotrigine + sodium valproate. At 3rd line, patients would then either switch to or receive as add-on cannabidiol + clobazam, clobazam, rufinamide or topiramate, which would imply that these are SoC. However, for the economic analysis SoC is described as a *"basket of treatments including: clobazam; levetiracetam, valproate, lamotrigine, topiramate, and rufinamide…"*[3] (see page 109). Note that by 3rd line valproate would only be given in combination.
- No dosage is defined in the decision problem, although the trial evidence evaluates both 0.7 mg/kg/day and 0.2 mg/kg/day versus placebo. The company were asked in the request for clarification to justify the dosages used. The company responded by stating that, "*In Study 1601, patients were randomised to receive either a 0.7 mg/kg/d or 0.2 mg/kg/d (maximum 26 mg/d) dose of fenfluramine or placebo. These dose-levels were selected based on data from Study S58545 (NCT02655198), a Phase 2 open-label, pilot, dose-finding trial in which a small cohort (n=13 patients with LGS aged 3-18 year) of refractory patients with LGS in Belgium were treated with fenfluramine as an add-on therapy to conventional therapy …. Fenfluramine has been generally well tolerated in this ongoing study, with no subject developing valvular heart disease or pulmonary arterial hypertension. These two doses were also studied in Phase 3, double-blind, placebo-controlled studies of fenfluramine in subjects with Dravet syndrome (DS) based on data from Study ZXIIS2015-04, an open-label proof-of-concept trial*

of fenfluramine in subjects with DS. …. Comparison of the seizure reduction results for the two dose-levels of fenfluramine in this study suggested a dose-response effect on seizure frequency. The pattern of individual responses in the fenfluramine 0.2 mg/kg/day group supported the selection of 0.2 mg/kg/day as the minimally effective dose." [3] The EAG is satisfied with this response.

2.3 Comparators

The NICE scope originally defined the comparator as established clinical management (ECM) without fenfluramine hydrochloride, which may include:

1. Combinations of anti-seizure medications, including but not limited to:
    - CBD + CLB
    - sodium valproate
    - lamotrigine
    - rufinamide
    - topiramate
    - felbamate
    - clobazam
    - levetiracetam
2. Ketogenic diet
3. Vagus nerve stimulation
4. Surgery

The original decision problem in the CS[1] described exactly the same comparator.

EAG comment:

- In the company response to the request for clarification concerning the definition of the decision problem intervention (see above), the company stated that it had also amended the comparator in the decision problem, as follows: "*In response, the comparators in the decision problem have been reframed in Table 4. Indeed, as cannabidiol with clobazam is the only established clinical add-on therapy to have been formally appraised by NICE, and accepted as a clinically and cost-effective option, it is also the only therapy with sufficient trial data to permit a robust comparison. Therefore, the two relevant comparators are: cannabidiol with clobazam + SoC and SoC alone. The other ASMs and the non-pharmaceutical treatments are not considered as comparators but constitute the SoC 'basket.*'".[3] The company restricted their specific comparator to cannabidiol + clobazam + SoC on the premise that only cannabidiol + clobazam + SoC has been evaluated by NICE as a 3rd line therapy in a Single Technology Appraisal (STA). However, whilst this is true, NICE guidelines have recommended other 3rd line therapies in addition to cannabidiol + clobazam. National Guideline 217 (NG217, Section 6.2.5) states that: "*If second-line treatment is unsuccessful, consider the following as third-line add-on treatment options for people with Lennox–Gastaut syndrome: a) cannabidiol in combination with clobazam if the child is over 2 years, in line with NICE's technology appraisal guidance on cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome, b) clobazam, c) rufinamide, d) topiramate*."[3] All these should therefore also be considered as specific comparators alongside cannabidiol + clobazam (i.e., clobazam + SoC, rufinamide + SoC and topiramate + SoC). This would more readily answer the key question: is fenfluramine a more effective 3rd line add-on treatment than other 3rd line add-on treatments?

- Having said this, the EAG accepts that direct randomised comparisons between fenfluramine + SoC and the alternative 3rd line anti-seizure medications (ASMs) + SoC are not available in the literature. A network meta-analysis (NMA) of randomised controlled trials (RCTs) evaluating each 3rd line treatment + SoC against SoC would therefore be useful. This would permit an indirect estimate of the effect of one 3rd line treatment + SoC to another 3rd line treatment versus SoC. This is discussed further in Section 3.3.
- The EAG also requested more details about the nature of the SoC. The EAG first asked the company to clarify if SoC could ever be a single concomitant therapy. In response, the company stated that, "*In line with the licensed therapeutic indications as per the SmPC, fenfluramine would not be added to a specific therapy. As per the clarification in question A6a. and the reframed decision problem, the intervention is "fenfluramine in addition to current SoC". Despite published guidelines, there is no established standard approach to LGS treatment. Physicians typically adjust or change treatments to enhance their effectiveness in reducing seizures. Individualised anti-seizure therapy is initiated based on the patient's syndrome type, treatment goals, AEs and preferences. Current SoC varies due to the refractory nature of LGS; and given the heterogeneity of the disease, it is not clinically or statistically meaningful to compare the intervention to individual or specific combinations of ASMs beside cannabidiol with clobazam + SoC. Indeed, as illustrated in the response of question A 12. of this document, LGS patients included in Study 1601 received a wide range of possible treatment options."*[3] The problem with this response is that the nature of the therapy on to which fenfluramine or cannabidiol + clobazam are added might affect the effectiveness of these as adjunctive therapies.

2.4 Outcomes

The NICE scope lists the following outcome measures:

- 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
- health-related quality of life (HRQoL) (patients and carers)

The decision problem differed in terms of outcomes. The outcomes covered by the decision problem were: seizure frequency (drop seizure), response rate (percentage of reduction of drop seizures within these categories: <25%; 25-50%; 50-75%; >75%), mortality (Sudden Unexpected Death in Epilepsy [SUDEP] and non-SUDEP including status epilepticus), adverse events (AEs) of treatment and HRQoL (patients and carers).

The differences between the NICE scope and the decision problem are summarised in Table 2.2.

Table 2.2: Differences between the NICE scope and the decision problem in terms of outcomes

NICE outcome	Decision problem	Differences
Seizure frequency (overall and by seizure type)	Seizure frequency (drop seizure)	Decision problem only covers drop seizures

NICE outcome	Decision problem	Differences
Proportion of people seizure-free (overall and by seizure type)	-	Not covered by decision problem
Response rate (overall and by seizure type)	Response rate (percentage of reduction of drop seizures within these categories: <25%; 25-50%; 50-75%; >75%)	Decision problem only covers response rate related to drop seizures
Seizure severity	-	Not covered by decision problem
Incidence of status epilepticus	-	Not covered as a single outcome by decision problem
Mortality	Mortality (SUDEP and non-SUDEP including status epilepticus)	Decision problem includes status epilepticus with mortality
AEs of treatment	AEs of treatment	No differences
HRQoL (patients and carers)	HRQoL (patients and carers)	No differences
AE = adverse event; HRQoL = health-related quality of life; NICE = National Institute for Health and Care Excellence; SUDEP = sudden unexpected death in epilepsy		

EAG comment:

- The outcome of seizure frequency is restricted to drop seizures in the decision problem, and to drop seizures and tonic-clonic seizures in the CS[1] clinical efficacy report, but other seizure types are not included, despite the population comprising people with a variety of seizure presentations. In the request for clarification the company was asked to provide a fuller justification for this restriction, and to provide further data for other seizure types if appropriate. The company responded by stating that, "*as mentioned in the decision problem of the CS[1] (page 17), "only drop seizures, characteristic seizures of LGS and primary and key secondary endpoints in the RCT (Study 1601) for fenfluramine, are considered in the company submission." Drop seizures (or drop attacks) can be caused by many different seizure types. In Study 1601, drop seizures are classified as GTC, secondary generalised tonic-clonic (SGTC), tonic, atonic, or tonic/atonic that are reviewed and confirmed as resulting in a drop for each subject based on the definition from Epilepsy Study Consortium (ESC): "seizures involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface, or that could have led to a fall or injury depending on the subject's position at the time of the seizure." Measuring and utilising drop seizures therefore encompasses, as per above, the trial population including patients with "multiple seizure types, including tonic and tonic or atonic seizures". To note, since drop seizures result in physical events such as falls and injuries, the data collection for these seizures is considered more easily identifiable, and the accuracy of measurement can be better compared to other seizures. In contrast, the count of non-motor or non-drop seizures tends to vary considerably, likely because of the challenge in consistently counting these subtler seizures*."[3] The EAG accepts the logic of using the most easily measured and verified seizure outcome available, but also notes that this prevents any evaluation of the effects of fenfluramine on less severe seizures, which are also of importance to patients. The assumption that efficacy in reducing severe seizures automatically implies efficacy in reducing less severe seizures may not necessarily hold, because less severe types of seizures may differ from drop seizures in more ways than just severity. For example, they may

differ in terms of pathophysiology, which might lead to different responses to treatment. This therefore remains a key issue.

- Seizure severity is not included as an outcome in the decision problem, despite being included in the NICE scope. No explanation is provided for this. The company were asked to provide an explanation in the request for clarification. The company stated that, "*As mentioned in the decision problem of the CS[1] (page 17), the "seizure severity" was not listed as an outcome as "The severity of seizures was captured through the types of seizures: GTC seizures leading to drops are associated with higher healthcare resource use, and this was captured in the model [through the management costs]." Indeed, GTC seizures are more severe than other types of seizures, for instance, the risk of SUDEP is highly correlated with the experience of uncontrolled and frequent GTC seizures. Patients with any number (one or more) of GTC seizures in the previous year are 27 times more likely to die suddenly compared with people with epilepsy who have not experienced any GTC seizures. Therefore, the use of GTC seizures was the best proxy possible to capture seizure severity as it was not an endpoint collected during fenfluramine's clinical trial. To note, in the only NICE evaluation done on LGS (TA615), "seizure severity" did not appear as an outcome in the decision problem*".[3] The EAG accepts the value of generalised tonic-clonic (GTC) drop seizures as a proxy for seizure severity, but thinks that a continuous measure might be more useful.
- Mortality is not included as an adverse outcome in the decision problem, despite being included in the NICE scope. No explanation is provided for this. The company was asked to provide an explanation in the request for clarification. The company stated that, *"Mortality is included in the decision problem (CS, Table 1, page 17). It is explained that, in the model, mortality accounted for SUDEP and non-SUDEP. Non-SUDEP includes death from accidental causes and status epilepticus 'mortality (SUDEP and non-SUDEP including status epilepticus)."*[3] The EAG is satisfied with this response.

2.5 Other relevant factors

No sub-groups were considered by the company.

EAG comment:

- The lack of sub-groups appears to be a weakness of the submission. Sub-grouping for characteristics that are agreed (pre-hoc) to have a plausible effect on outcome can demonstrate differential effects across population strata. This may be important if the target United Kingdom (UK) population are found to have different population characteristics to the trial population. If these differing characteristics have been shown to influence outcome in a sub-group analysis, reasonable assumptions about the external validity of the trial data to the target population can be made. The company were asked to consider sub-grouping the trial analyses for any patient characteristics that might be thought to influence outcome and to provide population characteristics for the UK target population so that an evaluation of any differences with the trial population can be made. The company stated in response that, "*Subgroups were examined in efficacy analyses and AE summaries. These included subgroups based on age, sex, weight, number of concomitant ASMs, number of prior ASMs, baseline drop seizure frequency (DSF), race, and region. The subgroup analyses were not adequately powered and therefore should be considered exploratory. The observed ranges of the CIs were what would be expected in exploratory analyses that included a small number of subjects. Generally, the analysis results were consistent across all relevant subgroups. This is why no subgroup trial analyses based on patient characteristics were presented in the CS. UK clinical experts were*

consulted following receipt of these clarification questions, and there was no mention of any patient characteristics (sub-groups) that may impact treatment outcome. Rather overall comments were provided on how patients are managed based on the impact ASMs have on certain aspects such as behavioural changes for all patients. One clinician mentioned that LGS is – "such an individualised disease with multiple aetiologies so very hard to identify a specific sub-group". Patient characteristics within the fenfluramine clinical trials have been said to match observed characteristics within UK clinical practice. Furthermore, in NICE evaluation of CBD in LGS (TA615), no subgroup on ASMs were presented as the company stated in their clarification questions that 'these subgroups have small population numbers with low statistical powering."[3] The EAG would have liked to have seen the data for the exploratory sub-group analyses (which were not presented by the company in the clarification response), so that the EAG could have made a judgement on the validity of the company's decision to exclude sub-group analyses from the CS.[1] In addition, whilst clinical opinion suggesting the similarity of the trial and UK target populations is useful, it would have been very helpful if objective data on the UK target population, in terms of plausible confounding variables such as age or ethnicity, had been provided. It is therefore not possible to confirm the external validity of the trial to the target population. This remains a key issue.

- Sub-grouping for specific combinations of the concomitant STAs used in the trial is discussed separately in Section 3.2.3.1

The CS,[1] the NICE scope, and the European Medicine Agency (EMA) and Food and Drug Administration (FDA) marketing authorisations (MAs) do not contain information on the appropriate 'stopping rules' for fenfluramine in LGS.

EAG comment:

- This information is important in economic modelling. The company was therefore asked about the appropriate 'stopping rules' for fenfluramine in LGS. The company replied that, "*Similar to cannabidiol (TA615), 'stopping rules' for fenfluramine are not mentioned within the NICE scope, by EMA or FDA authorities. Therefore, the appropriate stopping rule can be identified by confirming with clinicians what percentage reduction would be applied in UK clinical practice. Following receipt of the clarification questions, UK clinical experts were asked this question and they stated a 25% to 30% reduction in drop seizure frequency would be a reasonable reduction and 6 months should be given before assessing the outcome. This closely aligns with what has been accepted for cannabidiol in treatment LGS (TA615), and clinicians mentioned that also applying the 30% stopping rule for fenfluramine would be appropriate and implementable in clinical practice. Results from additional scenario analysis implementing the 30% stopping rule at 6 months within the cost-effectiveness model (question B11c) can be observed once the company provides the additional analysis to NICE on 21st September 2023.*"[3] The EAG is satisfied with this response.

The EMA MA was granted on 18/12/2020 for the use of fenfluramine in LGS or DS,[4] and FDA MA was granted on 28/03/2022 for the use of fenfluramine in LGS.[5]

In summary, the company amended their decision problem as shown in Table 2.3 below.

Table 2.3: The decision problem (amended after clarification)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Population	People aged 2 and over with LGS whose seizures are inadequately controlled by ECM.	People aged 2 and over with LGS whose seizures are inadequately controlled by ECM.	As per final NICE scope.
Intervention	Fenfluramine hydrochloride.	Fenfluramine hydrochloride in addition to current SoC.	Fenfluramine is not given alone as it is indicated for the treatment of seizures associated with LGS as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.
Comparator(s)	ECM without fenfluramine hydrochloride, which may include combinations of: ASMs, including but not limited to: • CBD + CLB • sodium valproate • lamotrigine • rufinamide • topiramate • felbamate • clobazam • levetiracetam Ketogenic diet Vagus nerve stimulation Surgery	CBD + CLB in addition to SoC, or SoC alone. SoC may include combinations of: ASMs, including but not limited to: • sodium valproate • lamotrigine • rufinamide • topiramate • felbamate • clobazam • levetiracetam Ketogenic diet Vagus nerve stimulation Surgery	Fenfluramine is expected to be provided as an alternative treatment option to CBD + CLB (as per fenfluramine's EMA Orphan Maintenance Assessment Report January 2023). As cannabidiol is the only established clinical add-on therapy to have been formally appraised by NICE, and therefore accepted as a clinically and cost-effective option, it is also the only therapy with sufficient trial data to permit a robust comparison. A primary clinical and economic comparison of fenfluramine + SoC against cannabidiol (with clobazam) + SoC as the comparator is considered the most appropriate, relevant, and robust comparison to address the decision problem in this appraisal. The company also provide an analysis to compare fenfluramine + SoC versus SoC alone.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Outcomes	The outcome 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 • AEs of treatment • HRQoL (patients and carers)	The outcome measures to be considered include: • seizure frequency (drop seizure) • response rate (percentage of reduction of drop seizures within these categories: <25%; 25-50%; 50-75%; >75%) • mortality (SUDEP and non-SUDEP including status epilepticus) • AEs of treatment • HRQoL (patients and carers)	Only drop seizures, characteristic seizures of LGS and primary and key secondary endpoints in the RCT (Study 1601[2]) for fenfluramine, are considered in the company submission. The proportion of people seizure-free is not considered in the model as the proportion of patients who are (drop) seizure-free was very low in the Phase 3 trials of fenfluramine and cannabidiol (either 0 or 1 patient per treatment arm). The severity of seizures was captured through the types of seizures: GTC seizures leading to drops are associated with higher healthcare resource use, and this was captured in the model. Incidence of status epilepticus is not a model outcome per se, but non-SUDEP was considered including status epilepticus deaths.

Based on Table 4 in company response to request for clarification[3]

AEs = adverse events; ASMs = anti-seizure medication; CBD + CLB = cannabidiol + clobazam; CS = company submission; EAG = Evidence Assessment Group; ECM = Established clinical management; EMA = European Medicines Agency; GTC = generalised tonic-clonic; HRQoL = health-related quality of life; LGS = Lennox-Gastaut syndrome; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; RCT = randomised controlled trial; SoC = standard of care; STA = Single Technology Appraisal; SUDEP = sudden unexpected death in epilepsy

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[1, 6] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[7, 8] The EAG has presented only the major limitations of each search strategy in the report.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for Appendix D: Identification, selection and synthesis of clinical evidence (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched /Updated
Electronic databases			
Embase	Ovid	Since inception	05/10/22 07/06/23
MEDLINE (ALL)	Ovid	Since inception	05/10/22 07/06/23
CENTRAL	EBM Reviews (Ovid)	Since inception	05/10/22 07/06/23
HTA database	EBM Reviews (Ovid)	Since inception	05/10/22
CDSR	EBM Reviews (Ovid)	Since inception	05/10/22 07/06/23
DARE	EBM Reviews (Ovid)	Since inception	05/10/22
Conferences			
American Epilepsy Society	Internet	2020–June 2023	05/10/22 07/06/23
The International Society for Health Economics and Outcomes Research	Internet	2020–June 2023	05/10/22 07/06/23
International League Against Epilepsy	Internet	2020–June 2023	05/10/22 07/06/23
European Epilepsy Congress	Internet	2020–June 2023	05/10/22 07/06/23
European Paediatric Neurology Society	Internet	2020–June 2023	05/10/22 07/06/23
American Academy of Neurology	Internet	2020–June 2023	05/10/22 07/06/23
Trials registries			
ClinicalTrials.gov	https://clinicaltrials.gov	Since inception	05/10/22 07/06/23

Resource	Host/Source	Date Ranges	Date searched /Updated
HTA global bodies			
NICE	Internet	Since inception	05/10/22 07/06/23
SMC	Internet	Since inception	05/10/22 07/06/23
CADTH	Internet	Since inception	05/10/22 07/06/23
PBAC (Australia)	Internet	Since inception	05/10/22 07/06/23
IQWiG & GBA (Germany)	Internet	Since inception	05/10/22 07/06/23
Institute for Clinical and Economic Review (US)	Internet	Since inception	05/10/22 07/06/23
HAS (France)	Internet	Since inception	05/10/22 07/06/23
All Wales Therapeutics and Toxicology Centre	Internet	Since inception	05/10/22 07/06/23
INAHTA	Internet	Since inception	05/10/22 07/06/23
NIHR HTA	Internet	Since inception	05/10/22 07/06/23
Guidelines			
EMA	Internet	Since inception	05/10/22 07/06/23
NICE	Internet	Since inception	05/10/22 07/06/23

CADTH = Canadian Agency for Drugs and Technologies in Health; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Reviews of Effects; EBM = evidence based medicine; EMA = European Medicines Agency; GBA = German Federal Joint Committee; HAS = Haute Autorité de Santé; HTA = Health Technology Assessment; INAHTA = International HTA database; IQWiG = Institute for Quality and Efficiency in Health Care; NIHR = National Institute of Health Research; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; US = United States

EAG comment:

- Searches were undertaken in October 2022 and updated in June 2023 to identify relevant clinical evidence for the clinical efficacy of fenfluramine and other treatments for LGS. The CS, Appendix D and the Company's response to clarification provided sufficient details (including database host(s), date searched, and ranges covered) for the EAG to appraise the literature searches.[1, 3, 6]
- The databases 'EBM Reviews - Health Technology Assessment' and 'EBM Reviews - Database of Abstracts of Reviews of Effects (DARE)' were excluded from the update searches as they had been discontinued by the time of searching.

- A broad range of databases and grey literature including trials registers, conference proceedings and Health Technology Assessment (HTA) websites were searched. The bibliographies of relevant systematic literature reviews (SLRs)/meta-analyses were handsearched to identify additional relevant papers.
- Database searches were not restricted by publication date or language.
- Searches were well structured, transparent and reproducible, and a good range of subject indexing terms (MeSH/EMTREE) and free text was used.
- The EAG noted that in Appendix D, Table 1 the company reported a search of "*MEDLINE and MEDLINE In-process (via Ovid)*".[6] The EAG queried if this search included MEDLINE daily update and MEDLINE Epub Ahead of Print, the company confirmed that the search was run on MEDLINE ALL which contains these segments.
- Separate searches to retrieve information regarding AEs for safety outcomes for fenfluramine were not conducted. In their response to clarification the company reported "*Additional information on the safety of fenfluramine was retrieved from the UCB clinical study report (CSR), as described in Appendix D, section 1.1.2. No other additional searches were conducted to retrieve data on AEs for fenfluramine*".[3] However these searches were limited to RCTs, and guidance by the Centre for Reviews and Dissemination (CRD)[9] and Golder et al.[10] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that AEs that are long-term, rare or unanticipated are not missed.

3.1.2 Inclusion criteria

A SLR conducted in October 2022, was performed by the company to identify all RCTs investigating the efficacy and safety evidence of fenfluramine and the other ASMs in LGS.

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.2.

Table 3.2: Eligibility criteria used in the systematic review

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Children and/or adults with LGS,	Other epilepsy types or syndromes including epileptic symptoms.
Intervention	1. Pharmacological interventions medications, including, but not limited to: a. fenfluramine b. cannabidiol c. sodium valproate d. lamotrigine e. rufinamide f. topiramate g. felbamate h. clobazam i. levetiracetam 2. Ketogenic diet 3. Vagus nerve stimulation Interventions may be given in addition to ECM.	No restrictions stated.

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	Interventions may also be given as monotherapy or in combination with each other.	
Comparators	No restriction on comparator applied.	None.

Outcomes	• Seizure frequency (overall and by seizure type [e.g., drop attacks])
	• Response rate (overall and by seizure type)
	• Seizure severity
	• Behavioural impact
	• Incidence of status epilepticus
	• Mortality
	• AEs
	  ○ Any TEAEs
	  ○ Any SAEs
	  ○ Any Grade 3/4 AEs
	  ○ AESI (i.e., somnolence, lethargy, status epilepticus, decreased weight, decreased appetite, psychiatric AE)
	  ○ Treatment discontinuation or patient withdrawals
		Studies not reporting on outcomes of interest

Study design	• RCTs, including crossover within RCT and randomised dose finding and formulation studies with either a control or active control arm) • Open-label extension or follow-up of RCT* • Non-RCTs* • Single-arm clinical trials* • Systematic reviews/meta-analyses of RCTs or non-randomised studies	• RWE studies • Non-systematic reviews • *In vitro* studies • Studies in animals • Comments • Letters • Editorials • Case reports • Case-series
Date	Database search: no restriction Conference abstracts: 2020-June 2023	-
Language	No restriction	-
Other	None	-

Based on Table 8 of Appendix D of the CS[6]

*A hierarchical screening approach was employed whereby available RCTs from the literature search were screened for inclusion first. Following completion of full-text screening and review of available evidence, a pragmatic decision was made to include only RCT evidence for the SLR. This is because RCTs are considered the most robust type of study design for producing an unbiased estimate of the intervention effects. Long-term open-label extension studies were not included for data extraction as they were not considered relevant for the NMA due to potential biases.

Clinical effectiveness	Inclusion criteria	Exclusion criteria
AE = adverse event; AESIs = adverse event of special interest; CS = company submission; ECM = established clinical management; LGS = Lennox-Gastaut syndrome; NMA = network meta-analysis; RCT = randomised controlled trial; RWE = real world evidence; SAE = serious adverse event; SLR = systematic literature review; TEAE = treatment emergent adverse event		

EAG comment:

- The alteration of the protocol for study type after the onset of the SLR presents a risk of bias. Applying the restriction after the potential unveiling of the results of non-randomised studies opens up the possibility that the restriction may have been prompted by non-conducive results in those studies. The SLR should, of course, have been restricted to RCTs in the first instance, but the impression is given that the company only forfeited the inappropriately wide scope when this was not seen to offer a benefit.
- In terms of the population and comparators the SLR protocol fits with the decision problem and NICE scope.
- In terms of the outcomes, the SLR covers all the decision problem and NICE scope outcomes, with the addition of 'behavioural impact'.
- The selection criteria did not have a restriction on language, but eight studies were excluded in full-text screening for "Not in English". The company was asked to clarify the inclusion criteria for language and assess these excluded articles for inclusion. The company stated in response that, "*Systematic literature searches were conducted with the eligibility criterion of being written in English only. Table 8 in CS Appendices should have indicated 'Language: English,' similar to the other tables presenting PICOS (Tables 57, 67, and 82 in the CS Appendices). Figure 1 in the CS Appendices is considered accurate; it shows that eight records were excluded because they were not written in English.*"[3] The EAG is satisfied with this response.

3.1.3 Critique of data extraction

Studies were screened against the population, intervention, comparison, outcomes, and study type (PICOS) eligibility criteria (as outlined in Table 3.2 above) in the DistillerSR platform by two independent reviewers with discrepancies being 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.

During the full-text screening, top-level information was recorded on the trial/study name, trial registration number, setting, interventions (e.g., name, dose and frequency), and sample size. This information was used to map out related publications reporting on the same study population and to detect duplicate publications to avoid any potential data overlap during data abstraction.

Although the SLR originally considered any clinical trial design (i.e., randomised, non-randomised controlled and single-arm trials), as well as open-label extension studies, the selection criteria were retrospectively adjusted to systematically include only RCTs. This decision was made as other clinical trial designs and open-label extension studies were not considered relevant for the purposes of the NMA.

EAG comment:

- Methodology used in the SLR appears adequate.

3.1.4 Quality assessment

A risk of bias analysis was conducted for all included 16 primary publications using the Cochrane Risk of Bias Assessment (RoB) Tool 2.0 (Table 3.3). Overall, the company thought that most concerns did not impact the overall integrity of any individual study as the bias was considered not to have impacted on the key outcomes of interest.

Table 3.3: Risk of bias in the included RCTs

Study, Year	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall judgement
Knupp, 2022[2] ZX008-1601 (NCT03355209) Fenfluramine versus placebo	Low	Low	Low	Low	Low	Low
Hahn, 2022[11] ELEKTRA (NCT03650452) Soticlestat versus placebo	Low	Low	Low	Low	Low	Low
Dalic, 2022[12] ACTRN12621001233819 CM-DBS versus control	Low	Low	Low	Low	Low	Low
Auvichayapat, 2016[13] (NCT02731300) Cathodal tDCS versus sham	Low	Low	Low	Low	Low	Low
Devinsky, 2018[14] GWPCARE3 (NCT02224560) Cannabidiol versus placebo	Low	Low	Low	Low	Low	Low
Thiele, 2018[15] GWPCARE4 (NCT02224690) Cannabidiol versus placebo	Low	Low	Low	Low	Low	Low
Arzimanoglou, 2016[16] Study 303 (NCT01405053) Rufinamide versus placebo	Low	Low	High	Low	Low	High High attrition rate
Ohtsuka, 2014[17] E2080-J081-304 (NCT01146951) Rufinamide versus placebo	Some concern	Low	Low	Low	Low	Some concern Baseline differences between groups
Ng, 2011[18]	Low	Low	High	Low	Low	High

Study, Year	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall judgement
OV-1012 (NCT00518713) Clobazam versus placebo						High attrition rate
Conry, 2009[19] Clobazam (dose comparison)	Low	Low	Low	Some Concern	Low	Some concern Missingness of study control arm
Glauser, 2008[20] Study 022 Rufinamide versus placebo	Low	Low	Low	Low	Low	Low
Motte, 1997[21] Lamotrigine versus placebo	Low	Low	Some Concern	Low	Low	Some concern High attrition rate
Jensen, 1994[22] Felbamate versus placebo	Low	Low	Low	Low	Low	Low
Ritter, 1993[23] Felbamate versus placebo	Low	Low	Some Concern	Low	Low	Some concern High attrition rate
Sachdeo, 1999[24] Topiramate (6 mg/kg) versus placebo	Low	Low	Low	Low	Low	Low
Crumrine, 1989[25] Cinromide versus placebo	Low	Low	Some Concern	Low	Low	Some concern High attrition rate
Based on Table 21, CS Appendices[6] CS = company submission; RCT = randomised controlled trial; tDCS = transcranial deep cortical stimulation						

EAG comment:

- The EAG questions the accuracy of the positive evaluation of the 'randomisation process' in 15/16 studies, because most of the studies did not provide evidence of the use of allocation concealment. Only 4/16 studies mentioned the use of an interactive web-response system, and other studies did not mention other conventional approaches such as the sealed envelope method.

3.1.5 Evidence synthesis

The database searches returned 1,970 records. After removing 700 duplicates, 1,270 records were screened at the title and abstract level, of which 977 were excluded and 293 were included for full-text screening. After full-text screening, 38 publications were included reporting on 16 unique studies in LGS (Table 3.4).

Figure 3.1 shows the final literature selection procedure, with the number of records excluded at each stage.

Table 3.4: Primary and secondary publications for LGS efficacy studies included in the SLR

Trial Name	Primary publications	Secondary publications
Study 1601[2] (NCT03355209)	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. Jun 1 2022;79(6):554-564. doi:10.1001/jamaneurol.2022.0829	UCB. Clinical Safety Report – Fintepla Bishop K, Isquith P, Giola G, et al. Fenfluramine Improves Everyday Executive Functioning in Patients With Lennox-Gastaut Syndrome: Analysis of Phase 3 Data (P12-8.004). Neurology. 2022;98(18 Supplement):3017 Bishop KI, Isquith PK, Gioia GA, et al. Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (< 5 years) with Dravet syndrome. Epilepsy & Behavior. 2023;138:108994
ELEKTRA[11] (NCT03650452)	Hahn CD, Jiang Y, Villanueva V, et al. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox-Gastaut syndrome (ELEKTRA). Epilepsia. Oct 2022;63(10):2671-2683. doi:10.1111/epi.17367	Hahn CD, Jiang Y, Villanueva V, et al. Efficacy, safety and tolerability of soticlestat (TAK-935/OV935) as adjunctive therapy in pediatric patients with dravet syndrome and lennox-gastaut syndrome (ELEKTRA). Neurology. 2021;96(15 SUPPL 1)73rd Annual Meeting of the American Academy of Neurology, AAN 2021. Virtual Clinicaltrials.gov. A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 (OV935) as an Adjunctive Therapy in Pediatric Patients With Developmental and/or Epileptic Encephalopathies (NCT03650452). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT03650452
ESTEL[12] (ACTRN12621001233819)	Dalic LJ, Warren AEL, Bulluss KJ, et al. DBS of Thalamic Centromedian Nucleus for Lennox-Gastaut Syndrome (ESTEL Trial). Ann Neurol. Feb 2022;91(2):253-267. doi:10.1002/ana.26280	Dalic L, Antoniou X, Spiegl C, Warren A, Bulluss K, Roten A, et al., editors. Generalised epileptic fast activity is a biomarker for changes in seizure frequency in Lennox-Gastaut syndrome. EPILEPSIA; 2022: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA Dalic LJ, Warren AE, Spiegel C, Thevathasan W, Roten A, Bulluss KJ, et al. Paroxysmal fast activity is a biomarker of treatment response in deep brain stimulation for Lennox–Gastaut syndrome. Epilepsia. 2022;63(12):3134-47

Trial Name	Primary publications	Secondary publications
GWPCARE4[15] (NCT02224690)	Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. Mar 17 2018;391(10125):1085-1096. doi:10.1016/s0140-6736(18)30136-3	Gunning B, Mazurkiewicz-Beldzinska M, Chin RFM, et al. Cannabidiol in conjunction with clobazam: analysis of four randomized controlled trials. Acta Neurologica Scandinavica. 2021;143(2):154-163. doi:https://dx.doi.org/10.1111/ane.13351 Ostrovsky DA, Ehrlich A. Addition of Cannabidiol to Current Antiepileptic Therapy Reduces Drop Seizures in Children and Adults With Treatment-Resistant Lennox-Gastaut Syndrome. Explore. 2018;14(4):311-313. doi:https://dx.doi.org/10.1016/j.explore.2018.04.005 Privitera M, Bhathal H, Wong M, et al. Time to onset of cannabidiol (CBD) treatment effect in Lennox-Gastaut syndrome: Analysis from two randomized controlled trials. Epilepsia. 2021;62(5):1130-1140. doi:https://dx.doi.org/10.1111/epi.16878 Auvin S, Nortvedt C, Fuller DS, Sahebkar F. Seizure-free days as a novel outcome in patients with Lennox-Gastaut syndrome: post hoc analysis of patients receiving cannabidiol in two randomized controlled trials. Epilepsia. 2023
GWPCARE3[14] (NCT02224560)	Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. May 17 2018;378(20):1888-1897. doi:10.1056/NEJMoa1714631	Gunning B, Mazurkiewicz-Beldzinska M, Chin RFM, et al. Cannabidiol in conjunction with clobazam: analysis of four randomized controlled trials. Acta Neurologica Scandinavica. 2021;143(2):154-163. doi:https://dx.doi.org/10.1111/ane.13351 Privitera M, Bhathal H, Wong M, et al. Time to onset of cannabidiol (CBD) treatment effect in Lennox-Gastaut syndrome: Analysis from two randomized controlled trials. Epilepsia. 2021;62(5):1130-1140. doi:https://dx.doi.org/10.1111/epi.16878 Clinicaltrials.gov. Efficacy and Safety of GWP42003-P for Seizures Associated With Lennox-Gastaut Syndrome in Children and Adults (NCT02224560). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT02224560

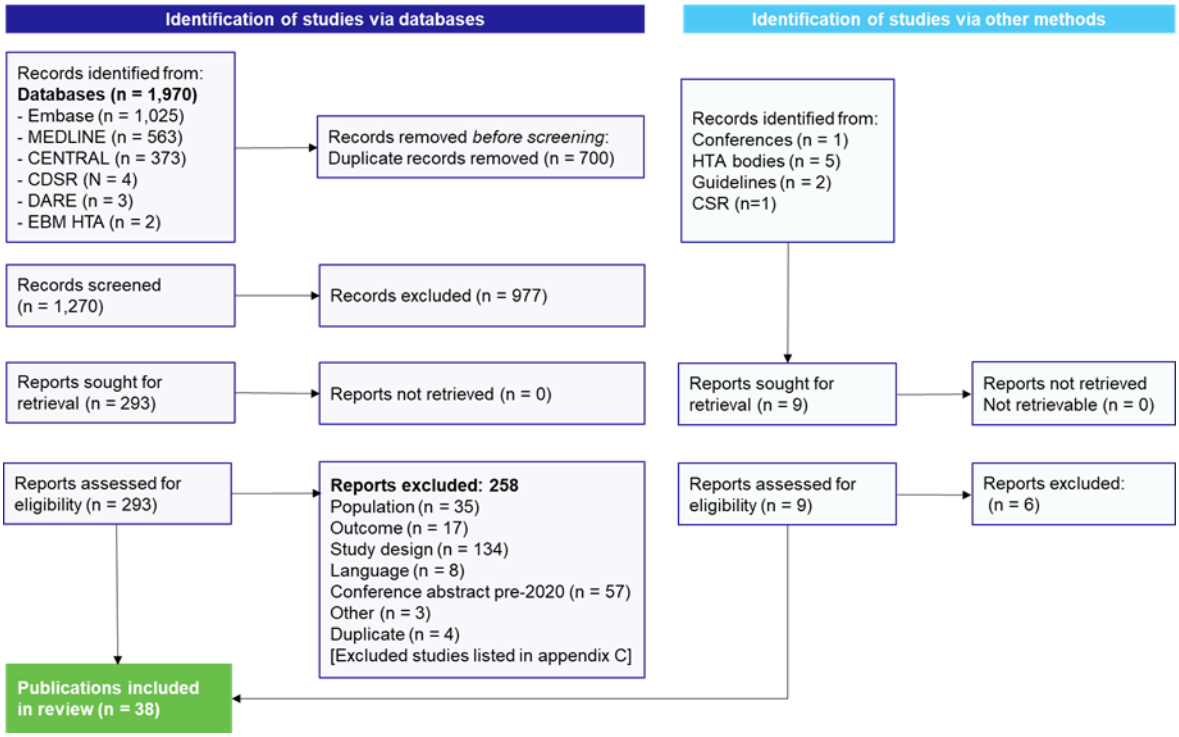
Trial Name	Primary publications	Secondary publications
		Auvin S, Nortvedt C, Fuller DS, Sahebkar F. Seizure-free days as a novel outcome in patients with Lennox-Gastaut syndrome: post hoc analysis of patients receiving cannabidiol in two randomized controlled trials. Epilepsia. 2023
Auvichayapat, 2016[13] (NCT02731300)	Auvichayapat N, Sinsupan K, Tunkamnerdthai O, Auvichayapat P. Transcranial Direct Current Stimulation for Treatment of Childhood Pharmacoresistant Lennox-Gastaut Syndrome: A Pilot Study. Front Neurol. 2016;7:66. doi:10.3389/fneur.2016.00066	Clinicaltrials.gov. Transcranial Direct Current Stimulation, Treatment of Childhood Drug-Resistant Lennox-Gastaut Syndrome, A Pilot Study (NCT02731300). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT02731300
Arzimanoglou, 2016 Study 303[16] (NCT01405053)	Arzimanoglou A, Ferreira JA, Satlin A, et al. Safety and pharmacokinetic profile of rufinamide in pediatric patients aged less than 4 years with Lennox-Gastaut syndrome: An interim analysis from a multicenter, randomized, active-controlled, open-label study. Eur J Paediatr Neurol. May 2016;20(3):393-402. doi:10.1016/j.ejpn.2015.12.015	Clinicaltrials.gov. Study of Rufinamide in Pediatric Subjects 1 to Less Than 4 Years of Age With Lennox-Gastaut Syndrome Inadequately Controlled With Other Anti-epileptic Drugs (NCT01405053). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT01405053 Auvin S, Williams B, McMurray R, Kumar D, Perdomo C, Malhotra M. Novel seizure outcomes in patients with Lennox-Gastaut syndrome: Post hoc analysis of seizure-free days in rufinamide Study 303. Epilepsia Open. 2019;4(2):275-280. doi:https://dx.doi.org/10.1002/epi4.12314 Arzimanoglou A, Ferreira JA, Satlin A, et al. Safety and pharmacokinetic profile of rufinamide in pediatric patients aged less than 4 years with Lennox-Gastaut syndrome: An interim analysis from a multicenter, randomized, active-controlled, open-label study. Eur J Paediatr Neurol. May 2016;20(3):393-402. doi:10.1016/j.ejpn.2015.12.015
Ohtsuka, 2014[17] E2080-J081-304 (NCT01146951)	Ohtsuka Y, Yoshinaga H, Shirasaka Y, Takayama R, Takano H, Iyoda K. Rufinamide as an adjunctive therapy for Lennox-Gastaut syndrome: a randomized double-blind placebo-controlled trial in Japan. Epilepsy Res. Nov 2014;108(9):1627-36. doi:10.1016/j.eplepsyres.2014.08.019	Clinicaltrials.gov. A Placebo-Controlled, Double-Blind Comparative Study of E2080 in Lennox-Gastaut Syndrome Patients (Study E2080-J081-304; NCT01146951). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT01146951

Trial Name	Primary publications	Secondary publications
Ng, 2011[18] **Secondary publications:** **OV-1012 (NCT00518713)**	Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology. Oct 11 2011;77(15):1473-81. doi:10.1212/WNL.0b013e318232de76	Cochrane Central Register of Controlled Trials. Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Clobazam (0.25, 0.5 and 1.0 mg/kg/day) in Patients with Lennox-Gastaut Syndrome. https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2007-004322-24-LT, 2008 | added to CENTRAL: 31 March 2019 | 2019 Issue 3 Paolicchi JM, Ross G, Lee D, Drummond R, Isojarvi J. Clobazam and Aggression-Related Adverse Events in Pediatric Patients with Lennox-Gastaut Syndrome. Pediatric Neurology. 2015;53(4):338-342. doi:https://dx.doi.org/10.1016/j.pediatrneurol.2015.06.021
Conry, 2009[19]	Conry JA, Ng YT, Paolicchi JM, et al. Clobazam in the treatment of Lennox-Gastaut syndrome. Epilepsia. May 2009;50(5):1158-66. doi:10.1111/j.1528-1167.2008.01935.x	No secondary publications identified.
Glauser, 2008[20] **Study 022**	Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology. May 20 2008;70(21):1950-8. doi:10.1212/01.wnl.0000303813.95800.0d	Arzimanoglou A, Pringsheim M, Kluger GJ, Genton P, Perdomo C, Malhotra M. Safety and efficacy of rufinamide in children and adults with Lennox-Gastaut syndrome: A post hoc analysis from Study 022. Epilepsy Behav. Sep 9 2021;124:108275. doi:10.1016/j.yebeh.2021.108275 McMurray R, Striano P. Treatment of Adults with Lennox-Gastaut Syndrome: Further Analysis of Efficacy and Safety/Tolerability of Rufinamide. Neurol Ther. Jun 2016;5(1):35-43. doi:10.1007/s40120-016-0041-9
Sachdeo, 1999[24]	Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G. A double-blind, randomized trial of topiramate in Lennox–Gastaut syndrome. Neurology. 1999;52(9):1882. doi:10.1212/WNL.52.9.1882	No secondary publications identified.
Motte, 1997[21]	Motte J, Trevathan E, Arvidsson JF, Barrera MN, Mullens EL, Manasco P. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. Lamictal	No secondary publications identified.

Trial Name	Primary publications	Secondary publications
	Lennox-Gastaut Study Group. N Engl J Med. Dec 18 1997;337(25):1807-12. doi:10.1056/nejm199712183372504	
Jensen, 1994[22]	Jensen PK. Felbamate in the treatment of Lennox-Gastaut syndrome. Epilepsia. 1994;35 Suppl 5:S54-7. doi:10.1111/j.1528-1157.1994.tb05969.x	No secondary publications identified.
Ritter, 1993[23]	Ritter FJ, Leppik IE, Dreifuss FE, et al. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). New England Journal of Medicine. 1993;328(1):29-33. doi:https://dx.doi.org/10.1056/NEJM199301073280105	No secondary publications identified.
Crumrine, 1989[25]	Crumrine P, Dreifuss FE, Corwin H, et al. Double-blind, placebo-controlled evaluation of cinromide in patients with the Lennox-Gastaut Syndrome. Epilepsia. 1989;30(4):422-429	No secondary publications identified.

Based on Table 9, CS Appendices[6]
CS = company submission; DBS = deep brain stimulation; E2080 = rufinamide; SLR = systematic literature review; TAK-935 = sotilestat

Figure 3.1: PRISMA flow diagram



Based on Figure 1 in CS Appendices[6]
CS = company submission; HTA = Health Technology Assessment; CSR = clinical study report; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

From these 16 RCTs, pairwise analyses for the key outcomes were conducted.

3.1.5.1 Pairwise analyses from the SLR

Response rate for drop attacks

Response rate as measured by achieving a ≥25%, ≥50%, ≥75% or 100% reduction in drop attack frequency from baseline to the point of participant follow-up, was reported by nine of the identified studies (Table 3.5). The definitions of drop seizures varied significantly between studies, but in most cases drop seizures were defined as atonic or tonic seizures that led or could lead to falls.

EAG comment:

- Results from the pairwise comparisons in the 16 included RCTs are not fully reported, with no between-group confidence intervals (CIs) or p values for response rates (Table 14 in CS appendices)[6].

Table 3.5: Percentage of patients achieving ≥25%, ≥50%, ≥75% reduction in drop attacks from baseline and seizure freedom

Author, Year	Timepoint	Intervention	N	Drop seizure			
				≥25% reduction	≥50% reduction	≥75% reduction	Seizure freedom
				%	%	%	%
Knupp, 2022[2] Study 1601 (NCT03355209)	14 weeks	Fenfluramine (0.2 mg/kg)	89	46%	27%	9%	1%
		Fenfluramine (0.7 mg/kg)	87	51%	26%	8%	0%
		Placebo	87	31%	9%	3%	1%
Hahn, 2022[11] ELEKTRA (NCT03650452)	20 weeks	Soticlestat (100-300 mg)	43	-	16%	12%	0%
		Placebo	45	-	13%	0%	0%
Dalic, 2022[12] ESTEL (ACTRN12621001233819)	24 weeks	CM-DBS	10	-	-	-	-
		Control	9	-	-	-	-
Auvichayapat, 2018[13] NCT02731300	4 weeks	Cathodal tDCS	15	-	-	-	-
		Sham	7	-	-	-	-
Devinsky, 2018[14] GWPCARE3 (NCT02224560)	14 weeks	Cannabidiol (10 mg/kg)	73	63%	36%	11%	0%
		Cannabidiol (20 mg/kg)	76	62%	39%	25%	0%
		Placebo	76	43%	14%	3%	0%
Thiele, 2018[15] GWPCARE4 (NCT02224690)	14 weeks	Cannabidiol (20 mg/kg)	86	64%	44%	20%	0%
		Placebo	85	44%	24%	8%	0%
Arzimanoglou, 2016[16] Study 303 (NCT01405053)	106 weeks	Rufinamide (45 mg/kg)	25	-	-	-	-
		Any other ASM	11	-	-	-	-
Ohtsuka, 2014[17] E2080-J081-304 (NCT01146951)	12 weeks	Rufinamide (1,000-3,200 mg)	28	-	-	-	-
		Placebo	30	-	-	-	-
Ng, 2011[18]	15 weeks	Clobazam (0.25 mg/kg)	58	64%	43%	28%	8%

Author, Year	Timepoint	Intervention	N	Drop seizure			
				≥25% reduction	≥50% reduction	≥75% reduction	Seizure freedom
				%	%	%	%
Secondary publications: OV-1012 (NCT00518713)		Clobazam (0.50 mg/kg)	62	79%	59%	38%	12%
		Clobazam (1.0 mg/kg)	59	84%	78%	63%	25%
		Placebo	59	49%	32%	11%	4%
Conry, 2009[19]	7 weeks	Clobazam (0.25 mg/kg)	32	56%	38%	25%	6%
		Clobazam (1.0 mg/kg)	36	89%	83%	67%	22%
Glauser, 2008[20] Study 022	12 weeks	Rufinamide (45 mg/kg)	74	-	43%	-	-
		Placebo	64	-	17%	-	-
Sachdeo, 1999[24]	11 weeks	Topiramate (6 mg/kg)	48	-	28%	17%	2%
		Placebo	50	-	14%	6%	0%
Motte, 1997[21]	16 weeks	Lamotrigine (100-400 mg)	79	-	37%	-	-
		Placebo	90	-	22%	-	-
Jensen, 1994[22]	10 weeks	Felbamate (45 mg/kg)	36	-	-	-	-
		Placebo	35	-	-	-	-
Ritter, 1993[23]	10 weeks	Felbamate (45 mg/kg)	37	-	-	-	-
		Placebo	36	-	-	-	-
Crumrine, 1989[25]	18 weeks	Cinromide (20-40 mg/kg)	26	-	-	-	-
		Placebo	30	-	-	-	-

Based on Table 14, CS Appendices[6]
ASM = anti-seizure medication; CM-DBS = centromedian deep brain stimulation; CS = company submission; kg = kilograms; mg = milligrams; N = sample size; tDCS = transcranial deep cortical stimulation

Seizure frequency

Changes in seizure frequency were typically reported as a percentage change in the median seizure frequency over a 28-day period at study baseline compared to the frequency during the final 28-day period of study follow-up (Tables 3.6 and 3.7).

Table 3.6: Change from baseline in total and DSF

Author, Year	Timepoint	Intervention	N	Total seizures			Drop seizures		
				Baseline seizure frequency (median)	Seizure frequency (median CFB)	Mean difference versus placebo (95% CI)	Baseline seizure frequency (median)	Seizure frequency (median CFB)	Mean difference versus placebo (95% CI)
Knupp, 2022[2] Study 1601 (NCT03355209)	14 weeks	Fenfluramine (0.2 mg/kg)	89	106	-11.8% (range NR)	-6% (-19.9% to 7.9%)	85	-14.6% (range NR)	-10.5% (-25% to 4%)
		Fenfluramine (0.7 mg/kg)	87	111	-26.3% (range NR)	-18.2% (-19.9% to 7.9%)	83	-26.5% (range NR)	-19.9% (-31% to -8.7%)
		Placebo	87	68	-8.4% (range NR)	-	53	-7.6% (range NR)	N/A
Hahn, 2022[11] ELEKTRA (NCT03650452)	20 weeks	Soticlestat (100–300 mg)	43	159.7	-	-	67.3	-	-14.81% (-34.47 to 4.62%)
		Placebo	45	153.5	-	-	89.8	-	NA
Dalic, 2022[12] ESTEL (ACTRN12621001233819)	24 weeks	CM-DBS	10	70[†**]	-35.2% (-50.8 to -19.6%)	-36.3% (-83.6% to 11.09%)	-	-	-
		Control	9	85[†**]	-16.9% (-36.5 to 2.8%)	N/A	-	-	-
Auvichayapat, 2018[13] NCT02731300	4 weeks	Cathodal tDCS	15	80.7[‡**] (54.4)	-	-	-	-	-
		Sham	7	93.4[‡**] (59.9)	-	-	-	-	-

Author, Year	Timepoint	Intervention	N	Total seizures			Drop seizures		
				Baseline seizure frequency (median)	Seizure frequency (median CFB)	Mean difference versus placebo (95% CI)	Baseline seizure frequency (median)	Seizure frequency (median CFB)	Mean difference versus placebo (95% CI)
Arzimanoglou, 2016[16] Study 303 (NCT01405053)	106 weeks	Rufinamide (45 mg/kg)	25	-	-7.1%* (-79.2, 3,644.0)				
		Any other ASM	12	-	-20.2%* (-83.30, 143.10)				
Devinsky, 2018[14] GWPCARE3 (NCT02224560)	14 weeks	Cannabidiol (10 mg/kg)	73	165	-36.4% (range NR)	-19.5% (-30.4% to -7.5%)	86.9	-37.2% (range NR)	-19.2% (-31.2% to -7.7%)
		Cannabidiol (20 mg/kg)	76	174.3	-38.4% (range NR)	-18.8% (-31.8% to -4.4%)	85.5	-41.9% (range NR)	-21.6% (-34.8% to -6.7%)
		Placebo	76	180.6	-18.5% (range NR)	N/A	80.3	-17.2% (range NR)	N/A
Thiele, 2018[15] GWPCARE4 (NCT02224690)	14 weeks	Cannabidiol (20 mg/kg)	86	144.6	-41.2% (range NR)	-21.13% (-33.26% to -9.37%)	71.4	-43.9% (range NR)	-17.21% (-30.32 to -4.09%)
		Placebo	85	176.7	-13.7% (range NR)	NA	74.7	-21.8% (range NR)	NA
Ohtsuka, 2014[17] E2080-J081-304 (NCT01146951)	12 weeks	Rufinamide (1000–3200 mg)	28	253.0	-32.9% (-87.30, 15.40)	-	-	-	-
		Placebo	30	296.7	-3.1% (-52.20, 133.00)	-	-	-	-

Author, Year	Timepoint	Intervention	N	Total seizures			Drop seizures		
				Baseline seizure frequency (median)	Seizure frequency (median CFB)	Mean difference versus placebo (95% CI)	Baseline seizure frequency (median)	Seizure frequency (median CFB)	Mean difference versus placebo (95% CI)
Conry, 2009[19]	7 weeks	Clobazam (0.25 mg/kg)	32	-	-	-	-	-12% (range NR)	-
		Clobazam (1.0 mg/kg)	36	-	-	-	-	-85% (range NR)	-
Ng, 2011[18] Secondary publications: OV-1012 (NCT00518713)	15 weeks	Clobazam (0.25 mg/kg)	58	-	-34.8% (95% CI -52.5, -17.2)	-	40.9	-41.2% (95% CI -57.6, -24.9)	-29.1% (NR)
		Clobazam (0.50 mg/kg)	62	-	-45.3% (95% CI -62.5, -28.1)	-	23.5	-49.4% (95% CI -65.4, -33.4)	-37.3% (NR)
		Clobazam (1.0 mg/kg)	59	-	-65.3% (95% CI -83.5, -47.2)	-	28.9	-68.3% (95% CI -85.1, 51.5)	-56.1% (NR)
		Placebo	59	-	-9.3% (95% CI -26.3, 7.6)	-	35.5	-12.1% (95% CI -27.8, -3.6)	N/A
Glauser, 2008[20] Study 022	12 weeks	Rufinamide (45 mg/kg)	74	290	-32.7% (-92.3, 381.4)	-	92	-42.5% (range -100 to 1,191)	-
		Placebo	64	205	-11.7% (-82.8, 550.6)	-	92.5	1.4% (range -100 to 710)	-
Sachdeo, 1999[24]	11 weeks	Topiramate	46	267	-	-	90	-14.8%	-

Author, Year	Timepoint	Intervention	N	Total seizures			Drop seizures		
				Baseline seizure frequency (median)	Seizure frequency (median CFB)	Mean difference versus placebo (95% CI)	Baseline seizure frequency (median)	Seizure frequency (median CFB)	Mean difference versus placebo (95% CI)
		(6 mg/kg)						(range NR)	
		Placebo	50	244	-	-	98	5.1% (range NR)	-
Motte, 1997[21]	16 weeks	Lamotrigine (100–400 mg)	79	-	-32.0% (range NR)	-	14.5	-34.0% (range NR)	-
		Placebo	90	-	-9.0% (range NR)	-	11.6	-9.0% (range NR)	-
Jensen, 1994[22]	10 weeks	Felbamate (45 mg/kg)	35	-	-	-	-	-	-
		Placebo	36	-	-	-	-	-	-
Ritter, 1993[23]	10 weeks	Felbamate (45 mg/kg)	37	1,617	-19.0% (-99.0, 437.0)	-	-	-	-
		Placebo	36	716	4.0% (-74.0, 176.0)	-	-	-	-
Crumrine, 1989[25]	18 weeks	Cinromide (20–40 mg/kg)	26	208	181	-	-	-	-
		Placebo	30	139	129	-	-	-	-

Based on Table 15, CS Appendices[6]
ASM = anti-seizure medication; CFB = change from baseline; CI = confidence intervals; CM-DBS= centromedian deep brain stimulation; CS = company submission; DSF = drop seizure frequency; kg = kilogram; mg = milligram; N = sample size; N/A = not applicable; NR = not reported; tDCS= transcranial direct current stimulation
*The study population notably differed from other studies (only patients below 4 years old were included).

Table 3.7: Change from baseline in GTC and TCT seizure frequency

Author, Year	Timepoint	Intervention	N	GTC seizures			Tonic-clonic seizures		
				50% response rate	Seizure frequency (median CFB)	Seizure frequency; mean difference versus placebo (95% CI)	≥50% response rate	Seizure frequency (median CFB)	Seizure frequency; mean difference versus placebo (95% CI)
Knupp, 2022[2] Study 1601 (NCT03355209)	14 weeks	Fenfluramine (0.2 mg/kg)	89	63%	-58.2% (range NR)	-60.4% (-84.9% to -36%)	-	-	-
		Fenfluramine (0.7 mg/kg)	87	50%	-45.7% (range NR)	-50.3 (-76.7% to -23.8%)	-	-	-
		Placebo	87	18%	3.7% (range NR)	N/A	-	-	-
Hahn, 2022[11] ELEKTRA (NCT03650452)	20 weeks	Soticlestat (100–300 mg)	43	-	-	-	-	-	-
		Placebo	45	-	-	-	-	-	-
Dalic, 2022[12] ESTEL (ACTRN12621001233819)	24 weeks	CM-DBS	10	-	-	-	-	-	-
		Control	9	-	-	-	-	-	-
Auvichayapat, 2018[13] NCT02731300	4 weeks	Cathodal tDCS	15	-	-	-	-	-	-
		Sham	7	-	-	-	-	-	-
Devinsky, 2018[14] GWPCARE3 (NCT02224560)	14 weeks	Cannabidiol (10 mg/kg)	73	-	-	-	-	-	-0.3992 (-0.6455 to -0.1966)
		Cannabidiol (20 mg/kg)	76	-	-	-	-	-	-0.2795 (-0.5199 to -0.0286)

Author, Year	Timepoint	Intervention	N	GTC seizures			Tonic-clonic seizures		
				50% response rate	Seizure frequency (median CFB)	Seizure frequency; mean difference versus placebo (95% CI)	≥50% response rate	Seizure frequency (median CFB)	Seizure frequency; mean difference versus placebo (95% CI)
		Placebo	76	-	-	-	-	-	-
Thiele, 2018[15] GWPCARE4 (NCT02224690)	14 weeks	Cannabidiol (20 mg/kg)	86	-	-	-	0.5102	-	-0.2277 (-0.4494 to 0.0037)
		Placebo	85	-	-	-	0.2642	-	-
Ohtsuka, 2014[17] E2080-J081-304 (NCT01146951)	12 weeks	Rufinamide (1,000–3,200 mg)	28	-	-	-	-	-0.574 (-100; -14.7)	-
		Placebo	30	-	-	-	-	0.024 (-75.8; 450)	-
Ng, 2011[18] Secondary publications: OV-1012 (NCT00518713)	15 weeks	Clobazam (0.25 mg/kg)	58	-	-	-	-	-	-
		Clobazam (0.50 mg/kg)	62	-	-	-	-	-	-
		Clobazam (1.0 mg/kg)	59	-	-	-	-	-	-
		Placebo	59	-	-	-	-	-	-
Glauser, 2008[20] Study 022	12 weeks	Rufinamide (45 mg/kg)	74	-	-	-	-	-0.456 (-100; 789.2)	-
		Placebo	64	-	-	-	-	-0.181 (-100; 729.6)	-
Sachdeo, 1999[24]	11 weeks	Topiramate (6 mg/kg)	46	-	-	-	-	-	-

Author, Year	Timepoint	Intervention	N	GTC seizures			Tonic-clonic seizures		
				50% response rate	Seizure frequency (median CFB)	Seizure frequency; mean difference versus placebo (95% CI)	≥50% response rate	Seizure frequency (median CFB)	Seizure frequency; mean difference versus placebo (95% CI)
		Placebo	50	-	-	-	-	-	-
Motte, 1997[21]	16 weeks	Lamotrigine (100–400 mg)	79	-	-	-	0.43	-0.36 (range NR)	-
		Placebo	90	-	-	-	0.2	0.1 (range NR)	-
Jensen, 1994 [22]	10 weeks	Felbamate (45 mg/kg)	35	-	-	-	-	-	-
		Placebo	36	-	-	-	-	-	-
Ritter, 1993[23]	10 weeks	Felbamate (45 mg/kg)	37	-	-28.0% (-100. 172.0)	-	-	-	-
		Placebo	36	-	11.0% (-100. 203.0)	-	-	-	-
Crumrine, 1989[25]	18 weeks	Cinromide (20–40 mg/kg)	26	-	-	-	-	-	-
		Placebo	30	-	-	-	-	-	-

Based on Table 16, CS Appendices[6]
CFB = change from baseline; CI = confidence intervals; CM-DBS= centromedian deep brain stimulation; CS = company submission; GTC – generalised conic-clonic; kg = kilogram; mg = milligram; N = sample size; N/A = not applicable; NR = not reported; tDCS= transcranial direct current stimulation

Safety

Eight studies evaluating five separate interventions (cannabidiol, clobazam, fenfluramine, topiramate and centromedian deep brain stimulation [CM-DBS]) reported AEs (i.e., any, treatment-related adverse events [TRAE], treatment-emergent adverse events [TEAE]) during the treatment phase (Tables 3.8 and 3.9).

Table 3.8: Safety outcomes and treatment discontinuation

Author, Year	Timepoint	Intervention	N	Concomitant ASMs (n)	AEs		SAEs		Discontinuation due to AE n (%)	Discontinuation all causes n (%)
					Any n (%)	TRAE/ TEAE n (%)	Any n (%)	TEAE n (%)		
Knupp, 2022[2] 1601 (NCT03355209)	14 weeks	Fenfluramine (0.7 mg/kg)	87	3	-	78 (90.0)*	-	10 (11.5)	5 (5.7)	10 (11.5)
		Fenfluramine (0.2 mg/kg)	89	3	-	69 (78.0)*	-	4 (4.5)	4 (4.5)	7 (8)
		Placebo	87	3	-	65 (75.0)*	-	4 (4.6)	1 (1.1)	4 (4.6)
Dalic, 2022[12] ESTEL (ACTRN12621001233819)	24 weeks	CM-DBS	10	-	5 (55.6)	-	-	-	-	-
		Control	9	-	1 (10.0)	-	-	-	-	-
Hahn, 2022[11] ELEKTRA (NCT03650452)	20 weeks	Soticlestat (100-300 mg)	43	-	-	-	-	-	1 (2.2)	1 (2.2)
		Placebo	45	-	-	-	-	-	2 (4.4)	9 (20)
Arzimanoglou, 2016[16] Study 303 (NCT01405053)	106 weeks	Rufinamide (45 mg/kg)	25	1-3†	-	22 (88.0)*	-	-	-	10 (40)
		Any other ASM	12	1-3†	-	10 (83.3)*	-	-	-	8 (67)
Devinsky, 2018[14] GWPCARE3 (NCT02224560)	14 weeks	Cannabidiol (10 mg/kg)	67	3	56 (84.0)	-	13 (18.0)	-	1 (1.4)	2 (2.7)
		Cannabidiol (20 mg/kg)	82	3	77 (94.0)	-	13 (16.0)	-	4 (5.0)	9 (11.8)
		Placebo	76	3	55 (72.0)	-	7 (9.0)	-	1 (1.0)	2 (2.6)

Author, Year	Timepoint	Intervention	N	Concomitant ASMs (n)	AEs		SAEs		Discontinuation due to AE n (%)	Discontinuation all causes n (%)
					Any n (%)	TRAE/ TEAE n (%)	Any n (%)	TEAE n (%)		
Thiele, 2018[15] GWPCARE4 (NCT02224690)	14 weeks	Cannabidiol (20 mg/kg)	86	3	74 (86.0)	53 (62.0)	20 (23.0)	-	12 (14.0)	14 (16.3)
		Placebo	85	3	59 (69.0)	29 (34.0)	4 (5.0)	-	1 (1.0)	1 (1.2)
Ohtsuka, 2014[17] E2080-J081-304 (NCT01146951)	14 months	Rufinamide (1,000–3,200 mg)	29	-	26 (93.1)	17 (62.1)	1 (3.5)	-	4 (13.8)	4 (13.8)
		Placebo	30	-	21 (70.0)	5 (16.7)	1 (3.3)	-	1 (3.3)	1 (3.3)
Ng, 2011[18] Secondary publications: OV-1012 (NCT00518713)	15 weeks	Clobazam (0.25 mg/kg)	58	-	42 (72.4)	-	3 (5.2)	-	4 (6.9)	8 (13.8)
		Clobazam (0.50 mg/kg)	62	-	55 (88.7)	-	6 (9.7)	-	8 (12.9)	17 (27.4)
		Clobazam (1.0 mg/kg)	59	-	45 (76.3)	-	5 (8.5)	-	12 (20.3)	18 (30.5)
		Placebo	59	-	40 (67.8)	-	2 (3.4)	-	2 (3.4)	18 (30.5)
Conry, 2009[19]	7 weeks	Clobazam (0.25 mg/kg)	32	1-3†	-	27 (84.0)*	1 (3.0)	-	3 (10.0)	-
		Clobazam (1.0 mg/kg)	36	1-3†	-	31 (86.0)*	2 (6.0)	-	6 (19.0)	-
Glauser, 2008[20] Study 022	12 weeks	Rufinamide (45 mg/kg)	74	1-3†	60 (81.1)	-	2 (2.7)	-	6 (8.1)	10 (13.5)
		Placebo	64	1-3†	52 (81.3)	-	2 (3.2)	-	0 (0.0)	5 (7.8)

Author, Year	Timepoint	Intervention	N	Concomitant ASMs (n)	AEs		SAEs		Discontinuation due to AE n (%)	Discontinuation all causes n (%)
					Any n (%)	TRAE/ TEAE n (%)	Any n (%)	TEAE n (%)		
Sachdeo, 1999[24]	11 weeks	Topiramate (6 mg/kg)	46	-	-	-	-	12 (23.0)	0 (0.0)	1 (2.0)
		Placebo	50	-	-	-	-	5 (10.0)	0 (0.0)	0 (0)
Motte, 1997[21]	16 weeks	Lamotrigine (100-400 mg)	79	≤3†	-	-	-	-	3 (4.0)	-
		Placebo	90	≤3†	-	-	-	-	7 (8.0)	-
Jensen, 1994 [22]	10 weeks	Felbamate (45 mg/kg)	35	-	-	-	-	-	1 (2.8)	1 (2.8)
		Placebo	36	-	-	-	-	-	1 (2.9)	1 (2.9)
Ritter, 1993[23]	10 weeks	Felbamate (45 mg/kg)	37	≥2†	-	-	8 (21.6)	-	-	1 (2.7)
		Placebo	36	≥2†	-	-	3 (8.3)	-	-	1 (2.8)

Based on Table 17, CS Appendices[6]
*TEAE
†Reported as study inclusion criteria. Baseline median value not reported.AE = adverse event; ASM = anti-seizure medication; CM-DBS= centromedian deep brain stimulation; CS = company submission; kg = kilogram; mg = milligram; N = sample size; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; % = percentage

Table 3.9: AESI

Author, Year	Timepoint	Intervention	N	Somnolence n (%)	Lethargy n (%)	Status epilepticus n (%)	Weight loss n (%)	Decreased appetite n (%)
Knupp, 2022[2] 1601 (NCT03355209)	14 weeks	Fenfluramine (0.7 mg/kg)	87	15 (17.2)	5 (5.7)	3 (3)	7 (8.0)	31 (35.6)
		Fenfluramine (0.2 mg/kg)	89	9 (10.1)	2 (2.2)	0 (0)	2 (2.2)	18 (20.2)
		Placebo	87	9 (10.3)	2 (2.3)	1 (1)	2 (2.3)	10 (11.5)
Dalic, 2022[12] ESTEL (ACTRN12621001233819)	24 weeks	CM-DBS	10	-	-	-	1 (10.0)	-
		Control	9	-	-	-	1 (11.1)	1 (11.1)
Arzimanoglou, 2021[26] Study 022	12 weeks	Rufinamide (45 mg/kg) ≥16 years	25	7 (28.0)	-	-	-	3 (12.0)
		Placebo ≥16 years	21	4 (19.0)	-	-	-	1 (4.8)
		Rufinamide (45 mg/kg) <16 years	49	11 (22.4)	2 (8.0)	-	-	4 (8.2)
		Placebo <16 years	43	4 (9.3)	1 (4.8)	-	-	2 (4.7)
Thiele, 2018[15] GWPCARE4 (NCT02224690)	14 weeks	Cannabidiol (20 mg/kg)	86	13 (15.0)	4 (4.7)	1 (1.0)	2 (2.3)	11 (13.0)
		Placebo	85	8 (9.0)	0 (0.0)	1 (1.0)	2 (2.4)	2 (2.4)
Devinsky, 2018[14] GWPCARE3 (NCT02224560)	14 weeks	Cannabidiol (10 mg/kg)	67	14 (21.0)	-	7 (10.0)	-	11 (16.0)
		Cannabidiol	76	25 (30.0)	-	4 (5.0)	-	21 (26.0)

Author, Year	Timepoint	Intervention	N	Somnolence n (%)	Lethargy n (%)	Status epilepticus n (%)	Weight loss n (%)	Decreased appetite n (%)
		(20 mg/kg)						
		Placebo	76	4 (5.0)	-	3 (4.0)	-	6 (8.00)
Ohtsuka, 2014[17] E2080-J081-304 (NCT01146951)	12 weeks months	Rufinamide (1000–3200 mg)	28	6 (20.7)	-	8 (27.6)	-	5 (17.2)
		Placebo	30	1 (3.3)	-	5 (16.7)	-	2 (6.7)
Ng, 2011[18] OV-1012 (NCT00518713)	15 weeks	Clobazam (0.25 mg/kg)	58	-	-	0 (0.0)	-	-
		Clobazam (0.50 mg/kg)	62	-	-	0 (0.0)	-	-
		Clobazam (1.0 mg/kg)	59	-	-	0 (0.0)	-	-
		Placebo	59	-	-	0 (0.0)	-	-
Conry, 2009[19]	7 weeks	Clobazam (0.25 mg/kg)	32	4 (13.0)	3 (9.0)	0 (0.0)	-	-
		Clobazam (1.0 mg/kg)	36	7 (19.0)	4 (11.0)	0 (0.0)	-	-
Glauser, 2008[20] Study 022	12 weeks	Rufinamide (45 mg/kg)	74	8 (12.5)	-	3 (4.1)	-	-
		Placebo	64	18 (24.3)	-	0 (0.0)	-	-
Sachdeo, 1999[24]	11 weeks	Topiramate (6 mg/kg)	48	20 (42.0)	-	-	5 (10.0)	-
		Placebo	50	11 (22.0)	-	-	0 (0.0)	-
Motte, 1997[21]	16 weeks	Lamotrigine (100–400 mg)	79	3 (4.0)	-	-	-	-
		Placebo	90	4 (4.0)	-	-	-	-

Author, Year	Timepoint	Intervention	N	Somnolence n (%)	Lethargy n (%)	Status epilepticus n (%)	Weight loss n (%)	Decreased appetite n (%)
Ritter, 199[23]	10 weeks	Felbamate (45 mg/kg)	37	16 (43.0)	-	-		-
		Placebo	36	3 (8.0)	-	-		-

Based on Table 18, CS Appendices[6]
AESI = adverse event of special interest; CM-DBS= centromedian deep brain stimulation; CS = company submission; kg = kilogram; mg = milligram; N = sample size; % = percentage

EAG comment:

- The pairwise analyses were purely narrative and did not involve any meta-analyses. This made it difficult to discern any clear between-treatment effects. The SLR was used as the basis for the NMA, which is described in Sections 3.3 and 3.4. However, as will be detailed in those sections, a large number of potentially relevant studies were excluded, meaning that only one active comparator (cannabidiol) was considered.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Details of the included trials

Fenfluramine's clinical effectiveness has been evaluated in a large global clinical trial programme of LGS patients, which included a pivotal Phase 3 RCT of fenfluramine (Study 1601[2]) and its open label extension (OLE[27]) study.

Both studies are summarised below in Tables 3.10 and 3.11.

EAG comment:

- The validity of the efficacy measures depends on the measurement validity of the eDiary, an electronic, homebased handheld device provided to every subject, and used for recording of seizures. The company were asked to provide information of the measurement validity of these devices in the request for clarification. The company stated that, "*The use of diary data (either paper or electronic) has been the gold standard for data collection in epilepsy trials.eDiaries provide a more efficient and accurate means of collecting data in epilepsy trials. They enhance data quality, reduce administrative burdens, and offer a more patient-centered approach to data collection and monitoring. Various studies have demonstrated the accuracy of using eDiaries in epilepsy trials* (References 12 to 15 in the company response to clarification)*. The ESC recognise the quality of Signant Health and its devises, acknowledging its "considerable experience developing complex eDiaries and conducting epilepsy trials*."[3] The EAG is not convinced by the evidence that the company has provided. The first piece of evidence (company response to clarification reference 12) is a non-systematic review. The second piece of evidence (company response to clarification reference 13) is a poster presentation that contains no analyses evaluating accuracy, reliability or validity of the device. The final piece of evidence (company response to clarification reference 15) is a news article that provides no useful data. Altogether, the company has not provided any strong evidence supporting the validity of the eDiary as a measurement device. Therefore, the validity of much of the trial evidence is unclear. This is a key issue.

Table 3.10: Clinical evidence

Study Name	Study 1601, part 1, Knupp 2022	Study 1601, part 2 (OLE), Knupp 2023
Study title	A Two-Part Study of ZX008 in Children and Adults With Lennox-Gastaut Syndrome (LGS); Part 1: A Randomised, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults With LGS, Followed by Part 2: An Open-label Extension to Assess Long-Term Safety of ZX008 in Children and Adults With LGS.	
Trial registration	NCT03355209	
Study design	Phase 3 double-blind, placebo-controlled, multicentre, multinational RCT	Open-label extension study
Population	Children and adults, (n=263) aged 2 to 35 years, with ESC–confirmed LGS diagnosis who were using stable ASM regimens (≥1 and ≤4 concomitant ASMs) who met the following criteria: • Onset of seizures at age 11 years or younger • Multiple seizure types, including tonic and tonic or AS including countable motor seizures that result in drops • Stable 4-week seizure baseline with two or more drop seizures per week of GTC, secondary GTC (SGTC) (i.e., focal to bilateral tonic-clonic seizures), tonic, atonic, or tonic or AS • Abnormal cognitive development • Medical history showing electroencephalogram evidence of abnormal background activity with slow spike-and-wave pattern (<2.5 Hz)	Patients with a confirmed LGS diagnosis who completed Study 1601, part 1 (aged 2–35 years at entry into the core study) (n=247)
Intervention(s)	Fenfluramine (0.2 or 0.7 mg/kg) in addition to SoC	
Comparator(s)	Placebo in addition to SoC	None
Indicate if study supports application for marketing authorisation	Yes	Yes

Study Name	Study 1601, part 1, Knupp 2022	Study 1601, part 2 (OLE), Knupp 2023
Indicate if study used in the economic model	Yes	Yes
Rationale if study used in model	Pivotal phase 3 study in children and young adults with LGS treated with the investigational product. Provides individual patient-level data.	Extension of the pivotal phase 3 study in children and young adults with LGS treated with the investigational product. Used to provide longer-term data and support extrapolation assumptions beyond trial period.
Reported outcomes specified in the decision problem	• 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 effects of treatment • HRQoL (patients and carers)	• Seizure frequency (overall and by seizure type) • Response rate (overall and by seizure type) • Proportion of people seizure-free** • Adverse effects of treatment
All other reported outcomes	• Proportion of patients who achieved improvement (minimally, much, or very much improved) on the CGI-I scale, investigator assessed. • CGI-I rated by caregivers • Change in frequency of all countable motor seizures (GTC, tonic, clonic, atonic, tonic or atonic, and clearly recognisable focal) • Number of days free of drop seizures • Standardised colour doppler echocardiography to monitor cardiac valve structure/function and pulmonary arterial hypertension at screening, during treatment, and post-treatment	• Proportion of patients who achieved improvement (minimally, much, or very much improved) on the CGI-I scale • CGI-I rated by caregivers • Treatment retention rates

Study Name	Study 1601, part 1, Knupp 2022	Study 1601, part 2 (OLE), Knupp 2023
Based on Table 4, CS[1] *Definition of drop seizure: Seizures classified as GTC, SGTC, tonic, atonic, or tonic/atonic that are reviewed and confirmed as resulting in a drop for each subject by ESC based on the definition, "seizures involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface, or that could have led to a fall or injury depending on the subject's position at the time of the seizure." Synonymous with "seizures that result in drops," "seizures that result in drops (ESC-confirmed)," "drop seizures (ESC-confirmed)" and "ESC-confirmed drop seizures." **Proportion of people seizure-free was an outcome in fenfluramine trials, however, because the proportion of patients who are (drop) seizure-free was very low in the Phase 3 trials of fenfluramine and cannabidiol, this outcome was not considered in the model of this submission. ASM = anti-seizure medication; CGI-I = clinical global impression-improvement; CS = company submission; ESC = Epilepsy Study Consortium; GTC = generalised tonic-clonic; HRQoL = health-related quality of life; kg = kilogram; LGS = Lennox-Gastaut syndrome; mg = milligram; N = sample size; OLE = open label extension; RCT = randomised controlled trial; SGTC = secondarily generalised tonic-clonic; SoC = standard of care		

Table 3.11: Summary of trial methodology

Study Name	Study 1601, part 1, Knupp 2022	Study 1601, part 2 (OLE), Knupp 2023
Location	65 study sites: 34 in North America (Canada, United States, Mexico); 29 in Europe (Spain, Italy, Poland, France, Germany, Belgium, Netherlands, Denmark, Sweden); and two in Australia	65 study sites: 34 in North America (Canada, United States, Mexico); 29 in Europe (Spain, Italy, Poland, France, Germany, Belgium, Netherlands, Denmark, Sweden); and two in Australia
Trial design	Phase 3 double-blind, placebo-controlled, multicentre, multinational RCT (20-week trial duration)	Open-label extension study
Eligibility criteria for participants	Aged between 2 and 35 years, ESC–confirmed LGS diagnosis, using stable ASMs. Age of seizure onset: 11 years or younger, multiple seizure types (including tonic and tonic or AS), stable 4-week seizure baseline with two or more drop seizures per week, abnormal cognitive development, medical history showing EEG pattern of slow spike-and-wave complexes, (<2.5 Hz).	Patients with a confirmed LGS diagnosis who completed Study 1601, part 1 (aged 2–35 years at entry into the core study).
Settings and locations where data were collected	The main efficacy measures were based on seizures reported in the eDiary, an electronic, homebased handheld device (TrialMax TouchTM) provided to every subject. Additional scales and questionnaires were administered using a site-based electronic clinical outcome assessment tablet (TrialMax SlateTM, "Slate") provided to every clinical site. Clinic visits occurred at days 1, 15, 43 and 71; telephone assessment occurred at days 4, 8, 29, and 85. Final safety assessments occurred at days 99, 113 and 197.	The main efficacy measures were based on seizures reported in the eDiary, an electronic, homebased handheld device (TrialMax TouchTM) provided to every subject. Additional scales and questionnaires were administered using a site-based electronic clinical outcome assessment tablet (TrialMax SlateTM, "Slate") provided to every clinical site. Clinic visits occurred at days 1, 15, 30, 60, 90, 180 and 270; telephone assessment occurred at day 15. In some countries, a final safety assessment occurred up to 24 months after last dose.
Trial drugs (number in each group)	Fenfluramine 0.2 mg/kg (n=89), fenfluramine 0.7 mg/kg/day (n=87), placebo (n=87). Fenfluramine was administered orally twice daily as an oral solution of fenfluramine hydrochloride containing 2.2 mg/mL fenfluramine. Starting dose was 0.2 mg/kg/day, titrated up to target dose over 2 weeks, followed by a 12-week Maintenance period. The maximum dose of fenfluramine was 26 mg/day.	N=247, no comparator group. A subject who completed Maintenance and was eligible for enrolment in the OLE study[27] entered the Transition Period lasting 14 days between Visits 12 and 15, where patients were titrated to 0.2 mg/kg/day fenfluramine and remained at this dose for 1 month regardless of their randomised treatment arm in the RCT. After month 1, patients were flexibly titrated by

Study Name	Study 1601, part 1, Knupp 2022	Study 1601, part 2 (OLE), Knupp 2023
	A subject who completed Maintenance and was not continuing into the OLE study[27] entered the Taper Period, during which they tapered off study drug as shown in the table below in a blinded manner. At each taper step, the subject received product from a new bottle of study drug. A subject who withdrew during Maintenance entered Taper the day after withdrawal.	effectiveness and tolerability, up to a maximum of 0.7 mg/kg/day.
Permitted and disallowed concomitant medication	Other ASMs permitted but had to be stable dose for 4 weeks before screening and during trial; excluded if other use of cannabis evidenced by positive laboratory test, drugs that interact with central serotonin or current use of felbamate for <1 year.	Other ASMs permitted but had to be stable dose for 4 weeks before screening and during trial; Excluded if other use of cannabis evidenced by positive laboratory test, drugs that interact with central serotonin or current use of felbamate for <1 year.
Primary 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 DSF between baseline and the combined Titration + Maintenance Periods	To assess the long-term safety and tolerability of fenfluramine in children and adults with LGS regarding AEs, laboratory parameters, physical examination, neurological examination, Tanner Staging, cognition, vital signs, ECGs, ECHO, body weight, and BMI.
Primary outcomes	Percentage reduction in DSF/28 days[b]	N/A
Other outcomes used in the economic model or specified in the scope	Percentage of patients with ≥25%, ≥50%, ≥75% and 100% reduction from baseline in DSF Percentage reduction in total seizure[c] frequency from baseline; Proportion of patients who achieved improvement (minimally, much, or very much improved) on the CGI-I percentage reduction from baseline in frequency of seizures that typically results in drops (whether ESC confirmed or not), motor seizures (GTC, SGTC, TS, AS, tonic aclonic, clonic seizure, focal seizure, and hemiclonic seizure), nonmotor seizures (absence seizures, myoclonic seizure, focal seizures without clear observable motor signs, infantile spasms, and epileptic spasms) and individual seizures by type; • Parent or CGI-I; • Change from baseline in QOLCE questionnaire score;	**Efficacy Endpoints** Changes in seizure frequencies were compared to pre-randomisation baseline in the core study. Seizure subtype analysis assessed the median percentage reduction in GTC seizure, TS, AS, or TA in the subset of patients who experienced these seizure types at pre-randomisation baseline in the core study. ≥25%, ≥50%, and ≥75% seizure reduction responder levels Proportion of patients achieving seizure freedom or near seizure freedom (defined as patients who had ≤1 seizure during the treatment period). Median percentage increase in days free of drop seizures and median longest interval between drop seizures. CGI-I

Study Name	Study 1601, part 1, Knupp 2022	Study 1601, part 2 (OLE), Knupp 2023
	• Change from baseline in Vineland Adaptive Behaviour Scale score-II; • Incidence of status epilepticus episodes. • Incidence of rescue medication use • Incidence of hospitalisation to treat seizures	**Safety Endpoints:** Standardised two-dimensional colour doppler ECHO assessed cardiac valve function/structure and any evidence of PAH every 3 months as described in a previous cardiovascular safety study and the core study. TEAEs were recorded during the treatment period.
Pre-planned subgroups	None	None

Based on Table 5, CS[1]
[a]Including GTC, secondary GTC (i.e., focal to bilateral tonic-clonic seizures), tonic, atonic, or tonic or AS
[b]"ESC-confirmed"
[c]All countable seizures (i.e., motor and nonmotor)
AEs = Adverse Events; AS = atonic seizure; ASMs = anti-seizure medications; BMI = body mass index; CS = company submission; CGI-I = clinical global impression-improvement; DSF = drop seizures frequency; ECG = electrocardiogram; ECHO = echocardiogram; EEG = electroencephalogram; ESC = Epilepsy Study Consortium; GTC = generalised tonic-clonic; LGS = Lennox-Gastaut syndrome; OLE = open label extension; kg = kilogram; mg = milligram; N/A = not applicable; PAH = pulmonary arterial hypertension; RCT = randomised controlled trial; SGTC = secondary generalised tonic clonic

Study 1601[2] was a double-blind, randomised, placebo-controlled, multicentre trial conducted in patients aged 2 to 35 years with LGS, whose seizures were incompletely controlled with previous ASMs and those who experienced at least two drop seizures per week during the 4-week baseline.

The intervention was fenfluramine in addition to SoC and the comparator was SoC without fenfluramine (i.e., SoC + placebo). The RCT reported the percentage change in DSF from baseline as its primary endpoint.

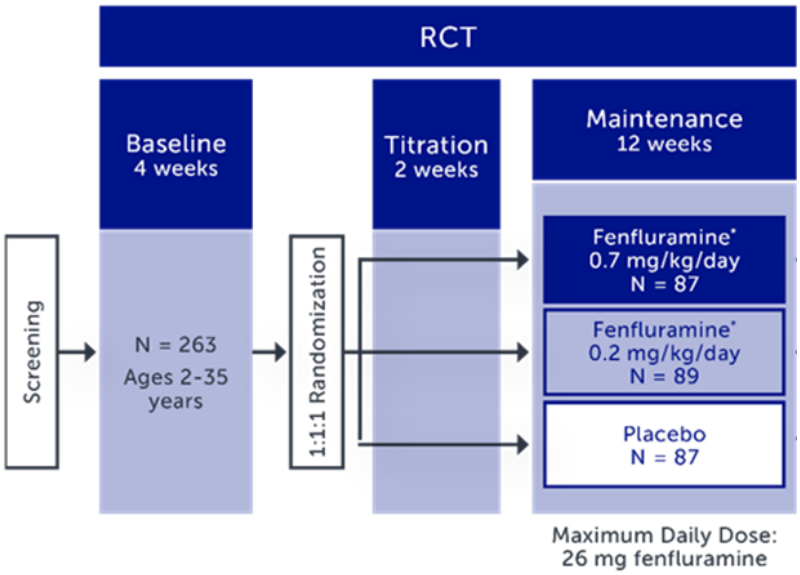
Study 1601 included four distinct phases: a 4-week baseline period (Baseline), a 2-week Titration period (Titration), a 12-week Maintenance phase (Maintenance), and a 2-week taper or transition Period (Taper/Transition). A subject who completed Maintenance and was not continuing into OLE study[27] tapered off the study drug during the Taper Period.

Upon completion of baseline in Study 1601, patients who qualified for the study entered the Titration period and 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 placebo. Randomisation was stratified by weight (<37.5 kg, ≥37.5 kg) to ensure balance across treatment arms.

The objective of the OLE study[27] was to evaluate the long-term safety and efficacy of fenfluramine in patients with LGS who participated in Study 1601.[2] During the OLE study, all patients were treated initially with fenfluramine 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study patients. After 1 month at a dose of 0.2 mg/kg/day, the investigator could adjust the dose for each subject based on effectiveness and tolerability. Effectiveness and safety/tolerability were assessed at months 1, 2, 3, 6, 9, and 12, with safety follow-up visits at 3 and 6 months after the last dose; in some countries, an additional follow-up occurred at 24 months after the last dose.

A summary of the trial design is shown in Figures 3.2 and 3.3.

Figure 3.2: Study 1601 trial design

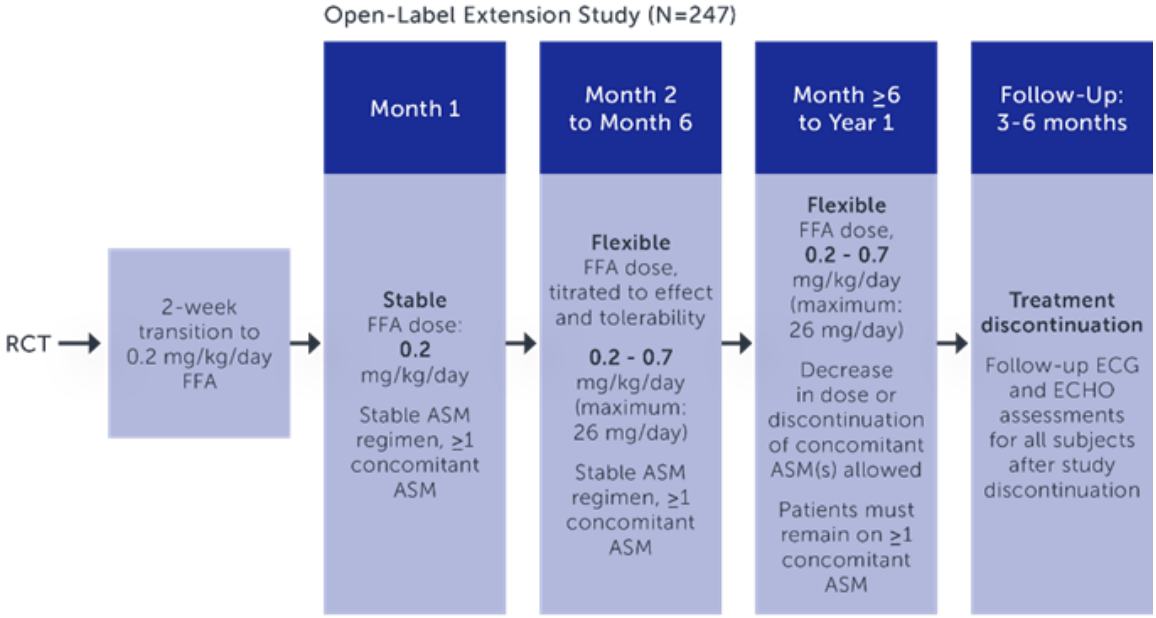


Based on Figure 7, CS[1]

*Fenfluramine was administered orally twice daily as an oral solution of fenfluramine hydrochloride containing 2.2 mg/mL fenfluramine

CS = company submission; kg = kilogram; mg = milligram; N = sample size; RCT = randomised controlled trial

Figure 3.3: OLE trial design



Based on Figure 8, CS[1]
ASM = anti-seizure medication; CS = company submission; ECG = electrocardiogram; ECHO = echocardiogram; FFA = fenfluramine; kg = kilogram; mg = milligram; N = study sample; OLE = open label extension; RCT = randomised controlled trial

3.2.1.1 Eligibility criteria

Children and adults, aged 2 to 35 years, with Epilepsy Study Consortium (ESC)–confirmed LGS diagnosis who were using stable ASM regimens (≥1 and ≤4 concomitant ASMs) were eligible for enrolment if they met the following criteria: (i) onset of seizures at age 11 years or younger; (ii) multiple seizure types, including tonic and tonic or atonic seizures; (iii) stable 4-week seizure baseline with 2 or more drop seizures per week of GTC, secondary GTC (i.e., focal to bilateral tonic-clonic seizures), tonic, atonic, tonic or atonic seizures; (iv) abnormal cognitive development; and (v) medical history showing EEG evidence of abnormal background activity with slow spike-and-wave pattern (<2.5 Hz).

Key exclusion criteria were degenerative neurological disease; history of hemiclonic seizures in the first year of life; only drop seizure clusters; previous or current exclusionary cardiovascular or cardiopulmonary abnormality that was detected on echocardiogram (ECHO), electrocardiogram (ECG), or physical examination; and concomitant cannabidiol use (cannabidiol was not an approved medication anywhere in the world at the time of study enrolment). Race and ethnicity data were self-reported by patients or their caregivers. The race and ethnicity categories were Asian, Black or African American, White, other (American Indian or Alaskan Native and Native Hawaiian or Other Pacific Islander), and unknown (not reported or missing).

3.2.1.2 Settings and locations where the data were collected

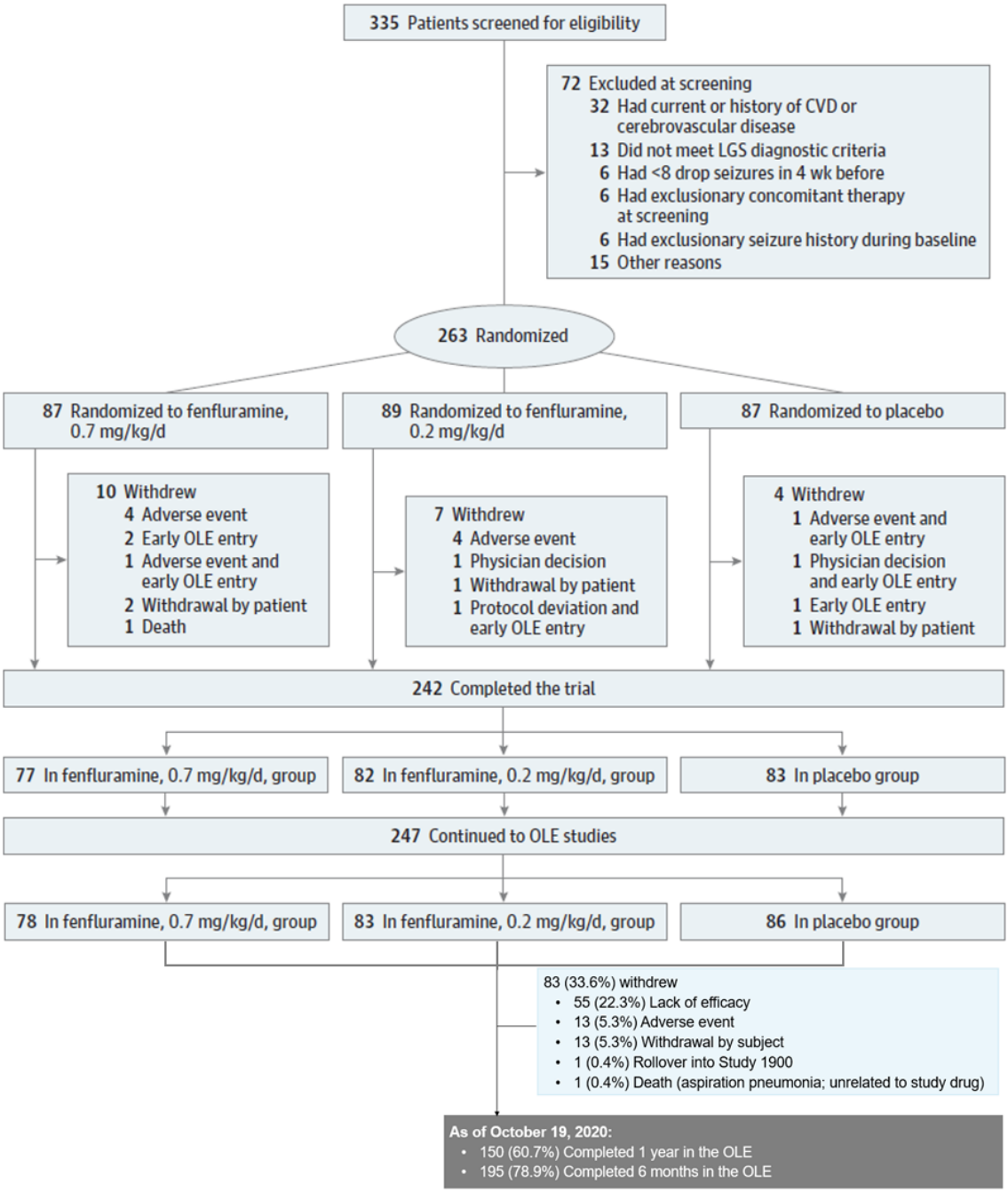
Patients were enrolled at 65 sites: 34 in North America (31 United States [US], two Canada, one Mexico), 29 in Europe (one Sweden, one Denmark, three Belgium, six Germany, six France, four Spain, five Italy, one Netherlands, two Poland), and two in Australia.

3.2.1.3 Patient flow in the studies

In total, 263 eligible patients were randomised to the 0.7 mg/kg/day fenfluramine group (n=87), 0.2 mg/kg/day fenfluramine group (n=89), and placebo group (n=87). Among the randomised patients, 21 withdrew from the study early, with the most common reason (n=9) being AEs across all groups. A total of 242 patients completed the trial, and 247 entered the OLE study.[27]

The OLE study[27] experienced delays in completion due to coronavirus disease 2019 (COVID-19) precautions that affected monitoring visits and posed scheduling challenges for in-person end-of-study visits. As a result, several participants who received the study drug were unable to attend their final in-person visit within the specified time frame of the protocol (365 ± 4 days). To ensure appropriate transition of care and accommodate these circumstances, their treatment was extended until they could attend the visit and suitable arrangements for their continued care could be made. To evaluate the progress of the trial, an interim analysis of the OLE study[27] was conducted using a snapshot of the clinical database collected on 19/10/2020. This specific date was chosen to ensure that the analysis included a minimum of 365 ± 4 days of exposure in the OLE[27] for almost all patients who remained in the trial. The effectiveness of the treatment, measured by the reduction in seizure frequency, was calculated at 3-month intervals over time, starting from Month 1 until the end of the study (i.e., last treatment dose) within the modified intention-to-treat (mITT) population. In the OLE study,[27] 83 (33.6%) patients withdrew; the most common reason for withdrawal was lack of efficacy (n=55, 22.3%). Patient count as of October 2020 is described in Figure 3.4.

Figure 3.4: **Patient flow in Study 1601 and OLE study**



Based on Figure 9, CS[1]

CS = company submission; CVD = cardiovascular disease; d = days; kg = kilogram; mg = milligram; LGS = Lennox-Gastaut syndrome; OLE = open label extension

3.2.2 Statistical analysis of the included trials

3.2.2.1 Endpoints

In Study 1601,[2] the primary endpoint of the study was the percentage change in confirmed drop seizures (including GTC, secondary GTC [focal to bilateral tonic-clonic], tonic, atonic, or tonic or atonic seizures) from baseline in the 0.7 mg/kg/day fenfluramine group compared to the placebo group.

Key secondary endpoints included evaluating the percentage change from baseline in drop seizure frequency (DSF) in the 0.2 mg/kg/day fenfluramine group, determining the responder rate of 50% or greater, and determining the proportion of patients who experienced improvement (ranging from minimal to much or very much improved) on the clinical global impression-improvement (CGI-I) scale. Additional secondary outcomes included evaluating the CGI-I ratings provided by caregivers, conducting subgroup analyses based on seizure type, assessing changes in the frequency of all countable motor seizures (such as GTC, tonic, clonic, atonic, tonic or atonic, and clearly recognisable focal seizures), and determining the number of drop seizure free days.

In the OLE study,[27] the primary objective was to assess the long-term safety and tolerability of fenfluramine (i.e., AEs, laboratory parameters, physical examination, neurological examination, Tanner Staging, cognition, vital signs, ECGs, ECHOs, body weight, and body mass index [BMI]). Effectiveness endpoints were also collected including: comparing changes in seizure frequencies to the pre-randomisation baseline in the core study, analysing the median percentage reduction in specific seizure subtypes for patients experiencing them at baseline, evaluating responder levels based on seizure reduction (≥25%, ≥50%, and ≥75%), determining the proportion of patients achieving seizure freedom or near seizure freedom (defined as having ≤1 seizure during treatment), measuring the median percentage increase in days free of drop seizures and the longest interval between drop seizures, and using the CGI-I scale to assess overall improvement.

The study groups in Study 1601[2] were determined by treatment received, with no additional planned subgroup analyses. The analysis sets used are defined as followed:

- Randomised population (n=263): All patients randomised to receive study treatment. This is the intention-to-treat (ITT) population.
- Modified intention to treat (mITT) population (n=263): All randomised patients who received at least one dose of fenfluramine or placebo and for whom at least 1 week of diary data was available.
- Per protocol (PP) population (n=209): All randomised patients who received at least one dose of fenfluramine or placebo, completed at least 4 weeks of the Maintenance period, and had no important protocol deviations that would have a significant impact on clinical outcome.
- Safety (SAF) population (n=263): All randomised patients who received at least one dose of fenfluramine or placebo.

3.2.2.1 Efficacy

Efficacy parameters were summarised by descriptive statistics. Two-sided statistical significance testing (α=0.05) comparing each active treatment group with placebo were performed for the primary and secondary endpoints as described in the Sections below, unless otherwise noted. A serial gatekeeping strategy was developed to control the type 1 error rate for pairwise comparisons between active-treatment and placebo groups among the primary and key secondary efficacy parameters, as follows:

Step 1: The primary efficacy endpoint of percent change from baseline in DSF in Titration and Maintenance periods was formally tested first between the fenfluramine 0.7 mg/kg/day and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 2.

Step 2: The key secondary efficacy endpoint, the proportion of patients who achieve a ≥50% reduction from baseline in Titration and Maintenance periods, was compared between the fenfluramine 0.7 mg/kg/day and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 3.

Step 3: The key secondary endpoint, the proportion of patients who achieve improvement (minimally, much, or very much improved) in the CGI-I as assessed by the Principal Investigator, was compared between fenfluramine 0.7 mg/kg/day and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 4.

Step 4: The key secondary endpoint, percent change from baseline in DSF in Titration and Maintenance periods, was formally tested between the fenfluramine 0.2 mg/kg and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 5.

Step 5: The key secondary efficacy endpoint, the proportion of patients who achieve a ≥50% reduction from baseline in DSF, was compared between the fenfluramine 0.2 mg/kg and placebo groups. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 6.

Step 6: The key secondary endpoint, the proportion of patients who achieve improvement (minimally, much, or very much improved) in the CGI-I as assessed by Principal Investigator, was compared between the fenfluramine 0.2 mg/kg and placebo groups using a significance level of α=0.05 (2-sided).

The percent change from baseline in DSF was assessed using a nonparametric, rank analysis of covariance (ANCOVA) with treatment group and weight group (<37.5 kg, ≥37.5 kg) as factors; rank DSF per 28 days during Baseline as a covariate; and rank percentage change from baseline in DSF per 28 days during Titration and Maintenance as the response variable. The primary analysis compared the fenfluramine 0.7 mg/kg/day treatment group versus the placebo group at the α=0.05 level of significance. The difference between the fenfluramine 0.7 mg/kg/day treatment group and the placebo group in percentage change in DSF and its 95% CI were estimated using the Hodges-Lehmann (HL) method.

Number of drop seizure–free days and countable motor seizure–free days per 28 days, using the baseline as the covariate, was done with a similar nonparametric ANCOVA model as the primary endpoint analysis.

Percentage of patients with at least a 50% reduction from baseline in DSF and additional response analyses were analysed using a logistic regression model that incorporated the same factors as the ANCOVA used in the primary analysis.

The CGI-I data comparison between each active-treatment group and the placebo group was conducted by the Cochran-Mantel-Haenszel (CMH) test stratified by weight group.

The longest drop seizure–free interval was analysed using nonparametric methods; summary statistics included median, mean, minimum, maximum, the 25^{th} and 75^{th} percentiles, and 95% CIs on the difference in medians between groups (HL estimator). The Wilcoxon rank sum test was used to test for differences between each active treatment group and placebo.

The quality of life in childhood epilepsy (QOLCE) was collected at visits 3 and 12. Descriptive statistics were presented for each QOLCE subscale and for the overall quality of life (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 patients. Each treatment group was compared pairwise with the others using pairwise Wilcoxon tests. The QOLCE domain data were listed by subject.

3.2.2.2. Safety

All safety analyses were performed for the Safety Population. Results were reported by treatment group and for the combined fenfluramine groups. The Safety Population was defined as all randomised patients who received at least one dose of study drug. The statistical approach is summarised in Table 3.12.

Table 3.12: Statistical methodology used

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
The null hypothesis for the primary efficacy endpoint in the double-blind phase was that mean decrease in DSF would be equal when adding fenfluramine at 0.7 mg/kg/day to current therapy placebo to current therapy.	Analyses of the primary and all secondary efficacy endpoints were performed on the mITT* population. And repeated on the PP Population**. Percentage change from baseline in DSF in Titration + Maintenance Periods was assessed using a nonparametric, rank ANCOVA at the α=0.05 level of significance. The difference between fenfluramine and placebo in percentage change in DSF and its 95% CI were estimated using the HL method. Proportion of fenfluramine patients who achieved a response was compared versus placebo using a logistic regression model. CGI-I was compared versus the placebo group using the CMH test stratified by weight group. Control of statistical analyses for multiplicity using a gatekeeping approach, where primary and key secondary endpoints were arranged in a hierarchy and tested sequentially.	Sample size assumption: 63 patients per group would identify 30% reduction in DSF with 90% power at 2-tailed significance level of 5% Assuming a 20% withdrawal rate prior to the start of Maintenance yielded a requirement for an additional 16 patients per group for a total of 79 patients per treatment group. Similar calculations for the fenfluramine 0.2 mg/kg/day group led to a total required sample size of 237. The required number of patients randomised was estimated to be approximately 250 due to the long Baseline, during which additional patients could already be enrolled by the time the randomisation target was met. The variability expected in the trial was estimated from a Phase 3 trial of clobazam in patients with LGS (Ng, 2011[18]), leading to an assumption that the SD would be 50%.	No imputation for missing data for primary analysis. Sensitivity analyses used two different methods for imputation of missing data due to subject drop out: worst value substituted for dropouts and a differential imputation method for dropouts.

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Based on Table 8, CS[1] *The mITT Population was defined as all randomised patients who received at least one dose of fenfluramine or placebo and for whom at least 1 week of diary data were available. Patients were analysed according to the treatment group to which they were randomised. **The PP Population was defined as all randomised patients who received at least one dose of study drug; who completed at least 4 weeks of diary data in Maintenance; who had no major protocol deviations that would have had a significant impact on clinical outcome in Study 1601; and who met the inclusion criterion for baseline drop seizure count. ANCOVA = analysis of covariance; CI = confidence interval; CGI-I = clinical global impression-improvement; CS = company submission; DSF = drop seizure frequency; HL = Hodges-Lehmann; kg = kilogram; mg = milligram; mITT = modified intent-to-treat; PP = per-=protocol; SD = standard deviation			

3.2.3 Baseline characteristics in the included trials

3.2.3.1 Study 1601

Patients had a median (range) age of 13 (2-35) years and consisted of 146 male (56%) and 117 female (44%) individuals. Median (range) number of ASMs used previously was seven (1-20). At baseline, 233 of 263 patients (89%) were using two to four concomitant ASMs (median [range] number, three [1-5]). Of these ASMs, the five most common were valproate (147 [56%]), clobazam (119 [45%]), lamotrigine (88 [33%]), levetiracetam (60 [23%]), and rufinamide (53 [20%]). At baseline, the median (range) DSF for all patients was 77 (2-2,943) per 28 days. The median (range) DSF was higher in the 0.7 mg/kg/day and 0.2 mg/kg/day fenfluramine groups compared to the placebo group (83 [7-1,803] and 85 [4-2,943] versus 53 [2-1,761] per 28 days respectively). Further details of the patient characteristics are reported in Table 3.13.

Table 3.13: Baseline characteristics of patients included in Study 1601

Baseline characteristics	Placebo	Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.7 mg/kg/day
Number randomised	87	89	87
Age, mean (SD), y	14 (8) Range 2-35	13 (8) Range 3-35	13 (7) Range 2-35
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 (14-1,761)	106 (4-2,943)	111 (10-1,897)
Total (motor and non-motor) seizure frequency per 28 days: median (IQR)	120 (14-1,761)	138 (14-2,967)	152 (10-5,472)
DSF per 28 days: median (IQR)	53 (2-1,761)	85 (4-2,943)	83 (7-1,803)

Baseline characteristics	Placebo	Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.7 mg/kg/day
Number or previous ASM use Mean (SD) Median (Range)	7 (4) 6 (1-19)	7 (4) 7 (1-18)	8 (4) 7 (1-20)
Concurrent ASM use Total Mean (SD) Total Median (Range)	3(1) 3 (1-4)	3 (1) 3 (1-5)	3 (1) 3 (1-4)
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)
Based on Table 6, CS[1] Reference: Knupp, 2022[2] *self-reported by patients or their caregivers ASM = anti-seizure medication; DSF = drop seizure frequency; kg = kilogram; mg = milligram; SD = standard deviation; IQR = interquartile range			

EAG comment:

- There was a large difference in baseline motor seizure frequency between placebo and intervention groups. This appears to be a large enough difference to influence outcome. The company were asked to comment on how this discrepancy could influence outcome, and to provide statistical adjustment to results if appropriate. The company stated that, "*All countable motor seizures were an "additional secondary" endpoint and not a key outcome of the trial. In order to mitigate baseline variability, the analyses used two approaches: A rank-based, nonparametric model was used. Ranks are much more robust to difference in scales than an untransformed analysis. The outcome measure used in the analysis model was percentage change from baseline. That means each subject was adjusted for their own baseline seizure frequency. Thus, the difference in baseline motor seizure frequency between treatment arms is a random effect that is not likely to influence the outcome*."[3] The EAG is satisfied with this response.
- The groups appeared to be reasonably well-matched in the proportion of patients taking each of the five concomitant medications. There were also similarities in the number of concomitant medications – three - taken by each patient. However, information on the proportion of patients using the specific combinations of concomitant medications that were used would be useful. In the request for clarification, the company were asked to provide the proportion of patients using the specific combinations of concomitant medications that were used. The company helpfully provided the following figure:

Figure 3.5: **Number of subjects taking combination of five concomitant ASMs in Study 1601 – Safety population**

Based on Table 5, Company response to clarification questions[3]
ASMs = anti-seizure medications; N = study sample; kg = kilogram; mg = milligram,

- This figure appears to suggest that there were some differences between arms for some of the specific combinations of concomitant ASMs given. Although the EAG is aware this is almost certainly a random effect, it is possible that these differences in the SoC added to the intervention and to placebo may have affected internal validity to some degree. Because the effects of each of these between-arm differences in certain combinations of concomitant ASMs will have varied in the degree to which they favoured the intervention or placebo arm, the EAG accepts that it is impossible to know the overall effect with any degree of certainty.
- The company were also asked if any other concomitant medications were used by any patients. The company stated that "*Regarding other concomitant medications received in Study 1601, the most common concomitant medications and non-pharmacological therapies (of patients overall) included the following: vagus nerve stimulation (VNS) (patients [ ]), paracetamol (patients ( ]), and melatonin (patients [ ]). It is noted in the trial that no patients received concomitant stiripentol (STP).*"[3] The EAG thanks the company for this useful extra information, but also notes that the information was not provided per arm. This contributes to the continuing uncertainty in the internal validity of the trial.
- The above point is important to evaluate the internal validity of the trial. However external validity in terms of the similarity between the concomitant medications used in the trial and those used in the UK target is also important. A difference in the concomitant medications may affect the representativeness of results from the trial to the target population because

effectiveness is likely to vary according to the combination of concomitant medications to which fenfluramine is added. The company were asked to provide information on how the specific combinations of concomitant medications used in the trial compare to the specific combinations of concomitant medications used in UK clinical practice. The company responded by stating that, "*Clinicians who were recently consulted (following receipt of these clarification questions) confirm that LGS treatment consists of a complex mix of treatments, and every patient is treated differently. Treatment is highly individualised, making it difficult to specify how any specific group of patients using a particular combination of ASMs will respond. No combinations have been seen to be more effective than others, and it has been specifically mentioned that combinations used in the fenfluramine trials do reflect that which is seen in clinical practice. This was also observed within the advisory board conducted earlier in 2023, where multiple clinicians practicing the treatment of LGS in the UK were asked to comment on the applicability of data within trials, and it was confirmed that baseline characteristics of patients, including the concomitant medications they are on, do reflect real clinical practice within the UK.*"[3] While the EAG respects the opinions of the clinical experts, hard data on the actual combinations of ASMs used in UK practice would have been useful.

- In order to know the effects of any difference in concomitant medications between trial and target population, subgroup analyses on the trial data, with stratification for different combinations of concomitant medications, may be helpful. The company were therefore asked to conduct subgroup analyses defined by the therapy to which fenfluramine is added, and to conduct analyses for all efficacy outcomes to estimate the effect of therapy to which fenfluramine is added, adjusting for any likely treatment effect modifiers. The company replied that, "*During an advisory board meeting, clinical experts agreed that patient profiles and treatment pathways in LGS are highly heterogeneous in clinical practice. Combining this with the fact that LGS is a rare disease with a relatively limited number of patients it is very difficult to provide/form meaningful subgroups that would represent specific patient groups in clinical practice. Furthermore, current clinical management varies due to the refractory nature of LGS and the course of the disease has no specific patterns that would help establish any meaningful subgroups of patients with ASM combinations. Due to there being such a large variation in the different combinations of concomitant medications used (see answer to question A12a), the analysis would become very complex and potentially lead to implausible conclusions on a small group of patients which are heterogenous in their response to treatments. This observation is in line with clinical expert opinion and this specific issue has been highlighted in other TAs including TA615. In addition, Study 1601 does not have the necessary sample sizes per specific ASM combinations to conduct analyses of efficacy outcomes by these subgroups of patients. To note: the efficacy of different ASM combinations within fenfluramine's DS studies were also assessed, and no significant or plausible differences/impact on efficacy were observed.*"[3] In view of the large number of specific combinations that were used in the trial, the EAG understands that any sub-group analyses would have been underpowered, and that the results might have been unhelpful. Nevertheless, given the lack of objective evidence on the similarity between the UK and the trial in terms of ASM combinations used, alongside the lack of evidence that ASM combinations do not affect outcome, it is not possible to be sure that the outcomes of the trial are fully applicable to those in the UK population. This is a key issue.

3.3.2.2 OLE study

The mean (standard deviation [SD]) age of patients in the OLE study[27] was 14 (8) years, with 168 (68.0%) of patients being <18 years of age. A total of 79 (32.0%) patients were ≥18 to 36 years. Approximately 55% of patients were male. During the OLE study,[27] a subject was required to remain on ≥1 concomitant ASM throughout the study. Most (98.4%) patients were receiving between one and five concomitant ASMs. The most commonly used (≥25% of patients) ASMs were valproate (all forms), clobazam, and lamotrigine. Most patients received a mean daily dose of fenfluramine between 0.3 and 0.5 mg/kg/day. Further details of the patient characteristics are reported in Table 3.14.

Table 3.14: Baseline characteristics of patients included in OLE study

Baseline characteristic	**Fenfluramine dose 0.2–0.7 mg/kg/day (maximum: 26 mg/day)**
Number of patients	247*
Mean age at entry, years (SD)	14 (8)
Age group, years, n (%) 2–<6 6–<12 12–<18 18–36	 28 (11.3) 69 (27.9) 71 (28.7) 79 (32.0)
Sex (%)	136 (55.1) male
Race and ethnicity: White Black or African American Asian Other, unknown, or multiple Not reported†	 199 (80.6) 12 (4.9) 8 (3.2) 8 (3.2) 20 (8.1)
DSF per 28 days determined during the core study: Median (IQR)	75 (4, 2943)
Number or previous ASM use: Median (range)	7 (1–20)
Concomitant medications, median (range) Valproate, all forms, n (%) Clobazam, n (%) Lamotrigine, n (%) Levetiracetam, n (%) Rufinamide, n (%) Cannabidiol, n (%)	3 (1–7) 149 (60.3) 112 (45.3) 87 (35.2) 57 (23.1) 52 (21.1) 12 (4.9)
Duration of exposure by age group at entry into core study, days, median (IQR) Paediatric: 2–<18 years (n=174) Adult: 18–36 years (n=73)	 364 (191–368) 364 (210–373)

Baseline characteristic	Fenfluramine dose 0.2–0.7 mg/kg/day (maximum: 26 mg/day)
Mean daily dose of fenfluramine (mg/kg/day), n (%) Up to 0.2 >0.2 to <0.3 0.3 to 0.5 >0.5 to 0.7	 6 (2.4) 67 (27.1) 113 (45.7) 60 (24.3)
Based on Table 7, CS[1] Reference: Knupp 2023[27] *A total of 247 patients had enrolled in the OLE as of 19/10/2020 (interim cut-off date) and had at least one dose of study drug and 1 month of diary data in the OLE. †Privacy laws in some regions/countries preclude disclosure of certain personal information. ASM = anti-seizure medication; CS = company submission; DSF = drop seizure frequency; kg = kilogram; mg = milligram; OLE = open label extension; SD = standard deviation; IQR = interquartile range	

EAG comment:

- There originally appear to be contradictions in the description of the OLE study.[27] In Figure 8 and Table 7 of the CS[1] (above) it appears that the OLE study did not involve any randomisation to different doses of fenfluramine or placebo. Instead, patients were started on 0.2 mg/kg/day fenfluramine and doses were then adjusted as tolerated, which would fit with the established format of an OLE study.[27] However, in Section B.2.3.1 of the CS[1] it is stated that "*patients who qualified for the OLE study entered the titration period and 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 placebo*." Figure 9 in the CS[1] gives a similar impression that randomisation to the three OLE groups was applied. In the request for clarification, the company were asked to clarify this. The company replied by stating that, "*No randomisation was applied in the OLE study, as explained in Section B.2.3.1 (page 40 of the CS) 'During the OLE study, all patients were treated initially with fenfluramine 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study patients. After 1 month at a dose of 0.2 mg/kg/day, the investigator could adjust the dose for each subject based on effectiveness and tolerability.' At the beginning of the paragraph, as noticed by the EAG, there is a misprint, and it should read 'Upon completion of baseline in Study 1601, patients who qualified for the OLE study entered the titration period and 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 placebo.'. Figure 8, Table 7 and Figure 9 are correct. In Figure 9, the division into three different treatments and dosages does not indicate randomization but rather shows that out of the 247 patients from Study 1601 who continued to the OLE study, 78 received 0.7 mg/kg/day of fenfluramine during Study 1601, 83 received 0.3 mg/kg/day of fenfluramine, and 86 received a placebo.*"[3] The EAG thanks the company for the confirmation that the OLE study[27] was not randomised.

3.2.4 Risk of bias in the included trials

A risk of bias analysis was conducted for all studies identified in the SLR, using the Cochrane RoB Tool 2.0. The tool assesses quality across five domains: randomisation process; deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported

result. Table 3.15 contains a summary of the quality assessment for Study 1601[2] and demonstrates this study was completed to the highest standards possible in the context of this rare disease, with an overall low risk of bias.

Table 3.15: Summary of quality assessment of Study 1601

Study name	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Judgement
Knupp, 2022[2] Study 1601 (NCT03355209) Fenfluramine versus placebo	Low	Low	Low	Low	Low	Low
Based on Table 9, CS[1] CS = company submission						

EAG comment:

- The trial protocol supplement to Knupp, 2022[2] does not describe any mechanism of allocation concealment. The risk of selection bias is therefore high, and the assignation of 'low' risk of bias to the randomisation process is inaccurate. Overall judgement of the risk of bias should therefore also be adjusted to 'serious risk of bias.'

3.2.5 Efficacy results in the included trials

Only outcomes included in the NICE scope, or the decision problem are included below. Seizure free days is an outcome that has been included in the trial results but is not presented here as it is not included in the NICE scope or the decision problem.

3.2.5.1 Percent change from baseline in DSF in Titration and Maintenance versus placebo in the fenfluramine 0.7 and 0.2 mg/kg/day arms

3.2.5.1.1 Study 1601

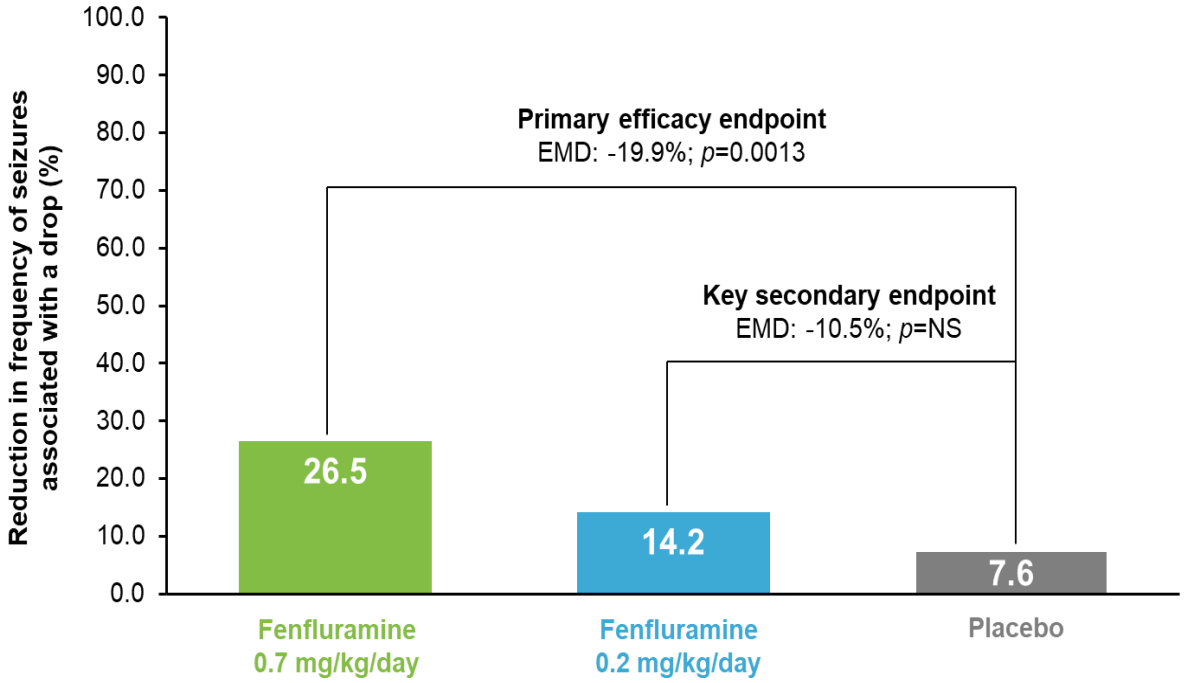
The primary endpoint of Study 1601[2] was expressed as the percentage change from baseline in DSF per 28 days during Titration and Maintenance for the fenfluramine 0.7 mg/kg/day group compared with the placebo group.

Based on this primary endpoint, a statistically significant benefit for fenfluramine 0.7 mg/kg/day was demonstrated. Median percentage reduction was -26.5% for the intervention group compared with -7.6% in the placebo one. The HL estimate of the median difference in percentage change from baseline in DSF between these two groups was -19.9 percentage points (95% CI: -31.02, -8.74) (p=0.0013)

As a key secondary endpoint (the fourth endpoint in the testing hierarchy), the change from baseline in DSF during Titration and Maintenance for the fenfluramine 0.2 mg/kg/day group was also compared with the placebo group using the same nonparametric ANCOVA model as for the primary endpoint. The difference between fenfluramine 0.2 mg/kg/day and placebo was not significant (p=0.0939). The median percentage reduction from baseline for the fenfluramine 0.2 mg/kg/day group was 14.2%, compared with 7.6% in the placebo group. The HL estimate of the median difference between the fenfluramine 0.2 mg/kg/day and placebo groups was -10.5 percentage points (95% CI: -24.99, 3.99).

Figure 3.6 illustrates the results of the Study 1601[2] for the primary and key secondary endpoints above mentioned.

Figure 3.6: **Primary and key secondary efficacy endpoint – Study 1601**



Based on Figure 12, CS[1]

CS = company submission; EMD = estimated median difference (Hodges-Lehmann estimate); NS = not significant

3.2.5.1.2 OLE study

Fenfluramine significantly reduced the median DSF which was maintained throughout the first 12 months of the OLE (Table 3.15). At Year 1 of the OLE, the median percentage reduction in DSF was -51.8% (p<0.0001) (Table 3.16).

Table 3.16: Key effectiveness endpoint: Change from Baseline in DSF per 28 days during the OLE Treatment Period Responder analysis (mITT)

Timepoint	mITT (n=241)
Frequency of seizures resulting in drops (ESC confirmed) per 28 days, mean (SD)	
Baseline, Study 1601[2]	188.70 (361.677)
Median % change from baseline in DSF per 28 days (p-value*)	
Study 1601[2], transition period	-23.10 (NR)
OLE study,[27] month 1	-4.18 (p<0.0001)
OLE study,[27] month 3	-39.42 (p<0.0001)
OLE study,[27] month 4-6	-37.12 (p<0.0001)
OLE study,[27] month 7-9	-42.69 (p<0.0001)
OLE study,[27] month 10-12	-51.77 (p<0.0001)
OLE study,[27] month 13-15	-50.53 (p<0.0001)

Based on Table 12, CS[1]
[a]The mean daily dose is calculated over the complete treatment duration in the OLE study,[27] using the sum of doses in mg/kg on each day and dividing by the duration of treatment in the OLE study.[27]
*P-value is from a Wilcoxon signed-rank test that the median % change from baseline is significantly different from 0.
CS = company submission; DSF = drop seizure frequency; ESC = Epilepsy Study Consortium; OLE = open label extension; kg = kilogram; mg = milligram; mITT = modified intention-to-treat; NR = not reported; SD = standard deviation; % = percentage

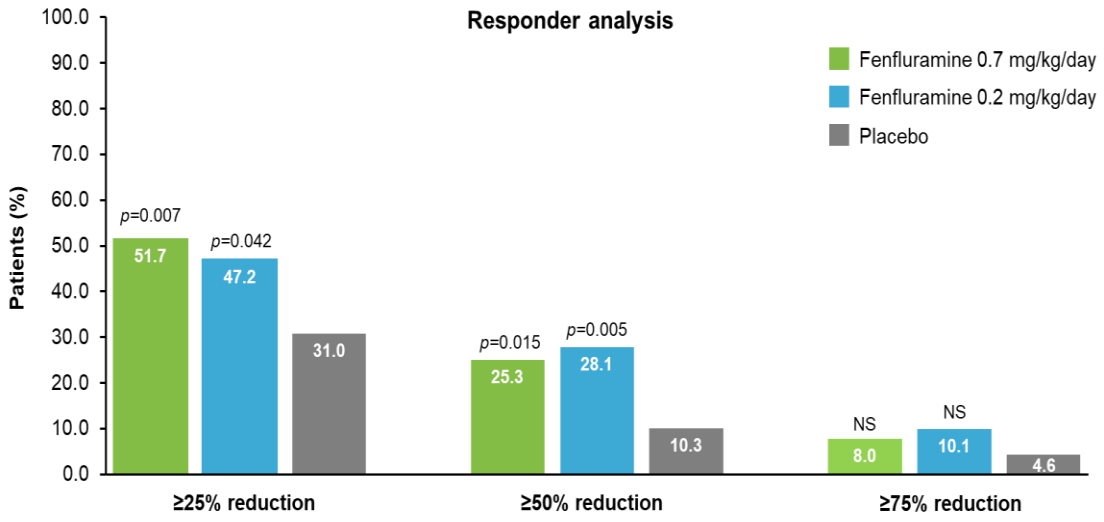
3.2.5.2 Proportion of patients achieving ≥25%, ≥50% or ≥75% reduction in DSF

*3.2.5.2.*1 Study 1601

Separate percentages of patients with a ≥50% reduction from baseline in DSF (50% responder rate) during Titration and Maintenance in the two fenfluramine arms compared with the placebo group, were key secondary endpoints. Patients in the fenfluramine 0.7 mg/kg/day group (25.3%) and fenfluramine 0.2 mg/kg/day group (28.1%) had a ≥50% statistically significant reduction from baseline in DSF during Titration and Maintenance versus the placebo group (10.3%) (p=0.0150).

Similar to the key secondary endpoint that evaluated the 50% responder rate during Titration and Maintenance, the percentages of patients with ≥25% and ≥75% reductions from baseline in DSF during Titration and Maintenance were compared between the fenfluramine groups and the placebo group using a logistic regression model. The percentage of patients with a ≥25% reduction was statistically significant in both the fenfluramine 0.7 mg/kg/day group (51.7%) (p=0.0065) and fenfluramine 0.2 mg/kg/day group (47.2%) (p=0.0417) compared with the placebo group. Statistical significance was not reached at the ≥75% reduction level for the fenfluramine 0.7 or 0.2 mg/kg/day groups compared with the placebo group (8.0%, 10.1% and 4.6% respectively) (p=0.2971 and p=0.1174, respectively) (Figure 3.7), however percentages changes were numerically higher.

Figure 3.7: Proportion of patients achieving ≥25%, ≥50% and ≥75% reductions from baseline in DSF during the Titration and Maintenance period

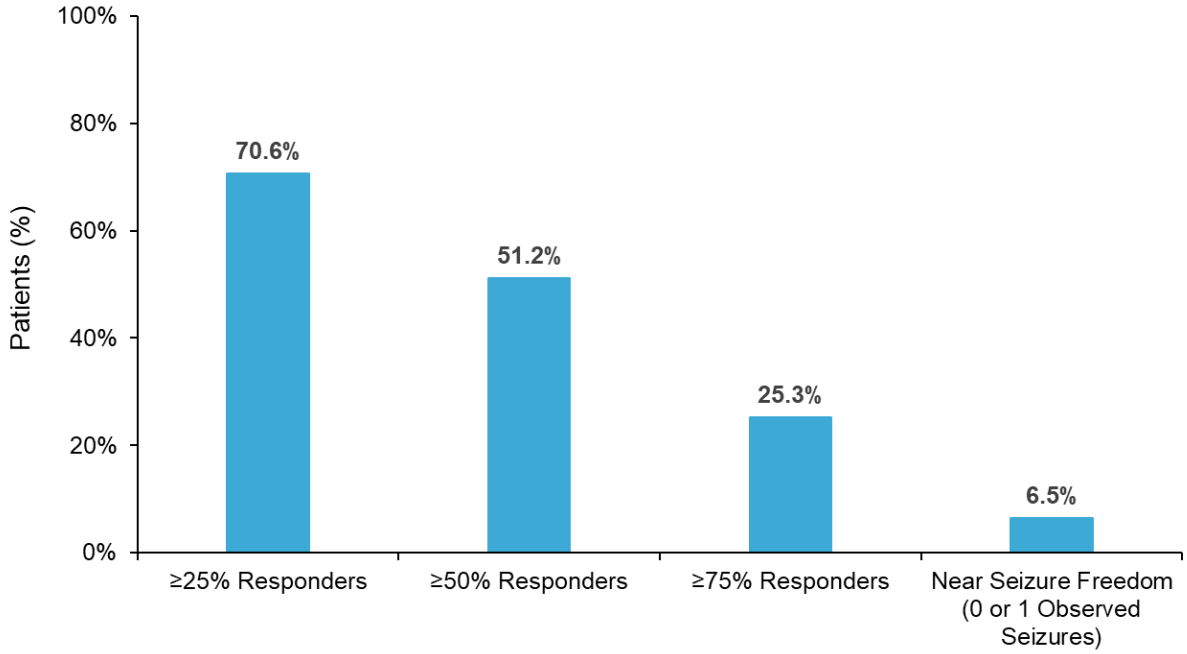


Based on Figure 13, CS[1]
CS = company submission; DSF = drop seizure frequency; kg = kilogram; mg = milligram; NS = not significant; T+M = Titration and Maintenance.

3.2.5.2.2 OLE study

The OLE analysis for typical drop seizures yielded similar results: 51.2% of patients responded with a clinically meaningful (≥50%) reduction, and 25.3% of patients demonstrated profound (≥75%) reduction in DSF for the overall OLE treatment period. 6.5% patients were near seizure-free (0 or 1 seizures observed) for typical drops during the entire OLE treatment period (Figure 3.8).

Figure 3.8: **Responder rates for drop seizures after 1 year of fenfluramine treatment**



Based on Figure 16, CS[1]
Note: Represents previous 3 months versus RCT baseline.
CS = company submission; RCT = randomised controlled trial; % = percentage

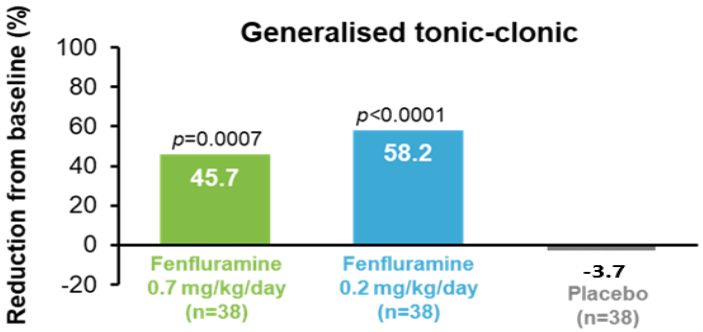
3.2.5.3 Frequency of GTC seizures

3.2.5.3.1 Study 1601

Generalised tonic-clonic seizures were not listed in the company decision problem. However, as the NICE scope included GTC seizures, the trial results for this outcome have been presented below.

Changes from baseline during Titration and Maintenance in the frequency of GTC seizures per 28 days were evaluated for the mITT population. The greatest median percentage decrease in the fenfluramine 0.7 mg/kg/day group relative to the placebo group was seen for GTC (45.7% decrease versus 3.7% increase, respectively; p=0.0005). Similar results were observed for the fenfluramine 0.2 mg/kg/day group for the change in GTC seizure frequency (58.2% decrease; p=0.0001) (Figure 3.9).

Figure 3.9: **Percentage reduction from baseline of GTC seizures in Study 1601**



Based on Figure 14, CS[1]
CS = company submission; GTC = generalised tonic-clonic; kg = kilogram; mg = milligram; % = percentage

3.2.5.3.2 OLE study
No data provided.

3.2.5.4 Proportion of patients seizure-free Titration and Maintenance and Maintenance only

Proportion of patients seizure-free were not listed in the company decision problem. However, as the NICE scope included 'proportion of patients seizure-free', the trial results for this outcome have been presented below.

3.2.5.4.1 Study 1601

Few patients achieving seizure-freedom were reported. Seizure freedom was achieved by one of 89 patients (1%) in the fenfluramine 0.2 mg/kg/day group, one of 87 patients (1%) in the placebo group, and zero of the 87 patients in the 0.7 mg/kg/day group. Near seizure freedom (defined as ≤1 observed seizure), was reported in one of 87 patients (1%) in the 0.7 mg/kg/day fenfluramine group, two of 89 patients (2%) in the 0.2 mg/kg/day fenfluramine group, and one of 87 patients (1%) in the placebo group.

3.2.5.4.1 OLE study

Notably, three (1.2%) patients were near drop seizure-free (zero or one seizures observed) during the entire OLE Treatment Period, and the number of patients who were near drop seizure-free increased to seven (2.9%) when assessed during Month 2 to End of Study (EOS).

3.2.5.5 Incidence of status epilepticus on rescue medication use and hospitalisation

Incidence of status epilepticus on rescue medication use and hospitalisation was not listed as a single outcome in the company decision problem. However, as the NICE scope included 'Incidence of status epilepticus on rescue medication use and hospitalisation', the trial results for this outcome have been presented below.

3.2.5.5.1 Study 1601

Status epilepticus is a condition in which a seizure lasts longer than 5 minutes or when seizures occur close together and the patient does not recover between episodes. It is an emergency condition that leads to use of rescue medication and emergency hospitalisation.

Seizures that evolved into status epilepticus were recorded by type and duration (>10 minutes). Status epilepticus lasting for <30 minutes was considered an AE, unless one of the other serious adverse

events (SAE) criteria (e.g., hospitalisation) was met. Two patients in the fenfluramine 0.7 mg/kg/day group (each of whom had one episode) and one subject in the placebo group (who had two episodes) had AEs of status epilepticus during Titration and Maintenance.

The number and percentage of patients with ≥1 incidence of status epilepticus using the composite definition during Titration and Maintenance was similar between the treatment groups: 41 (47.1%), 45 (50.6%), and 45 (51.7%) in the placebo, 0.2 mg/kg/day, and 0.7 mg/kg/day groups, respectively; p=0.6493 for the comparison of fenfluramine 0.7 mg/kg/day versus placebo and p=0.6546 for the comparison of fenfluramine 0.2 mg/kg/day versus placebo.

The mean (SD) number of episodes of status epilepticus per 28 days during Titration and Maintenance was 3.4 (10.2), 6.6 (22.6), and 4.6 (12.1) in the placebo, fenfluramine 0.2 mg/kg/day, and fenfluramine 0.7 mg/kg/day groups, respectively. Based on a nonparametric ANCOVA analysis, no difference between the treatment groups was observed (p=0.5402 for fenfluramine 0.7 mg/kg/day versus placebo, p=0.7136 for fenfluramine 0.2 mg/kg/day versus placebo).

The comparison between each of the fenfluramine groups and the placebo group in patients who used rescue medication during Titration and Maintenance was not significant (p=0.5142 for fenfluramine 0.2 mg/kg/day and p=0.5282 for fenfluramine 0.7 mg/kg/day).

The numbers and percentage of randomised patients who had hospital visits during the study to treat seizures in the fenfluramine 0.2 and 0.7 mg/kg/day groups (six [6.7%] and five [5.7%], respectively) were similar to the number and percentage in the placebo group (seven [8.0%]).

3.2.5.5.2 OLE study

No data provided.

3.2.5.6 Clinical Global Impression of Change – Improvement (CGI-I) rating

3.2.5.6.1 Study 1601

Parents/caregivers and study investigators independently rated how patients' symptoms had improved or worsened relative to baseline using the CGI-I scale. This provides an overall evaluation of a patient's response to treatment taking into consideration efficacy, safety, and tolerability.

In Study 1601, significantly more patients receiving fenfluramine 0.7 mg/kg/day were rated as "Very much", "Much improved" or "Minimally improved" by parents/caregivers (61.3%) and investigators (48.8%) compared with patients receiving placebo at the end of their treatment period (37% and 33.8%, p=0.0023 and p=0.0567 respectively). The lack of statistical significance between fenfluramine 0.7 mg/kg/day and placebo on the investigator-rated CGI-I scale stemmed primarily from a large percentage of patients in the placebo group who were rated as minimally improved. In contrast, the percentage of patients rated on the CGI-I by the investigator as having met a more stringent threshold of improvement (Much Improved or Very Much Improved, indicating a clinically meaningful improvement) at Visit 12 (end of study/early termination) was highly statistically significant in favour of patients receiving fenfluramine 0.7 mg/kg/day compared with patients receiving placebo (26.3% versus 6.3%, respectively; p=0.0007). This result indicates that the reduction in DSF in the fenfluramine 0.7 mg/kg/day group was associated with clinically meaningful improvements in clinical status as reflected by the CGI-I score (Table 3.17).

Table 3.17: CGI-I in Study 1601

Patient/caregiver reported outcomes and QoL endpoints	Placebo (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Fenfluramine 0.7 mg/kg/day (n=89)
Patient condition rating and QoL			
Percentage of patients with improvement[a] on CGI-I, investigator rating at Visit 12	33.8%	44.7%	48.8%
p-value for comparison with placebo		0.1565	0.0567
Percentage of patients with improvement[a] on CGI-I, parent/caregiver rating at Visit 12	37.0%	43.5%	61.3%
p-value for comparison with placebo		0.3960	0.0023
Percentage of patients with clinically meaningful improvement[b] on CGI-I, investigator rating at Visit 12	6.3%	20.0%	26.3%
p-value for comparison with placebo		0.0100	0.0007
Percentage of patients with clinically meaningful improvement[b] on CGI-I, Parent/caregiver rating at Visit 12	4.9%	27.1%	33.8%
p-value for comparison with placebo		0.0100	0.0100

Based on Table 11, CS[1]
[a]Improvement = minimally, much, or very much improved
[b]Clinically meaningful improvement = much improved or very much improved
CGI-I = clinical global impression-improvement; CS = company submission; kg = kilogram; mg = milligram; QoL = quality of life

3.2.5.6.2 OLE study

Nearly [redacted] and caregivers [redacted] rated their patients as having clinically meaningful improvement on the CGI-I, i.e., "Much Improved" or "Very Much Improved".

3.2.5.7 QOLCE paediatric QoL inventory

3.2.5.7.1 Study 1601

The QOLCE is an epilepsy-specific instrument to assess how epilepsy affects day-to-day functioning of children in various areas, including physical activities, wellbeing, cognition, social activities, behaviour, and general health. The results for the QOLCE in the fenfluramine treatment groups did not show significant differences in the overall score between treatment groups (Table 3.18).

Table 3.18: QOLCE in Study 1601

Patient/caregiver reported outcomes and QoL endpoints	Placebo (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Fenfluramine 0.7 mg/kg/day (n=89)
Patient condition rating and QoL			
QOLCE – overall QoL Mean change from baseline at visit 12 (SD)	[redacted]	[redacted]	[redacted]
p-value for comparison with placebo		[redacted]	[redacted]

Patient/caregiver reported outcomes and QoL endpoints	Placebo (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Fenfluramine 0.7 mg/kg/day (n=89)
Based on Table 11, CS[1] CS = company submission; kg = kilogram; mg = milligram; QoL = quality of life; QOLCE = Quality-of-Life in Childhood Epilepsy; SD = standard deviation			

3.2.5.7.2 OLE study

3.2.5.8 Caregiver QoL, anxiety and depression

3.2.5.8.1 Study 1601

Caregiver levels of anxiety and depression were also assessed in Study 1601[2] using the Hospital Anxiety and Depression Scale (HADS) and Zarit Caregiver Burden Inventory, respectively. Regarding the HADS, levels of anxiety for the parent/caregiver were near the high end of the normal range (0 to 7) at baseline in each treatment group. However, the changes from baseline in total scores for anxiety and depression were not significantly different between the fenfluramine groups and the placebo group, indicating that total emotional distress in parents/caregivers did not notably change in any of the treatment groups during the study. Similarly, no notable differences between each of the fenfluramine treatment groups and placebo group in change from baseline were observed in Index Scores or any of the Zarit Caregiver Burden Inventory categories at any visit (Table 3.19).

Table 3.19: HADS in Study 1601

Patient/caregiver reported outcomes and QoL endpoints	Placebo (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Fenfluramine 0.7 mg/kg/day (n=89)
Caregiver condition rating and QoL			
HADS – total score Mean change from baseline at Visit 12 (SD)	[redacted]	[redacted]	[redacted]
p-value for comparison with placebo		[redacted]	[redacted]
Zarit Caregiver Burden Inventory index – total score Mean change from baseline at Visit 12 (SD)	[redacted]	[redacted]	[redacted]
p-value for comparison with placebo		[redacted]	[redacted]
Based on Table 11, CS[1] CS = company submission; HADS = Hospital Anxiety and Depression Scale; kg = kilogram; mg = milligram; n = number of patients; QoL = quality of life; SD = standard deviation			

3.2.5.8.2 OLE study

Results of the QoL questionnaires (QOLCE, Zarit Caregiver Burden Inventory, HADS) were not yet available.

3.2.5.9 Mortality

3.2.5.9.1 Study 1601

No data provided.

3.2.5.9.2 OLE study

No data provided.

3.2.5.10 Sub-group analysis

No sub-group analyses were conducted in either study.

3.2.6 AEs in the included trials

During clinical development in LGS, fenfluramine showed a good safety and tolerability profile. Sustained retention rates in the use of fenfluramine during the OLE study[27] supported the evidence that fenfluramine is a generally well tolerated ASM. No case of valvular heart disease nor pulmonary arterial hypertension was reported at any point.

3.2.6.1 Adverse reactions in Study 1601

3.2.6.1.1 Most common treatment-emergent adverse events (≥10%) in Study 1601

In Study 1601[2] (Table 3.20 below), most patients (212 of 263 [81%]) experienced a TEAE (78 of 87 patients [90%] in the 0.7 mg/kg/day fenfluramine group; 69 of 89 [78%] in the 0.2 mg/kg/day fenfluramine group; 65 of 87 [75%] in the placebo group).

The most common TEAEs included decreased appetite (59 of 263 [22%]), somnolence (33 of 263 [13%]), and fatigue (33 of 263 [13%]). More patients in the fenfluramine treatment groups than in the placebo group experienced decreased appetite (31 of 87 [36%] in the 0.7 mg/kg/day fenfluramine group; 18 of 89 [20%] in the 0.2 mg/kg/day fenfluramine group; 10 of 87 [11%] in the placebo group).

Table 3.20: Most common TEAE (Study 1601)

	Fenfluramine 0.7 mg/kg/day (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Placebo (n=87)	Overall (N=263)
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)
Diarrhoea, n (%)	11 (13)	10 (11)	4 (5)	25 (10)
Pyrexia, n (%)	7 (8)	9 (10)	10 (11)	26 (10)
Fatigue, n (%)	16 (18)	8 (9)	9 (10)	33 (13)
Vomiting, n (%)	7 (8)	12 (13)	5 (6)	24 (9)

Based on Table 26, CS[1]
CS = company submission; kg = kilogram; mg = milligram; n = number of patients; TEAE = treatment emergent adverse events

3.2.6.1.2 SAEs and treatment discontinuation in Study 1601

In Study 1601[2] (Table 3.21 below), more patients in the 0.7 mg/kg/day fenfluramine group (10 of 87 [11%]) compared with the 0.2 mg/kg/day fenfluramine group (four of 89 [4%]) and the placebo group (four of 87 [5%]) experienced one or more serious TEAE. One SUDEP was reported which was unrelated to fenfluramine use. No cases of valvular heart disease or pulmonary arterial hypertension

were observed at any time during the trial. One patient (fenfluramine 0.7 mg/kg/day) had an end of study echocardiography read as mild aortic regurgitation (AR), but subsequent diagnostic transoesophageal echocardiography revealed absent AR and a normal aortic valve.

The most frequent TEAEs leading to study withdrawal were seizure (three patients in the 0.2 mg/kg/day fenfluramine group) and somnolence (three patients in the 0.7 mg/kg/day fenfluramine group).

Table 3.21: Serious TEAEs and treatment discontinuation (Study 1601)

Category	Fenfluramine 0.7 mg/kg/day (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Placebo (n=87)	Overall (N=263)
Patients with ≥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)

Based on Table 27, CS[1]
AE = adverse event; CS = company submission; kg = kilogram; mg = milligram; n = number of patients; TEAE = treatment emergent adverse events

3.2.6.1.3 Adverse events of special interest in Study 1601

Fenfluramine was previously marketed at significantly higher doses of 60-120 mg/day as an appetite suppressant for the treatment of obesity but was withdrawn from the market over 20 years ago due to its reported association with valvular heart disease. Based on its known AE profile and mode of action, the incidence of adverse events of special interest (AESI) listed in Table 3.22 were identified for collection in the protocols of Study 1601[2] and OLE study[27] interim analysis. Occurrence of lethargy, status epilepticus, and weight loss were generally of low prevalence. Decreased appetite was highest in fenfluramine 0.7 mg/kg/day.

Table 3.22: AESI in Study 1601

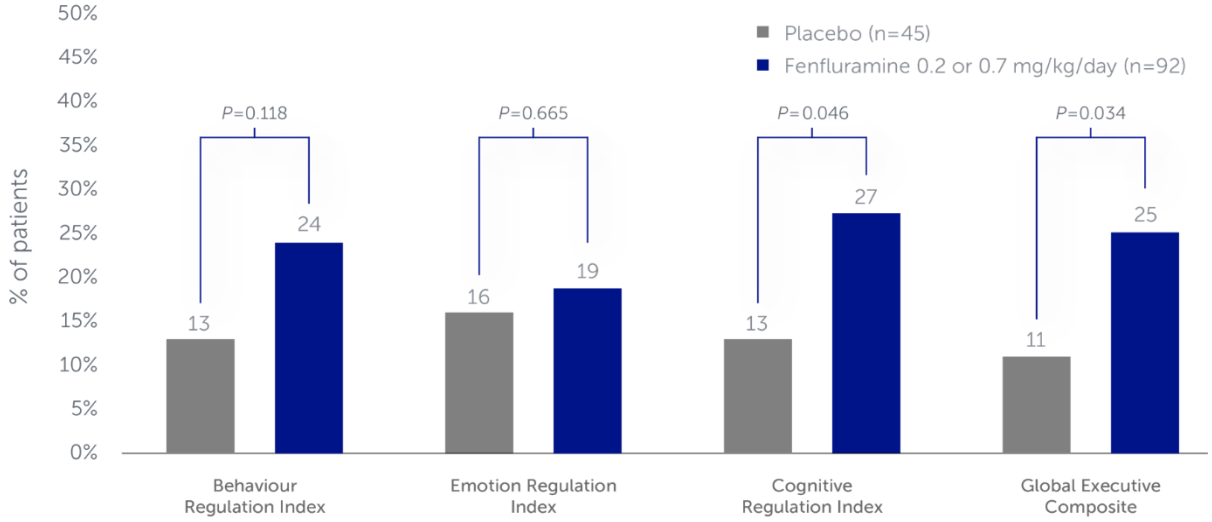
AESI	Fenfluramine 0.7 mg/kg/day (n=87)	Fenfluramine 0.2 mg/kg/day (n=89)	Placebo (n=87)
Somnolence, n (%)	15 (17.2)	9 (10.1)	9 (10.3)
Weight loss, n (%)	7 (8.0)	2 (2.2)	2 (2.3)
Decreased appetite, n (%)	31 (35.6)	18 (20.2)	10 (11.5)
Status epilepticus, n (%)	3 (3)	0 (0)	1 (1)
Lethargy, n (%)	5 (5.7)	2 (2.2)	2 (2.3)

Based on Table 29, CS[1]
AESI = adverse events of special interest; CS = company submission; kg = kilogram; mg = milligram; n = number of patients

Treatment with fenfluramine was not associated with clinically meaningful worsening in Cognitive Regulation Index (CRI) and Global Executive Composite (GEC) (Reliable Change Index [RCI] ≥80%) in any of the Behaviour Rating Inventory of Executive Function® Second Edition (BRIEF®-2)

indexes/composite T-scores compared to placebo (p>0.05). Indeed, in pooled analysis, including both 0.2 mg and 0.7 mg/kg dosing, significantly more children and young adults on fenfluramine showed clinically meaningful improvement in global executive functioning with specific improvement in the CRI (p<0.05; RCI ≥95% certainty) (Figure 3.9): approximately twice as many children and young adults showed clinically meaningful improvement after fenfluramine than after placebo in the cognitive regulation index (27% versus 13%) and GEC (25% versus 11%) (Figure 3.10).

Figure 3.10: **Clinically meaningful improvement (RCI ≥95% certainty) in BRIEF®-2 indexes/composite (pooled analysis including 0.2 and 0.7 mg/kg dose of fenfluramine)**



Based on Figure 25, CS[1]

BRIEF®-2 = Behaviour Rating Inventory of Executive Function® Second Edition; CS = company submission; kg = kilogram; mg = milligram; RCI = Reliable Change Index; % = percentage

Notes: p-values are active versus placebo; calculated by Somers' D. Highlighted p-values show statistical significance.

3.2.6.2 Adverse reactions in the OLE study

3.2.6.2.1 Most common treatment-emergent adverse events in OLE study

In the OLE study[27] (Table 3.23 below), the majority of patients (203 of 247 [82.2%]) experienced a TEAE, most of which were mild or moderate in severity (188 of 247 [76.1%]). The most common TEAEs were decreased appetite (40 of 247 [16.2%]) and fatigue (33 of 247 [13.4%]).

Table 3.23: Most common TEAEs OLE study

Category	N=247
Any TEAE, n (%)	203 (82.2)
Decreased appetite, n (%)	40 (16.2)
Fatigue, n (%)	33 (13.4)
Nasopharyngitis, n (%)	31 (12.6)
Seizure, n (%)	27 (10.9)
Based on Table 28, CS[1]	

Category	N=247
CS = company submission; OLE = open label extension; TEAE = treatment emergent adverse events; % = percentage	

3.2.6.2.2 Serious adverse events and treatment discontinuation

In the OLE study,[27] 40 of 247 patients (16.2%) experienced a serious TEAE, including nine patients (3.6%) with changes in seizure presentation, eight patients (3.2%) with status epilepticus, and five patients (2.0%) with pneumonia.

Twelve patients (4.9%) experienced a TEAE that led to study discontinuation, most commonly fatigue or change in seizure presentation (n=3, 1.2% each) and 94% of patients chose to continue receiving fenfluramine treatment. One patient died due to aspiration pneumonia, which was considered unrelated to fenfluramine.

Echocardiography revealed that no patient had developed valvular heart disease (VHD) or pulmonary arterial hypertension (PAH) by the interim analysis cut-off date:

- Two patients in the LGS programme demonstrated instances of mild AR without the presence of VHD.
- Neither subject exhibited valvular morphological (or structural) changes, nor did findings progress to a higher grade of regurgitation.
- One of these patients had two diagnostic transoesophageal ECHOs (a method with higher resolution than standard transthoracic ECHO); both patients demonstrated absent AR and normal valve structure.
- Both patients were examined by cardiologists, who concluded no VHD in either patient.
- Rates of mild AR observed in the study (two of 247 [0.8%]) are consistent with those seen in the screening period prior to treatment with fenfluramine (three of 335 [0.9%]).
- Both patients continue to be treated with fenfluramine without development of VHD.

3.2.6.2.3 AESI

In the OLE study,[27] weight changes from baseline ranged from weight loss of 22.4% to weight gain of 34.4%. Overall, body weight gain ≥7% of OLE baseline was reported at any visit for 32.4% of patients and body weight decrease ≥7% was reported for 17.0% of patients.

EAG comment:

- Fenfluramine was originally developed in the 1970s as a weight-loss drug but was withdrawn due to cardiac toxicity. The company were asked to comment on this, and to provide data from larger non-randomised sources in related populations to establish if cardiac AEs have been observed in children using fenfluramine. The company commented that, "*In the early 1960s, fenfluramine was introduced as a weight loss treatment for obese adults. However, its use led to reports of pulmonary arterial hypertension and cardiac valvulopathy, particularly when combined with phentermine, resulting in its withdrawal from the US and European markets in the late 1990s. Notably, fenfluramine was prescribed at 60mg/day with doses as high as 220 mg/day (median 56.5 mg/day), and the association with heart disease was complicated by the lack of pre-treatment echocardiograms and consideration of other risk factors. Since fenfluramine as a treatment to aid weight loss in obese adults was withdrawn from the market*

over 20 years ago, no other form of fenfluramine has been made commercially available, for any indication. The current marketing authorisation application for fenfluramine (as Fintepla®) is indicated in an entirely different population of patients with DS or LGS - two rare, severe and life-limiting forms of epilepsy that emerges in early infancy. The maximum clinical doses of fenfluramine for the treatment of DS or LGS are 0.7 mg/kg/day with a maximum total daily dose of 26 mg. Therefore, regardless of a patient's weight, these doses are substantially lower than those previously used to treat obesity. The risk-benefit profile of fenfluramine (as Fintepla®) in the treatment of DS or LGS is therefore completely different to the risk-benefit profile of the previously marketed fenfluramine product that was used and subsequently withdrawn for the treatment of obesity. As indicated in Section B2.10 of the CS Document B, during clinical development in LGS, no case of valvular heart disease (VHD) nor pulmonary arterial hypertension (PAH) was reported at any point. Furthermore, there have been no cases of VHD or PAH in over 1,500 patients treated with Fintepla® in clinical trials and the US registry, which includes all US patients who participated in DS and LGS clinical trials and all patients on the commercial drug as of February, 2022 (some patients have received up to 5 years of treatment) [Company response to clarification references 7, 27, 28]. No evidence of VHD or PAH has been found in over 30 years of safety data including evidence from prior fenfluramine studies in epilepsy and in Fintepla® studies with supporting echocardiogram data (29-31)"[3] The EAG thanks the company for this additional information and acknowledges the lack of evidence suggesting that fenfluramine could have adverse cardiac effects in the LGS population.

3.2.7 Ongoing studies

None.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The SLR identified 16 RCTs that evaluated fenfluramine, eight other ASMs and two electrical stimulation approaches in terms of their efficacy in people with LGS. Of these, six were excluded from the NMA because a) outcomes were reported outside the range of 10-20 weeks (n=3); b) there were no matching outcomes for comparison (n=2); or c) because a drug was not approved by the EMA (n=1). After an NMA feasibility assessment, a further RCT was excluded because of a very high baseline number of seizures. This left nine eligible RCTs for the NMA (Table 3.24).

Table 3.24: Summary of the trials used to carry out the indirect or mixed treatment comparison

Trial Name	Author, Year	Fenfluramine 0.2 mg/kg	Fenfluramine 0.7 mg/kg	Cannabidiol 10 mg/kg	Cannabidiol 20 mg/kg	Rufinamide 45 mg/kg	Felbamate 45 mg/kg	Lamotrigine 100-400 mg	Clobazam 0.25 mg/kg	Clobazam 0.50 mg/kg	Clobazam 1.0 mg/kg	Topiramate 6 mg/kg	Placebo
Study 1601	Knupp, 2022[2]	Yes	Yes										Yes

Trial Name	Author, Year	Fenfluramine 0.2 mg/kg	Fenfluramine 0.7 mg/kg	Cannabidiol 10 mg/kg	Cannabidiol 20 mg/kg	Rufinamide 45 mg/kg	Felbamate 45 mg/kg	Lamotrigine 100-400 mg	Clobazam 0.25 mg/kg	Clobazam 0.50 mg/kg	Clobazam 1.0 mg/kg	Topiramate 6 mg/kg	Placebo
GWPCARE3	Devinsky, 2018[14]			Yes	Yes								Yes
GWPCARE4	Thiele, 2018[15]				Yes								Yes
E2080-J081-304	Ohtsuka, 2014[17]					Yes							Yes
-	Ritter, 1993[23]						Yes						Yes
-	Jensen, 1994[22]						Yes						Yes
-	Motte, 1997[21]							Yes					Yes
OV-1012	Ng, 2011[18]								Yes	Yes	Yes		
-	Sachdeo, 1999[24]											Yes	Yes
Study 022	Glauser, 2008[20]					Yes							Yes

Based on Table 13, CS[1]
CS = company submission; kg = kilogram; mg = milligram

EAG comment:

- These initial six exclusions appeared appropriate. However, the NMA published in the CS appendices[6] excluded a further six RCTs, merely including three RCTs (that covered only fenfluramine, cannabidiol and placebo). Therefore, rufinamide, felbamate, lamotrigine, clobazam and topiramate were not included as comparators in the NMA. Of these, rufinamide, topiramate and clobazam are recommended as 3rd line medications by NICE (NG217) (which is the line of therapy for which fenfluramine is positioned) and these are therefore highly relevant comparators. The ideal network would contain all 3rd line medications and would therefore comprising the following 3rd line comparisons: fenfluramine + SoC versus SoC, cannabidiol/clobazam + SoC versus SoC, clobazam + SoC versus SoC, rufinamide + SoC versus SoC and topiramate + SoC versus SoC. Such a network would allow indirect estimates of the treatment differences between each of these 3rd line drugs (appropriately combined with SoC treatment) – for example, between fenfluramine + SoC and rufinamide and SoC.
- The rationale given for the six additional exclusions was that these excluded RCTs did not report all outcomes of interest or "most characteristics relevant to the disease". It was also implied that

the data from the excluded trials were outdated. The final explanation for the inclusion of only three RCTs was that "cannabidiol is the most recently approved LGS medication and is a main comparator to fenfluramine". These explanations for the dramatic reduction of the scope of the NMA appear weak. A separate NMA is carried out for each outcome of interest and so each RCT should have been allowed to contribute to the NMA for any relevant outcome that it covered; excluding an RCT because it did not cover all of the relevant outcomes appears wasteful. Furthermore, the reasons related to patient characteristics and recency require considerable strengthening before they can adequately explain the six exclusions. Finally, the fact that cannabidiol has been most recently approved and is a common comparator to fenfluramine does not in any way justify the exclusion of other comparators. Given that a proper consideration of the relative efficacy and cost effectiveness of add-on fenfluramine is not complete unless all the other add-on 3rd line option drugs are considered in the model, the company were asked to provide an NMA including data from all nine eligible RCTs. The company responded by stating that, "*The NMA report provided in the reference pack (UCB data on file NMA report) included the extended (broader) network analysis in Appendix F (including data from 9 RCTs). Major concerns were raised in the feasibility assessment, as the 6 excluded trials did not report all key patient characteristics including: baseline seizure frequency, number of prior ASMs used, and number of concomitant ASMs used (see Table 16 in the CS Document B) and most of these excluded studies were dated from 20-30 years old data and hence do not capture improvement in LGS medical care (concomitant ASMs), which is especially difficult to assess as they do not report information on concomitant ASMs. This transgresses the transitivity assumption needed for conducting the NMA for this network. Furthermore, although this extended network analysis has been provided separately in the NMA report and enclosed in the reference pack, the outcomes of interest for this network are not fully available. For instance, there were no outcomes available for median percent reduction in GTC seizures from this broader network.* [Table 3.24] *below provides a breakdown of all five NMA outcomes that were used and the available data from the GBA data network results (subgroup on cannabidiol with clobazam), ITT NMA network (no restriction on cannabidiol), and extended ITT network (no restriction on cannabidiol). We can note that the relative risk ratios from the ITT data network results (3 RCTs) and the ITT extended network results (9 RCTs) are similar for both the smaller and extended network as shown in* [Table 3.24] *below*."[3] The EAG thanks the company for the UCB data on file NMA report. This is extremely useful in providing a comparison between fenfluramine and its relevant 3rd line comparators. The results from this extended NMA (including all nine RCTs) are revealing. They show that [redacted], rufinamide and lamotrigine were [redacted] to fenfluramine. Similarly, [redacted], clobazam (1 mg/kg), rufinamide, cannabidiol (20 mg/kg) and topiramate were [redacted] fenfluramine to be [redacted], lamotrigine, felbamate, clobazam (1 mg/kg), clobazam (0.5 mg/kg), clobazam (0.25 mg/kg) and cannabidiol (10 mg/kg) [redacted]. A similar picture was seen for discontinuation due to AEs and SAEs. [redacted] fenfluramine was likely to be [redacted]. For [redacted], but only lamotrigine and cannabidiol (20 mg/kg) were included alongside fenfluramine and placebo in that NMA. Overall, the fuller (nine RCTs) NMA provides information suggesting that

[redacted], an extremely important piece of information that appears to have not been adequately discussed or considered in the CS.[1] The EAG notes the arguments provided by the company why these fuller NMA results are not considered in the CS.[1] These focus on *potential* intransitivity, but the EAG note that there is no evidence provided by the company that the excluded studies were actually different in terms of any of the factors described, only that data on these factors were absent. The EAG therefore remains unconvinced about the validity of the complete exclusion of these full NMA results from the CS,[1] particularly given that they conflict with the conclusions made in the more limited NMA presented in the CS.[1] The EAG also points out that the Table provided below (Table 3.25) by the company does not provide any NMA-based information on the efficacy of the other 3rd line treatment comparators, such as rufinamide or topiramate, and merely reports effects in the comparators that were included in the limited NMA. This therefore remains a key issue.

Table 3.25: NMA outcomes breakdown by treatment, studied population, and NMA network

		GBA data network results (three RCTs) – GBA data: (FFA-PBO-CBD + CLB (GBA))	ITT data network results (three RCTs) – ITT data: FFA-PBO-CBD	ITT extended network results (nine RCTs) – (FFA-PBO-CBD-CLB-TPM-RFM-LTG)
Studied population		**Subgroup: CBD + CLB (GBA)**	**No subgroup (no restrictions on cannabidiol) ITT: FFA-PBO-CBD**	**No subgroup (no restrictions on cannabidiol) ITT: FFA-PBO-CBD-CLB-TPM-RFM-LTG**
NMA outcome	**Treatment**	**Risk ratio with 95% CrI (versus placebo)**		
≥25% reduction in DSF				
	Fenfluramine (0.7 mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (10 mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (20 mg/kg)	[redacted]	[redacted]	[redacted]
≥50% reduction in DSF				
	Fenfluramine (0. 7 mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (10 mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (20 mg/kg)	[redacted]	[redacted]	[redacted]
≥75% reduction in DSF				
	Fenfluramine (0.7 mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (10 mg/kg)	[redacted]	[redacted]	[redacted]
	CBD (20 mg/kg)	[redacted]	[redacted]	[redacted]
Discontinuation due to AEs				
	Fenfluramine (0.7 mg/kg)	NR	[redacted]	[redacted]
	CBD (10 mg/kg)	NR	[redacted]	[redacted]
	CBD (20 mg/kg)	NR	[redacted]	[redacted]

		GBA data network results (three RCTs) – GBA data: (FFA-PBO-CBD + CLB (GBA))	ITT data network results (three RCTs) – ITT data: FFA-PBO-CBD	ITT extended network results (nine RCTs) – (FFA-PBO-CBD-CLB-TPM-RFM-LTG)
Studied population		**Subgroup: CBD + CLB (GBA)**	**No subgroup (no restrictions on cannabidiol)** **ITT: FFA-PBO-CBD**	**No subgroup (no restrictions on cannabidiol)** **ITT: FFA-PBO-CBD-CLB-TPM-RFM-LTG**
NMA outcome	**Treatment**	**Risk ratio with 95% CrI (versus placebo)**		
Median percent reduction in frequency of GTC seizures				
		Mean difference with 95% CrI (versus placebo)		
	Fenfluramine (0.7 mg/kg)	NR	[redacted]	NR
	CBD (10 mg/kg)	NR	[redacted]	NR
	CBD (20 mg/kg)	NR	[redacted]	NR

Based on Table 6, company response to request for clarification[3]

AE = adverse event; CBD + CLB = cannabidiol + clobazam; CrI = credible interval; DSF = drop seizure frequency; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; TPM = topiramate; RFM = rufinamide; LTG = lamotrigine; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); GTC = generalised tonic-clonic; ITT = intention-to-treat; kg = kilogram; mg = milligram; NMA = network meta-analysis; NR = not reported; RCT = randomised controlled trial

- The EAG asked the company to clarify the clinical heterogeneity of the studies in the NMA. The company responded by stating that, "*Detailed patient characteristics for all the trials included in the NMA are provided in B2.9.2.2 Table 15 in p.71-73 in CS Document B. They include age, gender, race, mean weight, number of previous ASMs (median), number of concurrent ASMs (median), 28-day median seizure frequency (all seizures) and 28 median DSF.* [Table 3.26] *below reported the patient characteristics for all the trials included in the NMA (as extracted from Table 15 of the CS Document B).Data on ASM-related inclusion/exclusion criteria and concomitant medications usage (%) in each trial are provided in Appendix D (Section D1.1.4.6 – in table 30 of the Appendices of the CS) and reported here in* [Table 3.27] *below. Comparability of RCTs is discussed in B2.9.2 NMA feasibility assessment. This section provides details of feasibility assessment which discussed comparisons of RCTs designs and characteristics in section B2.9.2.1, comparison of patient characteristics in B2.9.2.2, and conclusions on the feasibility assessment in B2.9.2.3. Finally, in section B2.9.6 Uncertainties in the ITC (p.87) limitations and uncertainties of the ITC analysis were discussed given the study and patient characteristics discussed in B2.9.2.1 and B2.9.2.2. Additional to the information provided in table 30 of Appendix D of the CS, the median number of previous ASMs and concomitant therapies are provided in* [Table 3.28]*. Data on specific combinations of concomitant therapies were not reported in any of the included studies."*[3] The EAG thanks the company for this information, and agrees that the CS[1] is clear in presenting the clinical heterogeneity of the RCTs included in the NMA.

Table 3.26: Patient baseline characteristics

Author, Year (Study Name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF[#]
Knupp, 2022[2] Study 1601 NCT03355209	Fenfluramine (0.2 mg/kg) (n=87)	13 (3–35) [paediatrics + adults]	46 (52.0)	75%	42.4 (20.9)	7	3	106	85
	Fenfluramine (0.7 mg/kg) (n=89)	13 (2–35) [paediatrics + adults]	54 (62.0)	80%	42.2 (21.4)	8	3	111	83
	Placebo (n=87)	13 (2–35) [paediatrics + adults]	46 (53.0)	82%	43.9 (20.7)	7	3	68	53
Devinsky, 2018[14] GWPCARE3 NCT02224560	Cannabidiol (10 mg/kg) (n=73)	15.4* (9.5) [paediatrics + adults]	40 (55.0)	84.9%	44.3 (26.2)	6	3	165	86.9
	Cannabidiol (20 mg/kg) (n=77)	16* (10.8) [paediatrics + adults]	45 (59.0)	88.2%	41 (20.6)	6	3	174.3	85.5
	Placebo (n=76)	15.3* (9.3) [paediatrics + adults]	44 (58.0)	90.8%	45.7 (23.2)	6	3	180.6	80.3
Thiele, 2018[15] GWPCARE4 NCT02224690	Cannabidiol (20 mg/kg) (n=86)	14.2 (NR) [paediatrics + adults]	45 (52.0)	87%	41.6 (21.5)	6	3	144.6	71.4
	Placebo (n=85)	13.3 (NR) [paediatrics + adults]	43 (51.0)	93%	39.6 (23)	6	3	176.7	74.7
Ohtsuka, 2014[17] E2080-J081-304	Rufinamide (1000–3200 mg) (n=28)	16.0* (7.1) [paediatrics + adults]	17 (60.7)	✗	39.0 kg (19.5)	✗	✗	253.0	✗

Author, Year (Study Name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF[#]
NCT01146951	Placebo (n=30)	13.9* (6.1) [paediatrics + adults]	19 (63.3)	✗	40.9 kg (18.0)	✗	✗	296.7	✗
Ritter, 1993[23]	Felbamate (45 mg/kg) (n=37)	12* (SD: NR) [paediatrics + adults]	27	✗	37 kg (SD: NR)	8	≥2[†]	1,617**	✗
	Placebo (n=36)	14* (SD: NR) [paediatrics + adults]	24	✗	40 kg (SD: NR)	8	≥2[†]	716**	✗
Motte, 1997[21]	Lamotrigine (100–400 mg) (n=79)	9.6* (5.2) [paediatrics + adults]	54 (68.0)	94%	32.5 kg (18.1)	✗	≤3[†]	✗	14.5[#¤]
	Placebo (n=90)	10.9* (5.9) [paediatrics + adults]	45 (50.0)	93%	34.3 kg (19.7)	✗	≤3[†]	✗	11.6[#¤]
Ng, 2011[18] OV-1012 NCT00518713	Clobazam (0.25 mg/kg) (n=58)	10.9* (7.2) [paediatrics + adults]	36 (62.1)	56.9%	33.6 kg (22.6)	✗	✗	✗	40.9[#¤]
	Clobazam (0.50 mg/kg) (n=62)	14.1* (10.4) [paediatrics + adults]	36 (58.1)	56.5%	35.1 kg (20.3)	✗	✗	✗	23.5[#¤]
	Clobazam (1.0 mg/kg) (n=59)	11.7* (8.5) [paediatrics + adults]	34 (57.6)	62.7%	34.7 kg (22.1)	✗	✗	✗	28.9[#¤]
	Placebo (n=59)	13.0* (9.2) [paediatrics + adults]	38 (64.4)	71.2%	36.5 kg (22.2)	✗	✗	✗	35.5[#¤]

Author, Year (Study Name)	Intervention	Age, median (SD/range)	Male, n (%)	Race (% White)	Mean weight (SD)	Number of previous ASMs (median)	Concurrent ASMs (median)	28-day median seizure frequency (all seizures)	28-day median DSF[#]
Sachdeo, 1999[24]	Topiramate (6 mg/kg) (n=48)	11.2* (SD: NR) [paediatrics + adults]	28	✗	36.7 kg (19.0)	✗	✗	267	90
	Placebo (n=50)	11.2* (SD: NR) [paediatrics + adults]	25	✗	31.6 kg (17.8)	✗	✗	244	98
Glauser, 2008[20] Study 022	Rufinamide (45 mg/kg) (n=74)	13 (4.0–35.0) [paediatrics + adults]	46 (62.2)	83.8%	35.9 kg (15.5–138.5)	✗	1-3[†]	290	92
	Placebo (n=64)	10.5 (4.0–37.0) [paediatrics + adults]	40 (62.5)	82.8%	33.5 kg (16.2–86.0)	✗	1-3[†]	205	92.5
Jensen, 1994[22]	Felbamate (45 mg/kg)	✗	✗	✗	✗	✗	✗	✗	✗
	Placebo	✗	✗	✗	✗	✗	✗	✗	✗

Based on Table 7, company response to clarification[3]
*Mean value
**Reported as average seizure frequency. Timepoint unclear.
†Reported as study inclusion criteria. Median value at baseline not reported.
#All baseline values are 28-day median frequencies, except values from Motte et al; 1997 and Ng et al. 2011 which report weekly values
ASMs = anti-seizure medications; CS = company submission; kg = kilogram; mg = milligram; NR = not reported; SD = standard deviation; % = percentage

Table 3.27: ASM-related inclusion/exclusion criteria and baseline concomitant medications usage (%) in each trial (Table 30 of Appendix D of the CS)

Trial Name	Author, Year	ASM-related inclusion	ASM-related exclusion	Treatment Arm	VPA	CLB	LTG	LEV	RFM	VNS	KD	CBZ	PHT	TPM	CZP	Other
Study 1601	Knupp, 2022[2]	-	-	Fenfluramine (0.2 mg/kg)	58	40	34	19	19	-	-	-	-	-	-	-
				Fenfluramine (0.7 mg/kg)	53	52	33	26	21	-	-	-	-	-	-	-
				Placebo	56	44	33	23	21	-	-	-	-	-	-	-
GWPCARE3	Devinsky, 2018[14]	Patients taking between one and four ASMs	-	Cannabidiol (10 mg/kg)	37	51	30	30	26	21	8	-	-	-	-	-
				Cannabidiol (20 mg/kg)	37	47	26	32	34	22	8	-	-	-	-	-
				Placebo	39	49	33	30	26	28	8	-	-	-	-	-
GWPCARE4	Thiele, 2018[15]	Patients taking one to four ASMs	-	Cannabidiol (20 mg/kg)	42	48	38	28	28	-	-	-	-	-	-	-
				Placebo	39	51	36	40	26	-	-	-	-	-	-	-
-	Ritter, 1993[23]	Patients taking no more than two ASMs	-	Felbamate (45 mg/kg)	NR											
				Placebo	NR											
-	Jensen, 1994[22]	-	-	Felbamate (45 mg/kg)	NR											
				Placebo	NR											
-	Motte, 1997[21]	-	Patients receiving more than three ASMs	Lamotrigine (100-400 mg)	67	-	-	-	-	-	-	20	13	-	-	14
				Placebo	56	-	-	-	-	-	-	33	14	-	-	10
OV-1012	Ng, 2011[18]	-	-	Clobazam (0.25 mg/kg)	NR											
				Clobazam (0.50 mg/kg)	NR											

Trial Name	Author, Year	ASM-related inclusion	ASM-related exclusion	Treatment Arm	VPA	CLB	LTG	LEV	RFM	VNS	KD	CBZ	PHT	TPM	CZP	Other
				Clobazam (1.0 mg/kg)	NR											
				Placebo	NR											
Study 022	Glauser, 2008[20]	Patients having a fixed-dose regimen of one to three concomitant ASMs	Patients receiving more than three ASMs	Rufinamide (45 mg/kg)	59.5	-	40.5	-	-	-	-	16.2	-	27	18.9	-
				Placebo	54.7	-	29.7	-	-	-	-	18.8	-	-	26.6	10.9
-	Sachdeo, 1999[24]	Patients being maintained on one or two standard ASMs	-	Topiramate (6 mg/kg)	NR											
				Placebo	NR											
E2080-J081-304	Ohtsuka, 2014[17]	-	-	Rufinamide (45 mg/kg)	89.3	42.9	46.4	-	-	-	-	-	-	-	-	-
				Placebo	93.3	16.7	73.3	-	-	-	-	-	-	-	-	-

Based on Table 8, company response to clarification[3]
ASMs – anti-seizure medications; CS = company submission; CBZ = carbamazepine; CLB = clobazam; CZP = clonazapam; KD = ketogenic diet; kg = kilogram; LEV = levetiracetam; LTG = lamotrigine; mg = milligram; NR = not reported; PHT = phenytoin; RFM = rufinamide; TPM = topiramate; VNS = vagus nerve stimulation; VPA = valproate

Table 3.28: Median number of previous ASMs and concomitant therapies

Author, Year (Study Name)	Intervention (N)	Number of previous AED (median)	Concurrent AEDs (median)	Other concomitant therapies, N (%)
Knupp, 2022[2] Study 1601	Fenfluramine (0.2 mg/kg) (n=87)	7	3	VGS: 23 (26) Keto diet: 5 (6)
	Fenfluramine (0.7 mg/kg) (n 89)	8	3	VGS: 27 (31) Keto diet: 5 (6)
	Placebo (n=87)	7	3	VGS: 32 (37) Keto diet: 1 (1)
Devinsky, 2018[14] GWPCARE3	Cannabidiol (10 mg/kg) (n=73)	6	3	VGS: 17 (22) Keto diet: 6 (8)
	Cannabidiol (20 mg/kg) (n=77)	6	3	VGS: 15 (21) Keto diet: 6 (8)
	Placebo (n=76)	6	3	VGS: 21 (28) Ket diet: 6 (8)
Thiele, 2018[15] GWPCARE4	Cannabidiol (20 mg/kg) (n=86)	6	3	VGS: 26 (30) Keto diet: 4 (5)
	Placebo (n=85)	6	3	VGS: 25 (29) Keto diet: 10 (12)
Ohtsuka, 2014[17] E2080-J081-304	Rufinamide (1000–3200 mg) (n=28)	NR	NR	NR
	Placebo (n=30)	NR	NR	NR
Ng, 2011[18] OV-1012	Clobazam (0.25 mg/kg) (n 58)	NR	NR	NR
	Clobazam (0.50 mg/kg) (n=62)	NR	NR	NR
	Clobazam (1.0 mg/kg) (n=59)	NR	NR	NR
	Placebo (n=59)	NR	NR	NR
Glauser, 2008[20]	Rufinamide (45 mg/kg) (n 74)	NR	1-3*	NR
	Placebo (n 64)	NR	1-3*	NR
Sachdeo, 1999[24]	Topiramate (6 mg/kg) (n=48)	NR	NR	NR
	Placebo (n=50)	NR	NR	NR
Motte, 1997[21]	Lamotrigine (100–400 mg) (n=79)	NR	≤3†	NR
	Placebo (n=90)	NR	≤3†	NR
Jensen, 1994[22]	Felbamate (45 mg/kg)	NR	NR	NR
	Placebo	NR	NR	NR

Author, Year (Study Name)	Intervention (N)	Number of previous AED (median)	Concurrent AEDs (median)	Other concomitant therapies, N (%)
Ritter, 1993[23]	Felbamate (45 mg/kg) (n=37)	8	≥2*	NR
	Placebo (n=36)	8	≥2*	NR
Based on Table 9, company response to clarification[3] *Reported as study inclusion criteria. Median value not reported. † ASMs = anti-seizure medication; kg = kilogram; mg = milligram; NR = not reported; VGS = valgus nerve stimulation				

3.4 Critique of the indirect comparison and/or multiple treatment comparison

As mentioned in the previous section, the NMA only included three RCTs, and therefore only covered fenfluramine and cannabidiol.

EAG comment:

- To reiterate the points made in the last section, the CS[1] does not justify the exclusion of 6/9 of the eligible RCTs from the NMA. The drastic narrowing of the NMA has the potential to distort the clinical efficacy findings, and therefore also invalidate any health economic conclusions. For example, it is possible that one of the excluded papers contains data from a comparator that may be more cost-effective than fenfluramine.

3.4.1 Results of the NMA of fenfluramine versus cannabidiol

In the UK, cannabidiol's approved indication is for treating LGS patients in conjunction with clobazam (cannabidiol + clobazam). However, the base-case clinical trial ITT patient population included a broader treatment scope with patients not systematically receiving clobazam with cannabidiol. Providing that subgroup analyses were reported for the cannabidiol + clobazam patients as part of the EMA dataset, this specific patient population was preferred to derive comparative data. An additional constraint was that these EMA data did not include safety data nor the ≥25% reduction in DSF, which is needed for the economic analysis. To address this gap, a second NMA analysis was performed on cannabidiol + clobazam data, based on additional key comparative cannabidiol + clobazam data published by the German HTA body (Federal Joint Committee - *Gemeinsamer Bundesausschuss* (GBA)). Unlike the EMA ITT dataset, these GBA documents contain some more cannabidiol + clobazam subgroup data on ≥25 / 50 / 75% reduction of convulsive seizures. Since definition of drop seizure vary, convulsive seizures were considered similar to drop seizures in this data set. Finally, since neither the median reduction in frequency of GTC seizures nor the discontinuation due to AEs were available using GBA cannabidiol + clobazam data, the ITT dataset was used by default for these two outcomes. A summary of the clinical outcomes available as well as the selected trial network for the analysis are summarised in Tables 3.29 and 3.30, respectively.

Table 3.29: Summary of the efficacy and safety outcomes available

NMA outcome	FFA-PBO-CBD (ITT)	CBD + CLB (EMA)	CBD + CLB (GBA)
Median percent reduction in frequency of GTC seizures	Yes	No	No
≥25% reduction in DSF	Yes	No	Yes

NMA outcome	FFA-PBO-CBD (ITT)	CBD + CLB (EMA)	CBD + CLB (GBA)
≥50% reduction in DSF	Yes	Yes	Yes
≥75% reduction in DSF	Yes	Yes	Yes
Discontinuation due to AEs	Yes	No	No

Based on Table 19, CS[1]
Note: shaded cells denote outcomes selected for base-case NMA analysis.
CBD + CLB = cannabidiol + clobazam; CS = company submission; DSF = drop seizure frequency; EMA = European Medicine Agency; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); GTC = generalised tonic-clonic; ITT = intention-to-treat; NMA = network meta-analysis

Table 3.30: NMA selected outcomes with their corresponding trial network

NMA outcome	Corresponding trial network
Median percent reduction in frequency of GTC seizures	ITT data: FFA-PBO-CBD
≥25% reduction in DSF	GBA data: (FFA-PBO-CBD + CLB (GBA))
≥50% reduction in DSF	GBA data: (FFA-PBO-CBD + CLB (GBA))
≥75% reduction in DSF	GBA data: (FFA-PBO-CBD + CLB (GBA))
Discontinuation due to AEs	ITT data: FFA-PBO-CBD

Based on Table 20, CS[1]
AEs = adverse events; CS = company submission; CBD + CLB = cannabidiol + clobazam; DSF = drop seizure frequency; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); GTC = generalised tonic-clonic; ITT = intention-to-treat; NMA = network meta-analysis

EAG comment:

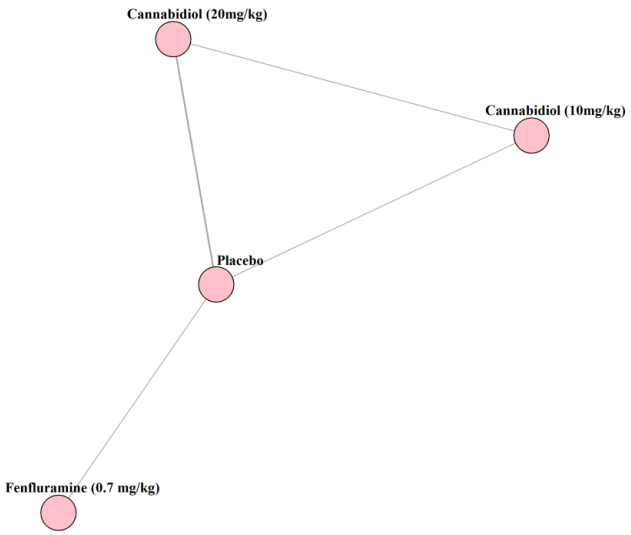
- Of the three studies included in the NMA, two involved cannabidiol given alongside concomitant medications, but neither of these studies wholly utilised the NICE scope and decision problem intervention of cannabidiol combined with clobazam. Instead, both studies used a variety of concomitant drugs, and only a sub-group of each study included clobazam amongst the other concomitant drugs. The drawbacks of using sub-groups in the NMA are correctly highlighted by the company, but it appears unlikely that this will cause significant systematic bias, as it is difficult to see how selection bias could occur through the same restricting factor (clobazam use) being applied to two randomly assigned groups in a double-blinded study. A more important issue is that the NMA has utilised these sub-groups as the source of cannabidiol-clobazam data for only the response outcome (25%, 50% and 75% reduction in frequency). The 'median percent reductions in frequency' and 'discontinuation due to adverse events' outcomes do not appear to use such sub-groups and instead report the results for the overall cannabidiol group, which is not a decision problem comparator. This is despite these two outcomes utilising the same two studies. In the request for clarification, the company were asked to explain why it did not use the cannabidiol/clobazam sub-grouped data for the other two outcomes in the NMA. The company were also asked, if appropriate, to provide sub-grouped analyses for these two outcomes. The company replied by stating that, "*The two*

outcomes including median percent reduction of GTC seizures and discontinuation due to AEs were not available from the cannabidiol/clobazam sub-grouped data (CBDwCLB GBA). Please see Question A20 for further details. Therefore, we had to rely on the (FFA-PBO-CBD ITT) network to obtain these two outcomes due to their absence in the cannabidiol/sub-grouped data (CBDwCLB GBA). Unfortunately, as mentioned in the previous answer A22.a, the two outcomes including median percent reduction of GTC seizures and discontinuation due to AEs were not available from the cannabidiol/clobazam sub-grouped data (CBDwCLB EMA) and (CBDwCLB GBA). Therefore, it is not possible to provide sub-grouped analyses for these two outcomes. Please see Table 6 for further details (question A20)."[3] The EAG is happy with this response.

3.4.1.1. Median percent reductions in frequency of GTC seizures (FFA-PBO-CBD)

The network of evidence for median percent reductions in frequency of GTC seizures is shown in Figure 3.11. A total of three studies with four unique treatments and 290 patients were included in the analysis. The relative effect estimates showed that fenfluramine (0.7 mg/kg), cannabidiol (10 mg/kg), and cannabidiol (20 mg/kg) were significantly superior versus placebo (Figure 3.12). Using surface under the cumulative ranking curve (SUCRA), fenfluramine (0.7 mg/kg) was ranked first among the four treatments (Table 3.31).

Figure 3.11: **Network diagram for median percent reductions in frequency of GTC seizures (FFA-PBO-CBD)**



Based on Figure 17, CS[1]

CS = company submission; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GTC = generalised tonic-clonic; kg = kilogram; mg = milligram

Figure 3.12: **Forest plot for median percent reductions in frequency of GTC seizures, fixed effects (FFA-PBO-CBD)**

Based on Figure 18, CS[1]
CrI = credible interval; CS = company submission; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GTC = generalised tonic-clonic; kg = kilogram; MD = mean difference; mg = milligram

Table 3.31: MD, probability of being the best, and SUCRA for median percent reductions in frequency of GTC seizures, fixed effects (FFA-PBO-CBD)

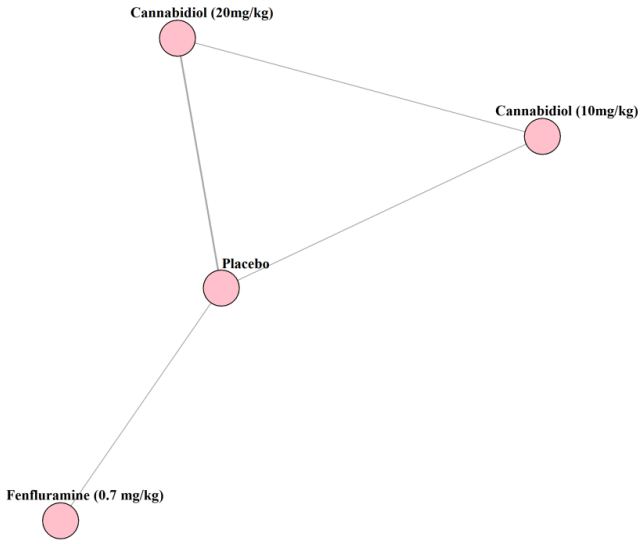
Treatment	MD with 95% CrI – (versus Placebo)	Probability of being the best	SUCRA
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 21, CS[1]
CrI = credible interval; CS = company submission; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GTC = generalised tonic-clonic; kg = kilogram; MD = mean difference; mg = milligram; SUCRA = Surface Under the Cumulative Ranking

3.4.1.2 ≥25%, ≥50% and ≥75% reduction in DSF (FFA-PBO-CBD + CLB (GBA))

The network of evidence for ≥25%, ≥50% and ≥75% reduction in DSF is shown in Figure 3.13. A total of three studies with four unique treatments and 368 patients were included in the analysis. The relative effect estimates showed that fenfluramine (0.7 mg/kg), cannabidiol (10 mg/kg), and cannabidiol (20 mg/kg) were significantly superior versus placebo except for the ≥75% reduction in DSF where solely cannabidiol (20 mg/kg) was significantly superior versus placebo (Figure 3.14, Figure 3.15, Figure 3.16). Using SUCRA, fenfluramine (0.7 mg/kg) was ranked first among the four treatments except for the ≥75% reduction in DSF where it was ranked third (Table 3.32).

Figure 3.13: **Network diagram for ≥25%, ≥50% and ≥75% reduction in DSF (FFA-PBO-CBD + CLB (GBA))**



Based on Figure 19, CS[1]
CS = company submission; CBD + CLB = cannabidiol + clobazam; DSF – drop seizure frequency; FFA-PBO = fenfluramine-placebo; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); kg = kilogram; mg = milligram

Figure 3.14: **Forest plot for ≥25% reduction in DSF, fixed effects (FFA-PBO-CBD + CLB (GBA))**

Based on Figure 20, CS[1]
CrI = credible interval; CS = company submission; CBD + CLB = cannabidiol + clobazam; DSF = drop seizure frequency; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); kg = kilogram; mg = milligram; RR = risk ratio

Figure 3.15: **Forest plot for ≥50% reduction in DSF, fixed effects (FFA-PBO-CBD + CLB (GBA))**

Based on Figure 21, CS[1]
CrI = credible interval; CS = company submission; CBD + CLB = cannabidiol + clobazam; DSF = drop seizure frequency; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); kg = kilogram; mg = milligram; RR = risk ratio

Figure 3.16: **Forest plot for ≥75% reduction in DSF, fixed effects (FFA-PBO-CBD + CLB (GBA))**

Based on Figure 22, CS[1]
CrI = credible interval; CS = company submission; CBD + CLB = cannabidiol + clobazam; DSF = drop seizure frequency; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); kg = kilogram; mg = milligram; RR = risk ratio

Table 3.32: RRs, probability of being the best, and SUCRA for ≥25%, 50% and 75% reduction in DSF, fixed effects FFA-PBO-CBD + CLB (GBA))

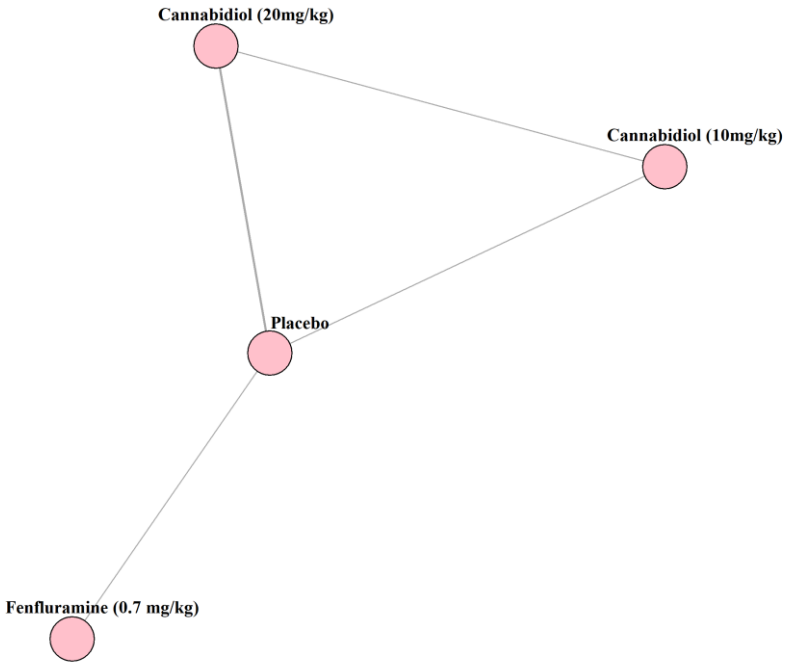
Treatment	RR with 95% CrI – (versus Placebo)	Probability of being the best	SUCRA
FFA-PBO-CBD + CLB (GBA)			
≥ 25% reduction in DSF			
Fenfluramine (0.7 mg/kg)	[redacted]	[redacted]	[redacted]
CBD + CLB (10 mg/kg)	[redacted]	[redacted]	[redacted]
CBD + CLB (20 mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
≥ 50% reduction in DSF			
Fenfluramine (0.7 mg/kg)	[redacted]	[redacted]	[redacted]
CBD + CLB (10 mg/kg)	[redacted]	[redacted]	[redacted]
CBD + CLB (20 mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
≥ 75% reduction in DSF			
Fenfluramine (0.7 mg/kg)	[redacted]	[redacted]	[redacted]
CBD + CLB (10 mg/kg)	[redacted]	[redacted]	[redacted]
CBD + CLB (20 mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

Based on Table 22, CS[1]
CrI = credible interval; CS = company submission; CBD + CLB = cannabidiol + clobazam; DSF = drop seizure frequency; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); kg = kilogram; mg = milligram; RR = risk ratio; SUCRA = surface under the cumulative ranking

3.4.1.3 Discontinuation due to AEs (FFA-PBO-CBD)

The network of evidence for discontinuation due to AEs is shown in Figure 3.17. A total of three studies with four unique treatments and 570 patients were included in the analysis. The relative effect estimates showed that cannabidiol (20 mg/kg) had significantly higher probability of discontinuation due to AEs versus placebo (Figure 3.18). Using SUCRA, cannabidiol (20 mg/kg) was ranked last among the four treatments (Table 3.33).

Figure 3.17: **Network diagram for discontinuation due to AEs (FFA-PBO-CBD)**



Based on Figure 23, CS[1]
AEs = adverse events; CS = company submission; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; kg = kilogram; mg = milligram

Figure 3.18: **Forest plot for discontinuation due to AEs, fixed effects (FFA-PBO-CBD)**

Based on Figure 24, CS[1]
AEs = adverse events; CrI = credible interval; CS = company submission; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; kg = kilogram; mg = milligram; RR = risk ratio

Table 3.33: RRs, probability of being the best, and SUCRA for discontinuation due to AEs, fixed effects (FFA-PBO-CBD)

Treatment	RR with 95% CrI – (versus Placebo)	Probability of being the best	SUCRA
Fenfluramine (0.7 mg/kg)	[redacted]	[redacted]	[redacted]
Cannabidiol (10 mg/kg)	[redacted]	[redacted]	[redacted]
Cannabidiol (20 mg/kg)	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

Based on Table 23, CS[1]
AEs = adverse events; CrI = credible interval; CS = company submission; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; kg = kilogram; mg = milligram; RR = risk ratios; SUCRA = surface under the cumulative ranking

3.4.1.4 Results summary

As cannabidiol is the main comparator to fenfluramine, a summary of the ITT scenario results is shown in Table 3.34. The effect measures of the fixed effects model are presented for the key outcomes used in the economic analysis. In the base-case analysis, the assessed efficacy outcomes favoured fenfluramine (0.7 mg/kg) significantly compared to placebo.

Table 3.34: Summary of ITT scenario results

Outcome	Effect measure	Preferred direction	Fenfluramine (0.7 mg/kg)	Cannabidiol (10 mg/kg)	Cannabidiol (20 mg/kg)
			versus Placebo		
Median percent reductions in frequency of GTC seizure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 24, CS[1]
AE = adverse event; CS = company submission; GTC = generalised tonic-clonic; ITT = intention-to- treat; MD = mean difference; kg = kilogram; mg = milligram; RR = risk ratio; ↘ = the lower the better

In the GBA data analysis, the assessed efficacy outcomes favoured fenfluramine (0.7 mg/kg) significantly compared to placebo, with the exception of "≥ 75% reduction in DSF" in which the result numerically favoured cannabidiol 20 mg/kg with clobazam (Table 3.35).

Table 3.35: Summary of results for (FFA-PBO-CBD + CLB (GBA)) network

Outcome	Effect measure	Preferred direction	Fenfluramine (0.7 mg/kg)	CBD + CLB (10 mg/kg)	CBD + CLB (20 mg/kg)
			versus Placebo		
≥25% reduction in DSF	RR	[redacted]	[redacted] (1.134, 2.345)	[redacted] (0.982, 1.840)	[redacted] (1.139, 1.859)
≥50% reduction in DSF	RR	[redacted]	[redacted] (1.443, 6.823)	[redacted] (1.249, 3.950)	[redacted] (1.573, 3.947)
≥75% reduction in DSF	RR	[redacted]	[redacted] (0.685, 11.876)	[redacted] (0.911, 20.503)	[redacted] (2.826, 35.463)

Based on Table 25, CS[1]
CS = company submission; CBD + CLB = cannabidiol + clobazam; DSF = drop seizure frequency; FFA-PBO-CBD = fenfluramine-placebo-cannabidiol; GBA = Federal Joint Committee (Gemeinsamer Bundesausschuss); kg = kilogram; mg = milligram; RR = risk ratio; ↗ = the higher the better

3.4.2 Methodology of the NMA

3.4.2.1 Trial data used in the base-case (selected endpoints)

In the fenfluramine trial, Study 1601,[2] the primary outcomes were captured through the 14-week treatment period (2-week Titration and 12-week Maintenance period). Since trials for many other ASMs have used different lengths of treatment duration, outcomes captured between 10- and 20-week timepoints were considered in this NMA. Selected outcomes of interest from the NMA are listed in Table 3.36 below.

Table 3.36: Selected outcomes of interest from the NMA

NMA outcome
Median percent reduction in frequency of GTC seizures
≥25% reduction in DSF

NMA outcome
≥50% reduction in DSF
≥75% reduction in DSF
Discontinuation due to AEs
Based on Table 17, CS[1] AEs = adverse events; CS = company submission; DSF = drop seizure frequency; GTC = generalised tonic-clonic; NMA = network meta-analysis

3.4.2.2 Statistical methods

The NMAs were conducted using the Bayesian framework on each of the continuous or binary outcomes of interest. The NMA produces estimates of the relative effects between any pair of treatments in the network, and also allows estimation of the ranking and hierarchy of interventions. The ITT population of the selected trials was used unless a specific outcome was only reported in a non-ITT population.

3.4.2.2.1 Continuous outcomes

Continuous outcomes were analysed using contrasted outcome measures with the associated CIs, e.g., estimated median differences from placebo were calculated using the HL estimate. Identity link was used to estimate the mean difference (MD) between treatments.

For trials with more than two arms, the standard error (SE) of the placebo arm was required as this determined the covariance of the differences. If interquartile range (IQR) was reported instead of SE, SD was first estimated using the IQR using the formula provided in the Cochrane Handbook:

$$SD \approx \frac{q3 - q1}{1.35}$$

Where q3 is the 3rd quartile and q1 is the 1st quartile from the IQR[28]. The SE was calculated using the SD and the sample size. If neither SE nor SE derived from IQR were available, the average SD of the placebo arms from other trials was used to impute the SE.

3.4.2.2.2 Binary outcomes

Binary outcomes were analysed using arm-level data consisting of the total number of patients and number of patients with events. If the number of patients with events was zero for one or more arms in a trial, no data adjustment or imputation was considered to correct the zero values, and the NMA with that trial included was considered infeasible. Log-binomial model was used to estimate the risk ratio (RR) between treatments.

The RR represents the probability of having an event in one treatment group versus the probability of having an event in the comparator group. A RR greater than one indicates a higher probability of having events in the treatment group compared to the comparator group, while an RR of less than one indicates a lower probability in the treatment group. The RR was used over odds ratio (OR) as it provides statistics that are easier to interpret and can be directly implemented in health economic models.

3.4.2.2.3 Fixed effects and random effects models

For each outcome and each scenario analysed, both fixed effects and random effects models were performed (Table 3.37). Placebo was used as the reference treatment in the analysis. The fixed effects models were presented as a base-case to accommodate the small number of studies and simple networks.

The random effects models were reported as supplementary results in the appendix Section D1.3. In most analyses conducted in this study, fixed effects models had better model fit (lower or similar deviance information criterion (DIC)) than random effect models. Additionally, fixed effects models had estimates that were closer to the trial results, compared with random effects models, which may have inflated uncertainty.

Table 3.37: NMA models for continuous and binary outcomes

Outcome type	Likelihood	Link	Model	Effect measure
Continuous	Normal	Identity	Fixed effects	Mean difference
			Random effects	Mean difference
Binary	Binomial	log	Fixed effects	Risk ratio
			Random effects	Risk ratio

Based on Table 18, CS[1]
CS = company submission

All analyses were performed using R version 4.2.2 within the R Studio environment. The "gemtc" package (version 1.0-1) was used to conduct the NMA using Bayesian methods, with 50,000 burn-in iterations, 100,000 actual iterations, and a thinning factor of 10. Model convergence was assessed using trace plots and Gelman-Rubin-Brooks plots of the potential scale reduction factor with a minimum cut-off below 1.05 by the final iteration.

3.4.2.2.4 Covariate adjustment

In the analysis of RCTs, adjustments for baseline covariates can lead to a significant rise in power when the covariates are highly predictive. Hernández et al. found that increases in power of greater than 20% are possible and this has been demonstrated with actual datasets in simulation studies and confirmed through an RCT in Turner et al. Other benefits of adjustment include protection against coincidental imbalances in important baseline covariates and [redacted]

There are several techniques available to adjust baseline characteristics in a trial, however, not all of them are possible. The most relevant technique to use in this analysis is meta-regression. However, meta-regression requires a sufficiently large number of trials for each regimen assessed, which, in the case of this analysis, was not possible due to the limited number of studies available for each regimen. Therefore, no covariate adjustment was used in this analysis.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None undertaken.

3.6 Conclusions of the clinical effectiveness section

The RCT evidence showed that fenfluramine at 0.7 mg/kg/day (+ SoC) was effective compared to placebo (+ SoC) for reducing the absolute frequency of drop seizures. Similarly, a greater proportion of patients taking this dose of fenfluramine (+ SoC) achieved ≥25% and ≥50% reduction in DSF compared to patients on placebo (+ SoC). Although the continuous outcome analysis showed that fenfluramine at 0.2 mg/kg/day (+ SoC) was not significantly different to placebo (+ SoC) for reducing the frequency of drop seizures, a greater proportion of patients taking 0.2 mg/kg/day of fenfluramine (+

SoC) achieved ≥25% and ≥50% reduction in DSF compared to patients on placebo (+ SoC). In addition, both doses of fenfluramine (+ SoC) reduced the frequency of GTC seizures compared to placebo (+ SoC), and both also improved the CGI-I to a greater extent than placebo (+ SoC).

In contrast, neither dose of fenfluramine (+ SoC) differed from placebo (+ SoC) in terms of achieving seizure free status or in affecting status epilepticus. Both doses (+ SoC) also failed to have an impact on QOLCE or HADS scores compared to placebo (+ SoC). Although there were only small differences in all AEs between fenfluramine (+ SoC) and placebo (+ SoC), 0.7 mg/kg/day of fenfluramine (+ SoC) led to over double the frequency of serious TRAEs as placebo (+ SoC). Therefore, although at face value the RCT evidence was suggestive of clinical benefits over placebo (+ SoC), particularly for the 0.7 mg/kg/day dose of fenfluramine (+ SoC), these were not observed for all outcomes, and the greater risk of AEs compared to the lower dose or placebo needs to be considered.

In addition, there were some unresolved questions about the quality of the trial evidence. One issue related to the eDiaries used for collection of data, which were not unequivocally demonstrated by the company to have measurement validity. Another problem related to the failure to collect data on the variety of seizure types that patients would have experienced. As explained in the report, efficacy in relation to one type of seizure does not imply similar efficacy in relation to others, even if the other seizure types are deemed to be of lesser severity. There were also questions about the internal validity of the trial data, largely because of ambiguity about the balanced use of non-pharmacological treatments across arms. Finally, external validity of the trial data to the UK target population was uncertain because the company did not objectively demonstrate that the UK target population had similar characteristics to the trial population, and no analyses had been carried out to rule out potential outcome modifiers (such as age, gender, ethnicity or particular combinations of concomitant drugs).

Even if these caveats are ignored or downplayed, and it is accepted that some efficacy of fenfluramine over placebo remains, this only covers half of the comparator aspect of the decision problem. Although it is initially essential to demonstrate a treatment effect that can be differentiated from the placebo effect, it is just as important to subsequently demonstrate that the intervention is as effective, or more effective, than alternative treatment approaches. The other half of the comparator aspect of the decision problem described the active comparator as cannabidiol + clobazam (+SoC), but this missed out other, equally valid comparators. The NG217 recommends three alternative 3rd line add-on therapies: clobazam, rufinamide and topiramate. All these could also have been considered as specific comparators alongside cannabidiol + clobazam (i.e., clobazam + SoC, rufinamide + SoC and topiramate + SoC). Head-to-head studies comparing these do not as yet exist, but indirect comparisons might be estimated in an NMA.

The company correctly developed an NMA and found nine relevant RCTs covering most of the relevant active comparators. Unfortunately, the company did not present this full NMA in the CS,[1] instead presenting a heavily annotated NMA that only included three RCTs, with cannabidiol + clobazam (+SoC) as the only active comparator. This reduced NMA demonstrated greater efficacy for fenfluramine (+ SoC) over cannabidiol + clobazam (+SoC) but it is very important to note that the full NMA containing all nine RCTs, which was made available to the EAG after the clarification process, did not demonstrate that fenfluramine was superior to all other 3rd line comparators. The results from this extended NMA (including all nine RCTs) show that [redacted], rufinamide and lamotrigine were [redacted] to fenfluramine. Similarly, [redacted], clobazam (1 mg/kg), rufinamide, cannabidiol (20 mg/kg) and topiramate [redacted] fenfluramine to be [redacted], lamotrigine, felbamate, clobazam (1 mg/kg), clobazam (0.5 mg/kg), clobazam (0.25 mg/kg) and cannabidiol (10 mg/kg) were [redacted]. A similar picture favouring the comparators was seen for discontinuation due to AEs and SAEs. [redacted]

[redacted]. The company's arguments why these fuller NMA results were not considered in the CS[1] focus on *potential* intransivity, but the EAG note that there is no evidence provided by the company that the excluded studies were actually different in terms of any of the factors described, only that data on these factors were absent.

The CS[1] and response to clarification[3] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence for the efficacy and safety of fenfluramine hydrochloride for treating LGS in people aged 2 and over. Searches conducted in October 2022 and update searches carried out in June 2023, were transparent and reproducible, and appropriate strategies were used. A broad range of databases, trials registers and grey literature sources (including conference proceedings and websites of HTA organisations) were searched. Overall, the EAG has no major concerns about the literature searches conducted, however separate AEs searches may have retrieved additional studies.

In summary, the EAG is unconvinced by the company's conclusions regarding the clinical efficacy of fenfluramine.

4. COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

Three SLRs were performed with the objectives to identify and select relevant: 1) cost-effectiveness analysis (CEA) studies (CS Appendix G[6]); 2) HRQoL studies (CS Appendix H[6]); and 3) costs and healthcare resource use studies (CS Appendix I[6]).

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.[1]

4.1.1.1 Searches for CEA review

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.[1, 6] The CADTH evidence-based checklist for the PRESS was used to inform this critique.[7, 8] The EAG has presented only the major limitations of each search strategy in the report.

The company provided separate searches for economic evaluations, costs and resource utilisation outcomes, and HRQoL data on LGS. These Sections were also informed by searches of additional sources previously reported in Appendix D along with other economic specific resources. Searches were performed in October 2022 with an update search in June 2023.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for Appendix G: Published cost effectiveness studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	Since inception	05/10/22 07/06/23
MEDLINE (ALL)	Ovid	Since inception	05/10/22 07/06/23
CENTRAL	EBM Reviews (Ovid)	Since inception	05/10/22 07/06/23
HTA database	EBM Reviews (Ovid)	Since inception	05/10/22
CDSR	EBM Reviews (Ovid)	Since inception	05/10/22 07/06/23
NHS EED	EBM Reviews (Ovid)	Since inception	05/10/22
Econlit	(Ovid)	Since inception	05/10/22 07/06/23

CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; EBM = Evidence-based medicine; EED = Economic Evaluation Database; HTA = Health Technology Assessment; NHS = National Health Service

EAG comment:

- Searches were undertaken in October 2022 and updated in June 2023 to identify relevant economic, HRQoL and cost data from the published literature on LGS. The CS, Appendix D and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[1, 3, 6]
- As previously reported the databases 'EBM Reviews - NHS Economic Evaluation Database' and 'EBM Reviews - Health Technology Assessment' were excluded from the update searches as they had been discontinued in 2015. This is also the case for searches reported in Appendices H & I.
- Searches were well structured, transparent and reproducible, and a good range of subject indexing terms (MeSH/EMTREE) and free text was used.
- A broad range of databases and grey literature sources including trials registers, conference proceedings, HTA websites, and specialist economics resources were searched. The reference lists of eligible studies were also screened to identify any further relevant publications not identified by the searches.
- At clarification the company confirmed that "*These grey literature searches were conducted as a single set of searches, and informed all sections of the CS (clinical and economic) and apply to Appendices D, G, H and I.*"[3] These additional searches are reported in Section 3.1.1, Table 3.1. The Table above and those in Appendices H & I and all related comments will focus only on those searches unique to identifying information on published cost effectiveness studies, HRQoL and resource use.
- The EAG noted a disparity in the number of hits reported for the CDSR in Appendix G of the CS.[6] Table 55 (n=3) which did not match the figure provided in Table 58 (n=4) PRISMA flow

diagram. The company confirmed that the number reported in the PRISMA flow chart was correct and provided an amended search strategy in their response to clarification.

- The EAG queried whether Tables 56, 66 and 81, which reported a search of the 'Database of Abstracts of reviews of effects' should have read 'National Health Service (NHS) Economic Evaluations Database (EED)' as in the PRISMA flow diagrams (Table 58, Figure 19 and Figure 21). The company confirmed that these should have been headed 'Search strategy in EBM Reviews - NHS Economic Evaluation Database'.[3]

Table 4.2: Data sources searched for Appendix H: HRQoL-life studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	Since inception	05/10/22 07/06/23
MEDLINE (ALL)	Ovid	Since inception	05/10/22 07/06/23
CENTRAL	EBM Reviews (Ovid)	Since inception	05/10/22 07/06/23
HTA database	EBM Reviews (Ovid)	Since inception	05/10/22
CDSR	EBM Reviews (Ovid)	Since inception	05/10/22 07/06/23
NHS EED	EBM Reviews (Ovid)	Since inception	05/10/22
Econlit	(Ovid)	Since inception	05/10/22 07/06/23

CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; EBM = Evidence-based medicine; EED = Economic Evaluation Database; HTA = Health Technology Assessment; NHS = National Health Service

EAG comment:

- Searches were undertaken in October 2022 and updated in June to identify HRQoL and utility/disutility values in LGS. The CS, Appendix H and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[1, 3, 6]
- A broad range of databases and grey literature sources including trials registers, conference proceedings, HTA websites, and specialist economics resources were searched.
- Searches were well structured, transparent and reproducible, and a good range of subject indexing terms (MeSH/EMTREE) and free text was used.
- Appendix H utilised the same searches of prefiltered resources searched via EBM reviews as reported in Appendix G but provided unique searches of both MEDLINE and Embase using appropriate facets for identifying HRQoL data.

Table 4.3: Data sources searched for Appendix I: Cost and healthcare resource identification, measurement and valuation (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	Since inception	05/10/22 07/06/23
MEDLINE (ALL)	Ovid	Since inception	05/10/22 07/06/23
CENTRAL	EBM Reviews (Ovid)	Since inception	05/10/22 07/06/23
HTA database	EBM Reviews (Ovid)	Since inception	05/10/22
CDSR	EBM Reviews (Ovid)	Since inception	05/10/22 07/06/23
NHS EED	EBM Reviews (Ovid)	Since inception	05/10/22
Econlit	(Ovid)	Since inception	05/10/22 07/06/23

CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; EBM = Evidence-based medicine; EED = Economic Evaluation Database; HTA = Health Technology Assessment; NHS = National Health Service

- Searches were undertaken in October 2022 and updated in June 2023 to identify costs and resource utilisation outcomes associated with LGS. The CS, Appendix I and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[1, 3, 6]
- A broad range of databases and grey literature sources including trials registers, conference proceedings, HTA websites, and specialist economics resources were searched. An additional search of the following four administrative databases was also reported:
    - Truven Health Analytics MarketScan Research Databases
    - Medicaid multi-state database of six US states
    - Vilua Healthcare research database
    - The UK Clinical Practice Research Datalink GOLD database
- Searches were well structured, transparent and reproducible, and a good range of subject indexing terms (MeSH/EMTREE) and free text was used.
- Appendix I utilised the same searches of prefiltered resources searched via EBM reviews as reported in Appendix G but provided unique searches of both MEDLINE and Embase using appropriate facets for identifying data related to costs and resource utilisation.
- The EAG queried what appeared to be a reporting error in Appendix I. Table 76 lines 17-21 had numbers in the 'original search' column when the EAG would expect these to be blank, as they relate to lines utilised in the update searches. The numbers also appeared to be a repeat of the numbers of the search line. The company confirmed that this was a reporting error and that the lines should have read N/A.[3]

4.1.2 Inclusion/exclusion criteria

Inclusion and exclusion criteria for the review on cost effectiveness studies, HRQoL studies and costs and resource use studies are presented in Table 4.4.

Table 4.4: Eligibility criteria for the SLRs

	Inclusion criteria	Exclusion criteria
Patient population	Children and/or adults with LGS	NR

Interventions/comparators	• Pharmacological interventions including, but not limited to:
	  o Fenfluramine
	  o Cannabidiol
	  o Sodium valproate
	  o Lamotrigine
	  o Rufinamide
	  o Topiramate
	  o Felbamate
	  o Clobazam
	  o Levetiracetam
	• Ketogenic diet
	• Vagus nerve stimulation
	• Current clinical management
	• Placebo
		NR

Outcomes(s) 1 (Published economic evaluations)	• Life years gained • QALYs gained • ICER/ICUR	NR

Outcomes(s) 2 (HRQoL studies)	• Utility values
	• QoL measures using an established questionnaire that can be mapped to utility values such as:
	  o EQ-5D
	  o SF-12/SF-36
	  o QOLIE-31/QOLIE-89
	  o QOLCE
		NR

Outcomes(s) 3 (Cost/resource use studies)	• 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:
	  o Hospitalisations
	  o Doctor visits
	  o Treatments
	  o Laboratory tests
		NR

Study design 1 (CEA studies)	• Cost-benefit analyses • Cost-effectiveness analyses • Cost-utility analyses • Cost-minimisation • Cost-consequence • Budget impact analyses • Other economic evaluations • SLRs of economic evaluations, costing studies, burden-of-illness studies	NR

	Inclusion criteria	Exclusion criteria
Study design 2 (HRQoL studies)	• Cost-benefit analyses • Cost-effectiveness analyses • Cost-utility analyses • Cost-minimisation • Cost-consequence • Budget impact analyses • Other economic evaluations • SLRs of economic evaluations, costing studies, burden-of-illness studies	NR
Study design 3 (Cost/resource use studies)	• Cost-benefit analyses • Cost-effectiveness analyses • Cost-utility analyses • Cost-minimisation • Cost-consequence • Budget impact analyses • Other economic evaluations • SLRs of economic evaluations, costing studies, burden-of-illness studies	NR
Based on Appendix G. H. and I of the CS[1] AEs = adverse events; CEAs = cost-effectiveness analyses; CS = company submission; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LGS = Lennox-Gastaut syndrome; QALY = quality adjusted life year; QoL = quality of life; QOLCE – Quality-of-Life in Childhood Epilepsy; SLRs = systematic literature reviews		

EAG comment: The EAG agrees that the inclusion criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The exclusion criteria and reasons for excluded identified studies was unclear to the EAG.

4.1.3 Conclusions of the cost effectiveness review

The CS[1] provides an overview of the included cost effectiveness, HRQoL and resource use and costs studies, but no specific conclusion was formulated.

EAG comment: The CS[1] and response to clarification[3] provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data from the published literature on LGS. Searches were conducted in October 2022 and update searches carried out in June 2023. Searches were transparent and reproducible, and appropriate strategies were used. A broad range of databases and grey literature sources were searched. Overall, the EAG has no major concerns about the literature searches conducted.

4.2 Summary and critique of company's submitted economic evaluation by the EAG.

4.2.1 NICE reference case checklist

Table 4.5: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with reference case
Perspective on costs	NHS and PSS	Consistent with reference case

Element of HTA	Reference case	EAG comment on CS
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Consistent with reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	EQ-5D health states were not directly provided by patients living with the condition and utility values may therefore differ from the health status of actual LGS patients
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Consistent with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with reference case

CS = company submission; EAG = Evidence Assessment Group; EQ-5D = EuroQol-5D; HTA = Health Technology Assessment; HRQoL = health-related quality of life; LGS = Lennox- Gastaut syndrome; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

4.2.2 Model structure

The company developed a Markov model in Microsoft Excel®, consisting of six mutually exclusive health states. In the CS[1], it was stated that the model was a semi-Markov model; nonetheless, this was corrected in the clarification response, and the company updated the term to Markov model, as there was no memory built in[3]. Four health states were based on percentage reduction in DSF from baseline: state 0, representing patients with less than 25% decrease in DSF; state 1, for patients in between 25% to >50% decrease in DSF; state 2, for patients experiencing 50% to >75% decrease in DSF; and state 3 for patients with more than 75% decrease in DSF. The model included two additional health states, one for discontinued patients and an absorbing death state (Figure 4.1). Discontinuation could occur at any model cycle throughout the time horizon either due to AE, lack of efficacy, or stopping rule.

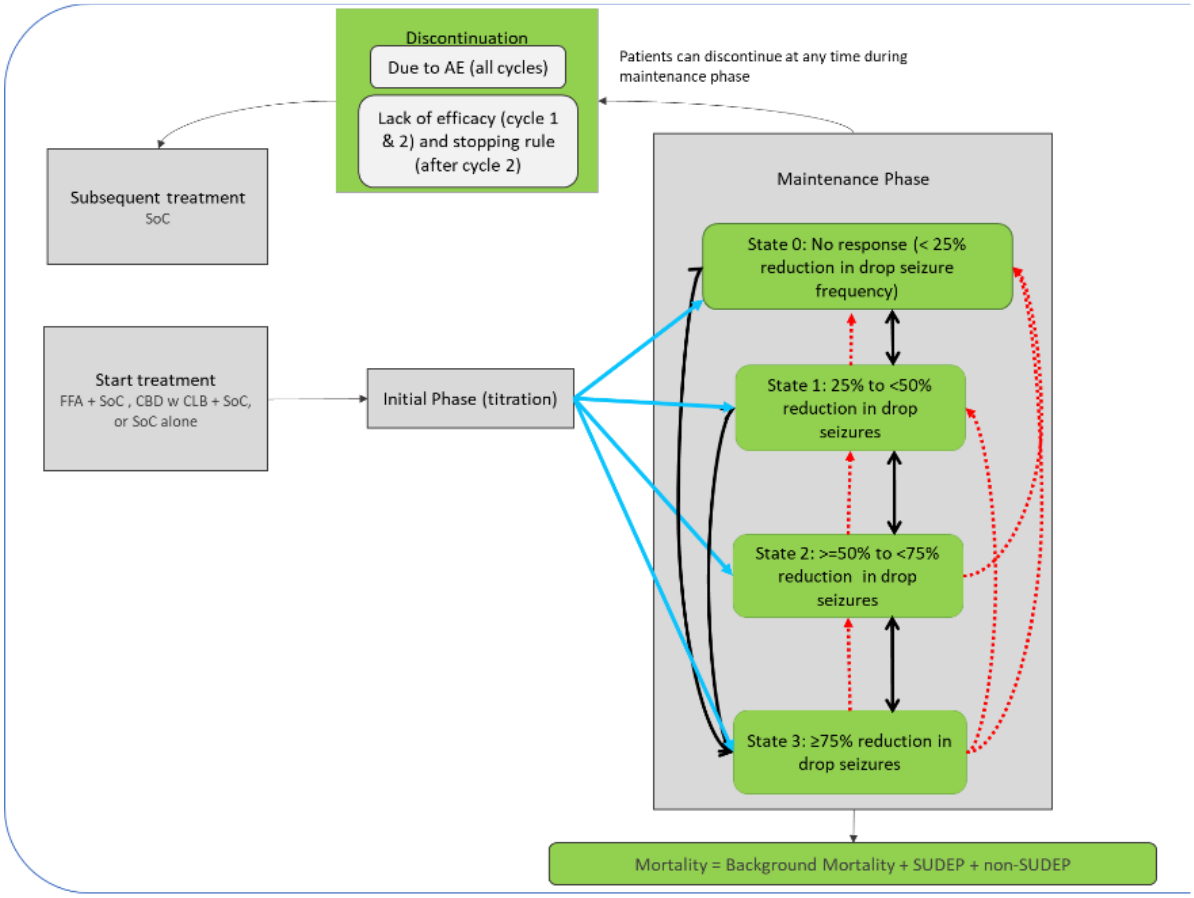
In the model, there were three main phases: Titration and Maintenance (Titration and Maintenance), treatment, and subsequent follow-up (Figure 4.1). The Titration and Maintenance phase was modelled for a duration of two weeks (T) and 3 months (M). State occupancy for all treatment arms was the same with 32% of patients in health state 0; 22% of patients in health state 1; 38% in health state 2; and 8% in health state 3, based on quartiles of drop-seizure distribution at baseline in Study 1601[2]. The model assumed that patients would remain in these health states during the Titration and Maintenance phase unless they would either discontinue due to AE or die. The treatment phase cycles lasted 3 months each. After cycle 1, patients moved to the corresponding health state based on the efficacy data from the NMA and treatment effect was modelled to be applied up to cycle 9 (i.e., 27 months). Data informing transition probabilities and state occupancies varied slightly between cycles (Section 4.2.6). After cycle 9, patients stayed in their corresponding state with only the potential competing occurrences of discontinuation or death.

The average number of drop seizures per 28 days in each health state was necessary to inform resource use, utility values and mortality. For health states 0 and 3, the mean drop seizures per 28 days were the observed median number of drop-seizures in Study 1601[2]. For states 1 and 2, a midpoint approach based on Neuberger et al.[29] was used. Here, the midpoint value for reduction in DSF was determined (i.e., for state 1, the midpoint between 25% and 50% reduction is 37.5%). Subsequently, the baseline number of drop seizures was multiplied by 1-the midpoint (i.e., for state 1, 70.5 is multiplied by (1-0.375)) (Table 4.6.).

Table 4.6: Observed and estimated absolute number of drop seizures per 28 days

	Median number of drop seizures observed in Study 1601	Estimated mid-point (%)	Median number of drop seizures used in the model
Baseline	70.5	0%	70.5
State 0	101.40	-43.8%	101.40
State 1	34.86	37.5%	44.06
State 2	38.16	62.5%	26.44
State 3	11.20	85.0%	11.20

Figure 4.1: **Model structure***



Based on Figure 26 of the CS[1]

*Legend: Green boxes: model states. Blue arrows: movements between states based on transition probabilities from baseline to cycle 1. Black arrows: movements between states based on transition probabilities based from cycle 2 to 9. Red arrows: Movements due to treatment waning.

AEs = adverse events; CBD + CLB = cannabidiol + clobazam; CS = company submission; FFA = fenfluramine; SoC = standard of care; SUDEP = sudden unexpected death in epilepsy

EAG comment: The main concerns of the EAG relate to: a) the model structure based on relative reduction in DSF; b) the lack of modelling non-drop seizures in the economic model; and c) the suitability of using a cohort-level model to reflect patient heterogeneity in LGS.

a) The Markov model developed by the company was structured based on the percentage reduction in DSF. In the economic model, health states represented different percentages of relative reduction in DSF (i.e., <25%, 25-<50%, 50%-<75%, and ≥75%), next to a discontinuation and death health state. The EAG is concerned that the use of relative reductions in drop seizures will result in patients 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. For example, patient A suffers from 120 drop seizures per 28 days and patient B suffers from 20 drop seizures per 28 days. If both patients would experience a drop seizure reduction of 30%, this would mean that both patients would be in health state 2 of the economic model despite patient A having 84 drop seizures and patient B having 14 drop seizures, per 28 days. This lacks face validity, as patients with significant differences in disease severity are not expected to have the same HRQoL and resource use. Moreover, this model structure deviated from other published models and NICE TA615[30], in which health states were based on the

absolute number of seizures. The company was asked to justify the use of relative reduction in DSF in clarification question B5, and stated that this approach was deemed more suitable for the current submission given the data available and that a similar approach had been used in three other studies[3]. Nevertheless, the EAG considers the company's model structure based on the percentage reduction in DSF a violation of good practice and prefers a model structure based on absolute seizure frequency in line with NICE TA615. Hence, the company should update their economic model accordingly.

b) Health states in the company's economic model were based on DSF only, while clinical trial data also reported a significant number of non-drop seizures in LGS patients. In clarification response B7, the company justified excluding non-drop seizures by stating that the impact of non-drop seizures on HRQoL and cost and resource use would already be captured by the impact of drop seizures[3]. As discussed in Section 2.4 of this report, the EAG acknowledges the benefit of using the most easily measured and verified outcome available. However, the impact of fenfluramine on non-drop seizures should also be evaluated and modelled separately, as a reduction of drop seizures does not necessarily mean a decrease in the frequency of non-drop seizures. This assumption could lead to an underestimation of HRQoL and costs, especially in health states with lower numbers of drop seizures (i.e., health state 3), as the non-DSF for patients in these health states is not necessarily low too. Given that more patients in the fenfluramine + SoC arm were modelled to be in these health states with low numbers of drop seizures (and for a longer time) relative to the comparators, not modelling non-drop seizures is, contrary to what the company stated in its clarification response, potentially not a conservative approach. Hence, the EAG would like to see an updated economic model and scenario analysis in which the impact of non-drop seizures is reflected in the modelling.

c) A Markov cohort model was developed by the company to represent the natural history of the disease, clinical pathway, and clinical outcomes reported for people with LGS. The EAG, however, is concerned that transition probabilities in the economic model are highly variable across patients due to the heterogeneous clinical presentation of LGS. Therefore, the EAG considers an individual patient model, as was used in a previous appraisal of fenfluramine for patients with Dravet syndrome (DS) (TA808)[31], to be potentially more suitable to reflect patient heterogeneity in LGS. In clarification response B8, the company justified the choice of a Markov cohort model given the limitations of the individual patient model for fenfluramine in DS (e.g., validity issues regarding unavailable individual patient-level data, criticised bootstrapping algorithm, need for meta-regression to analyse changes in DSF and seizure-free days, among others) and mentioned the alignment with other published models and ability to simulate long-term follow-up efficacy outcomes and treatment waning based on the model states[3]. Although the EAG considers an individual patient simulation to be potentially more suitable to represent the heterogeneous clinical presentation of LGS, it understands the additional complexity and need to gather unavailable data for individual patient models.

4.2.3 Population

Consistent with the NICE scope and its anticipated MA, the population considered in the CS[1] (CS Table 1) was people aged 2 and over with LGS whose seizures are inadequately controlled by established clinical management.

Baseline demographic characteristics included in the cost effectiveness model were informed by the phase 3 trial evidence for fenfluramine, Study 1601[2]. The key baseline patient characteristics in the economic model are listed in Table 4.7 below.

Table 4.7: Key baseline patient characteristics used in the economic model

	Mean	Source
Sex (%)	55.5%	Knupp et al. 2022[2]
Mean starting age	13.7	Knupp et al. 2022[2]
Age distribution		
2-<6 years	14.4%	Knupp et al. 2022[2]
6-<12 years	27.4%	
12-<18 years	29.3%	
>18 years	28.9%	
Median weight per age (kg)		
2-<6 years	17.6	Knupp et al. 2022[2]
6-<12 years	30.1	
12-<18 years	48.1	
18-<35 years	62.1	
>35 years	78.0	
Median drop-seizures per 28 days	70.5	UCB 2022 Fenfluramine Study Statistical Analysis[32]
kg = kilogram		

EAG comment: The main concern of the EAG relates to the uncertainty regarding population characteristics reflecting the UK target population. As mentioned in Section 2.5 of this report, although the clinical experts consulted by the company suggested similarity between the trial and the UK target population, the external validity of the patient characteristics could not be confirmed. Therefore, it remains uncertain whether the trial populations were representative of patients in UK clinical practice.

4.2.4 Interventions and comparators

The model cohort received either fenfluramine and SoC, cannabidiol + clobazam and SoC or SoC alone, which included a basket of ASM.

The intervention considered in the CS[1] was fenfluramine + SoC. As per summary of product characteristics (SmPC), fenfluramine was recommended to be administered by a starting dose of 0.1 mg/kg twice daily (0.2 mg/kg/day), increased to 0.4 mg/kg/day in week 2 (and increased as tolerated), and continued with a Maintenance dose of 0.7 mg/kg/day (increased as tolerated to a maximal recommended dose of 26 mg/day). The company's base-case used an average Titration dose of 0.3 mg/kg/day and an average Maintenance dose of 0.413 mg/kg/day for fenfluramine(the initial average Maintenance dose of 0.5 mg/kg/day was reduced by the company in the clarification response addendum). The 0.3 mg/kg/day Titration dose was derived from the SmPC, and the 0.5 mg/kg/day Maintenance dose was derived from the OLE study[27].

The comparator considered was cannabidiol + clobazam + SoC and SoC alone. For cannabidiol, the CS[1] base-case utilised a Titration dose of 5 mg/kg/day during the first 2 weeks. Then, the model used an initial cycle dose of 12 mg/kg/day and Maintenance dose after Titration and Maintenance of 16 mg/kg/day (the initial average Maintenance dose of 14 mg/kg/day was increased by the company in its clarification response addendum), based on real-world data[33] and expert opinion[34]. The model did not include a Titration dose for clobazam. The average dose of clobazam was 0.65 mg/kg/day, with a maximum dose of 60 mg/day.

The SoC consisted of a basket of comparators including clobazam, levetiracetam, valproate, lamotrigine, topiramate, and rufinamide. Table 4.8 includes the distribution of patients taking SoC ASM in each arm. Although felbamate, and non-pharmaceutical therapies were mentioned in the NICE scope (CS, Table 1)[1], these were not included as comparators in the economic model. The company justified the exclusion of felbamate stating that NICE recommended that felbamate is used only in centres providing tertiary epilepsy specialist care and when treatment with sodium valproate, lamotrigine, rufinamide and topiramate are ineffective or not tolerated. Non-pharmaceutical interventions were excluded based on a previous STA (NICE TA615), as the effects of one of the non-pharmaceutical interventions (i.e., vagus nerve stimulation) would be already included in the comparator and the model assumed to receive pharmaceutical treatments only as part of their SoC.

Table 4.8: SoC distribution per arm (CS, Table 60) *In the original CS, topiramate had a 0% distribution; this was corrected by the company in the clarification response B10

	Fenfluramine + SoC	CBD + CLB + SoC	SoC alone
Clobazam	44%	100%	44%
Levetiracetam	23%	23%	23%
Valproate	56%	56%	56%
Lamotrigine	33%	33%	33%
Topiramate*	14%	14%	14%
Rufinamide	21%	21%	21%
CBD + CLB = cannabidiol + clobazam; CS = company submission; SoC = standard of care			

EAG comment: The main concerns of the EAG relate to: a) the modelled fenfluramine Maintenance dose, b) the modelled cannabidiol Maintenance dose, c) not including all relevant comparators and d) the lack of a stopping rule for SoC.

a) In the CS[1] base-case, fenfluramine was modelled with Titration and Maintenance doses of 0.3 and 0.5 mg/kg/day, respectively. The Maintenance dose proposed by the company's original base-case is lower than the Maintenance dose recommended in the SmPC (i.e., 0.7 mg/kg/day) and different from the dosages that patients received in Study 1601[2] (0.2 mg/kg/day and 0.7 mg/kg/day), which was used to inform the indirect treatment comparison. The assumed 0.5 mg/kg/day Maintenance dose was based on data from the OLE study[27] and confirmed during an advisory board meeting with UK clinical experts. However, the company decreased the base-case Maintenance dose of fenfluramine from 0.5 mg/kg/day to 0.413 mg/kg/day in response to the request for clarification. The company based this decrease on "real world data and expert clinical opinion" but did not provide the full additional data and clinical opinion in the clarification addendum. The company suggested that the dose of 0.413 mg/kg/day would be comparable to the average dose of patients with DS who are not on stiripentol (0.44 mg/kg/day)[35]. The EAG agrees that, in clinical practice, doses will be titrated based on tolerability, efficacy and safety; however, the justification for the decrease in dose from 0.5 mg/kg/day to 0.413 mg/kg/day for fenfluramine was insufficient and seemed to contradict to the statement of clinical experts originally provided by the company, in which they stated that "*0.5 mg/kg/day of FFA [fenfluramine] on average is realistic*. Therefore, the EAG preferred using 0.5 mg/kg/day for fenfluramine in its base-case.
b) In the CS[1] base-case, cannabidiol was modelled to have a Titration dose of 12 mg/kg/day and a Maintenance dose of 14 mg/kg/day, respectively. Nonetheless, in response to the clarification response, the company increased the Maintenance dose of cannabidiol from 14 mg/kg/day to

16 mg/kg/day; stating that the cannabidiol dose could be closer to 20 mg/kg/day, as the mean modal dose in the OLE study was 23 mg/kg/day[36]. The company agreed that some clinicians would use a dose between 10 and 12 mg/kg/day, but that, if tolerated, cannabidiol could be up titrated until a response is achieved, as "*adequate reductions in drop seizure frequency are rarely seen at lower doses of cannabidiol, patients are either up titrated or treatment is discontinued*". However, a Maintenance dose of 16 mg/kg/day for cannabidiol contradicts the previous statement by the clinical experts provided by the company: "*The average dose of CBD [cannabidiol] used in practice varies and patients are titrated up to their maximum tolerated dose. An appropriate approach would be to assume a dose of 14mg/kg because clinicians do not see added clinical benefit beyond this point when also balancing tolerability. There are some patients, however, who are dosed towards the maximum licensed dose of 20mg/kg/day and others who are dosed closer to 12mg/kg/day.*"[37]. The company's initial average Maintenance dose of 14 mg/kg/day for cannabidiol was also higher than the average dose of 12 mg/kg/day that was agreed upon in the NICE appraisal for cannabidiol + clobazam for treating seizures associated with LGS (NICE TA615). Notably, the modelled cannabidiol treatment effectiveness in the current submission is informed by the same trials that informed the cannabidiol treatment effectiveness in TA614. The company was asked to provide justification for their assumed cannabidiol Maintenance dose in clarification question B12. The company responded that their assumption was based on an additional clinical expert consultation and acknowledged the variability in dosing assumption among patients but stated that 14 mg/kg/day would "*be considered highly conservative*". According to the cannabidiol SmPC for LGS, the recommended Maintenance dose is 10 mg/kg/day with a maximal recommended dose of 20 mg/kg/day. Considering the substantial uncertainty regarding the appropriate cannabidiol Maintenance dose, and the fact that the evidence to inform the effectiveness of cannabidiol in the economic model was informed by the same trials that were used in TA614, the EAG aligned its base-case with TA614 and modelled an average Maintenance dose of 12 mg/kg/day for cannabidiol.

c) The two comparators considered in the economic model were cannabidiol + clobazam + SoC and SoC alone. As extensively discussed in Section 2.3 of this report, NG127 also mentions clobazam, rufinamide, and topiramate as 3rd line add-on treatment options for this population, and should, therefore, be included in the model. Likewise, non-pharmaceutical therapies such as ketogenic diet, vagus nerve stimulation, and invasive surgery were recommended as additional treatment options for a proportion of patients with LGS in the UK (NG217)[38] and were part of the NICE decision scope. However, these were not included in the economic model despite being asked in clarification question B10, and being part of the studies included in the NMA (Table 9 of the clarification response)[3]. Therefore, the company should provide an updated economic model and scenario analyses, including all the relevant comparators described in the NG127.

d) No discontinuation due to lack of efficacy nor a stopping rule was applied to the SoC arm. In clarification response B11, the company argued that LGS patients will always be under the treatment of ASM combinations (i.e., SoC), and hence a stopping rule would not be possible for SoC. In addition, the company argued that since subsequent treatment would be defined to be equal to SoC, the stopping rule would have technically no effect on the results. However, the EAG considers it likely that when patients have a lack of efficacy in SoC, SoC will be adapted to the new situation of the patients. Hence, the SoC basket would change over time, potentially resulting in different effects and costs. The EAG therefore considers that the economic model should have reflected a stopping rule for treatments in the SoC arm that lack efficacy.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is three months with a lifetime time horizon (86 years) and a half-cycle correction is applied.

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness were the NMA results including Study 1601[2] for fenfluramine + Soc and SoC alone[2], and GWPCARE 3[14] and 4[15] for cannabidiol. Since cannabidiol is only approved in the UK in conjunction with clobazam, data on cannabidiol + clobazam + SoC patients in the GWPCARE 3 and 4 trials was used, which was available via the German HTA body.[39] The NMA results were used for cycle 1 (Titration and Maintenance) only, while for subsequent cycles the fenfluramine open label extension study[32] and GWPCARE 5[36] OLE study for cannabidiol + clobazam + SoC were used. These studies were used to obtain evidence for the reduction of DSF health states, discontinuation rates and AEs for fenfluramine + SoC, cannabidiol + clobazam + SoC and SoC alone.

4.2.6.1 Transition probabilities between reduction in drop seizure frequency health states

Titration and Maintenance cycle 1 based on NMA results

For the first cycle, transition probabilities between reduction in DSF health states for fenfluramine + SoC and cannabidiol + clobazam + SoC were based on a relative risk derived from the NMA results using a weighted average of the 10 mg/kg/day and 20 mg/kg/day subgroups of cannabidiol + clobazam + SoC (CS[1] Table 25)[39], while the SoC transition probabilities were directly derived from the SoC arm of Study 1601.[2]

Long-term efficacy (cycles 2-9) based on open label extension studies

Transition probabilities for cycles 2 to 5 were informed by the OLE studies for both fenfluramine + SoC and cannabidiol + clobazam + Soc.[32, 36] For fenfluramine + SoC, transition probabilities observed in month 9 to 12 (cycle 4 to 5) were also applied to cycle 6 to 9 as, according to the company's clarification response[3], *"the clinical trial data for fenfluramine state occupancy for >=25%, >=50%, >=75%, and 100% shows an increase in percentage of patients showing improvement from month 9 to month 12, from 65% to 71%, 42% to 51%, 19% to 25%, and 3% to 5% respectively"(*Table 4.9). Clinical trial state occupancy for cannabidiol + clobazam + SoC for cycle 4 to 5 showed stabilisation and therefore no change in state occupancy for cannabidiol + clobazam + SoC was applied from cycle 6 to 9 (except from discontinuation and death). Cycle 1 of the SoC arm was informed by the SoC + placebo arm of the fenfluramine trial.[2] Standard of care patients were assumed to remain in the same health state as in cycle 1. Table 4.9 shows state occupancies in the SoC, fenfluramine + SoC and cannabidiol + clobazam + SoC arms from cycle 2 to 9.

Table 4.9: State occupancy for the fenfluramine + SoC, cannabidiol + clobazam + SoC and SoC arm from cycle 2 to 9.

	Fenfluramine + SoC					
	State 0	**State 1**	**State 2**	**State 3**	**Discontinued**	**Dead**
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Fenfluramine + SoC					
	State 0	**State 1**	**State 2**	**State 3**	**Discontinued**	**Dead**
Cycle 4	[redacted]					
Cycle 5	[redacted]					
Cycle 6	[redacted]					
Cycle 7	[redacted]					
Cycle 8	[redacted]					
Cycle 9	[redacted]					
	Cannabidiol + clobazam + SoC					
	State 0	**State 1**	**State 2**	**State 3**	**Discontinued**	**Dead**
Cycle 2	0.235	0.153	0.153	0.222	0.231	0.006
Cycle 3	0.156	0.091	0.118	0.171	0.455	0.008
Cycle 4	0.124	0.073	0.085	0.144	0.563	0.011
Cycle 5	0.106	0.069	0.076	0.114	0.620	0.015
Cycle 6	0.095	0.062	0.068	0.101	0.657	0.018
Cycle 7	0.085	0.055	0.061	0.091	0.686	0.021
Cycle 8	0.078	0.050	0.056	0.083	0.709	0.025
Cycle 9	0.235	0.153	0.153	0.222	0.231	0.006
	SoC alone					
	State 0	**State 1**	**State 2**	**State 3**	**Discontinued**	**Dead**
Cycle 2	0.680	0.204	0.057	0.045	0.011	0.002
Cycle 3	0.671	0.201	0.056	0.045	0.022	0.006
Cycle 4	0.210	0.063	0.018	0.014	0.686	0.009
Cycle 5	0.163	0.049	0.014	0.011	0.751	0.013
Cycle 6	0.133	0.040	0.011	0.009	0.789	0.017
Cycle 7	0.113	0.034	0.009	0.008	0.814	0.021
Cycle 8	0.099	0.030	0.008	0.007	0.832	0.025
Cycle 9	0.087	0.026	0.007	0.006	0.844	0.029
SoC = standard of care						

Long-term follow up

After cycle 9, it was assumed that patients in all treatment arms would stay in their corresponding health state, except for a proportion of patients in which treatment is waning, treatment is discontinued or due to death.

4.2.6.2 Treatment discontinuation

Treatment discontinuation could occur due to AEs in all cycles, lack of efficacy in cycle 1 and 2 or due to a stopping rule for subsequent cycles. The average treatment duration was 3.7 years for fenfluramine + SoC and 2.8 years for cannabidiol + clobazam + SoC.

Treatment discontinuation due to AEs

Discontinuation due to AEs at Titration was informed by Study 1601[2] and was assumed to be the same for the fenfluramine + SoC and cannabidiol + clobazam + SoC arms, because data for cannabidiol +

clobazam + SoC was lacking. Discontinuation due to AEs at cycle 1 was informed by the NMA using a weighted average for the two cannabidiol dosages (10 and 20 mg/kg/day). For fenfluramine + SoC, the fenfluramine OLE study informed discontinuation due to AEs from cycle 2 to 5.[32] Discontinuation due to AEs was assumed to be 0% as from cycle 5. For cannabidiol + clobazam + SoC, the cannabidiol OLE study informed discontinuation due to AE from cycle 2 to 7.[36] Discontinuation due to AEs was assumed to be 0% as from cycle 7. Treatment discontinuation due to AEs in the SoC arm was determined from Study 1601[2] and assumed to be stable (i.e. 1.1% per cycle) over the time horizon (CS[1] Tables 43 and 44).[2]

Treatment discontinuation due to lack of efficacy and stopping rule

Treatment could be stopped due to lack of efficacy in cycle 1 and 2. In cycle 1, 0% of patients stopped treatment due to a lack of efficacy in the fenfluramine +SoC arm based on Study 1601.[2] In cycle 2, 7.3% of patients stopped treatment due to lack of efficacy in the fenfluramine + SoC arm based on the fenfluramine OLE study.[32] These percentages were assumed to be the same for the cannabidiol + clobazam + SoC arm.

After cycle 2, discontinuation due to lack of efficacy was determined by a stopping rule which dictates that all patients in state 0 (<25% reduction in drop seizure frequency) discontinued treatment after 3 months (i.e., 1 model cycle). Over time, patients could transit to state 0 due to treatment waning.

4.2.6.3 Treatment waning

Treatment waning was applied after cycle 9 in the economic model. Patients who experienced treatment waning transited to one of the health states with lower relative response, i.e., patients in health state 1 transited to health state 0, while patients in health state 3 could transit to health states 2, 1, and 0. Treatment waning was implemented in the model by considering two main elements. First the proportion of patients that experience treatment waning, which was 5.2% based on the last 3 months of the fenfluramine OLE study.[32] Second the deteriorating transition probabilities that describe the waning experienced by those patients. These deteriorating transition probabilities represent the transition probabilities observed in the last 3 months of observation of the fenfluramine OLE study[27] concerning only the transitions to maintain or worsen the health state.[32] This was applied to both fenfluramine + SoC and cannabidiol + clobazam + SoC as treatment waning data for cannabidiol + clobazam + SoC was lacking (Table 4.10). The proportion of patients that experiences treatment waning was 0% for SoC.

Table 4.10: Treatment waning probabilities for fenfluramine + SoC, cannabidiol + clobazam + SoC and SoC

		Fenfluramine + SoC			
		To			
		State 0	State 1	State 2	State 3
From	State 0	1.000	0.000	0.000	0.000
	State 1	0.013	0.987	0.000	0.000
	State 2	0.000	0.015	0.985	0.000
	State 3	0.000	0.003	0.008	0.989
		Cannabidiol + clobazam + SoC			
		To			
		State 0	State 1	State 2	State 3
From	State 0	1.000	0.000	0.000	0.000
	State 1	0.013	0.987	0.000	0.000
	State 2	0.000	0.015	0.985	0.000
	State 3	0.000	0.003	0.008	0.989
		SoC alone			
		To			
		State 0	State 1	State 2	State 3
From	State 0	1.000	0.000	0.000	0.000
	State 1	0.000	1.000	0.000	0.000
	State 2	0.000	0.000	1.000	0.000
	State 3	0.000	0.000	0.000	1.000

SoC = standard of care

4.2.6.4 Mortality

The model accounted for general population mortality, as well as SUDEP and non-SUDEP (Table 4.10). General population mortality was informed by age- and sex-adjusted national life tables in the UK. Baseline SUDEP mortality (0.233%) was informed by a DS publication due to lack of data for LGS, in line with NICE TA808.[31] In addition, the average number of drop seizures was determined to calculate the risk of SUDEP mortality for each health state, i.e., a higher number of drop seizures incurred an increased risk of SUDEP. Non-SUDEP mortality captured status epilepticus and accidental mortality, which was informed from a DS publication due to lack of data for LGS.[40] Accidental mortality was calculated as 21.40% of SUDEP and status epilepticus mortality combined, resulting in percentages between 0.028% (state 3) and 0.070% (state 0).

EAG comment: The main concerns of the EAG relate to: a) extrapolation of the fenfluramine treatment effect; b) a discrepancy between the clinical trial state occupancy and model state occupancy for fenfluramine; c) the treatment waning approach; d) the stopping rule; e) the midpoint approach to calculate absolute number of drop seizures in each health state; and f) NMA results only used for the modelling of treatment effectiveness in cycle 1.

a) Based on CS,[1] Figure 27, which shows the treatment effect of fenfluramine + SoC, cannabidiol + clobazam + SoC and SoC alone every 3 months during the trial period, the

treatment effectiveness for fenfluramine + SoC was assumed to increase after the observed study period (i.e. from cycle 5 to 9), while the treatment effectiveness for cannabidiol + clobazam + SoC was assumed to be stable. The EAG agrees with the company that the effectiveness of fenfluramine + SoC seems to increase over time during the trial period, however, is uncertain about the prolongation of this treatment effect after the observed period. Long-term efficacy data of fenfluramine in DS patients show that the treatment effect of fenfluramine is maintained until month 15 of the OLE study[27] but does not show an increased treatment effect[35]. Based on this study, a maintained treatment effect of fenfluramine was modelled in TA808.[31] This assumption is important, as, in the model, the QALYs accumulated during the observed trial period are higher for cannabidiol + clobazam + SoC than for fenfluramine + SoC, i.e. fenfluramine + SoC gains in total 0.73 QALY in the first year and cannabidiol + clobazam + SoC gains 0.75 QALY (Table 5.2). Hence, the incremental QALYs in favour of fenfluramine + SoC over the lifetime horizon were obtained in the unobserved period. Therefore, the EAG prefers a base-case analysis where the treatment effect for fenfluramine is maintained instead of increased after the observed period (i.e., in line with what was assumed for cannabidiol + clobazam + SoC).

b) The company provided an overview of clinical trial versus modelled health state occupancies in the first year in Table 18 of the clarification response.[3] For fenfluramine + SoC, there was a discrepancy between clinical trial state occupancy and the modelled state occupancy, causing an overestimation of patients in health states with better relative response in the fenfluramine + SoC arm. For example, while 25.3% of patients is in health state 3 at month 12 based on the clinical trial, the modelled percentage of patients in health state 3 at month 12 is 32%. The company explained that *"these differences were due in part to state occupancy in the model being determined from transition probabilities between states, and not based on state occupancies reported by clinical trial data (as was done for cannabidiol due to lack of transition probability data, and for SoC where it was assumed patients would remain in baseline health states). Additionally, clinical trial data encompasses ITT population, whereas the model health states (HS0, HS1, HS2 and HS3) are focused on treated population (the model holds a separate health state to accommodate patients that have discontinued treatment due to AE or lack of efficacy, including the stopping rule)."* The EAG deems this difference in modelling approach between treatments problematic, as it causes an overestimation of the fenfluramine + SoC treatment effect as compared to cannabidiol + clobazam + SoC and SoC alone. Moreover, considering only the treated population for fenfluramine + SoC (instead of the ITT population), while the ITT populations were used for cannabidiol + clobazam + SoC and SoC alone, is inconsistent. Therefore, the EAG prefers to use the clinical trial state occupancy of fenfluramine + SoC in the model in its base-case. As the EAG only had access to the proportions of patients in each health state for fenfluramine + SoC, the EAG calculated the number of patients in each health state by multiplying the proportion of patients to the total number of patients in the fenfluramine OLE study.[32]

c) The treatment waning approach used for both the fenfluramine + SoC and cannabidiol + clobazam + SoC arms seems inappropriate because of two reasons: 1) the way the deteriorating transition probabilities were calculated; and 2) the low proportion of patients to which treatment waning applied.

   Regarding the calculation of treatment waning (1): the deteriorating transition probabilities observed in the fenfluramine OLE study from month 9 to 12 were used.[32] The EAG notes that the deteriorating transition probabilities were calculated by only including the patients that stayed in their health state or deteriorated and excluded patients that improved. In this way, the percentage of patients with deteriorating transition probabilities is overestimated as it is not

calculated over the total number of patients on treatment. The EAG prefers 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.

Regarding the low proportion of patients experiencing treatment waning (2): using the company's approach, where deteriorating transition probabilities were applied to 5.2% of patients on treatment in both the fenfluramine + SoC and cannabidiol + clobazam + SoC arms, the transition probabilities describing treatment waning were extremely low: 0.013 for patients in health state 1, 0.015 for patients in health state 2 and 0.011 for patients in health state 3 (Table 4.10). The EAG considers these probabilities to be implausible, given that [redacted] and [redacted] of patients had already discontinued treatment with fenfluramine or cannabidiol after 12 months, respectively. Therefore, in the absence of any other data on treatment waning in fenfluramine and cannabidiol, the EAG explores an alternative scenario where the deteriorating transition probabilities are applied to 80% of patients on treatment in both the fenfluramine + SoC and cannabidiol + clobazam + SoC arm.

d) The company modelled a stopping rule for patients showing less than 25% reduction in DSF, assessed every 3 months. However, in TA808 the Committee deemed a stopping rule of "30% at 6 months", i.e. patients stopped treatment if they had less than 30% reduction in DSF over a period of 6 months, most appropriate for fenfluramine in DS.[31] The Committee reasoned that this was the most appropriate clinical threshold and in line with current practice of cannabidiol. The EAG prefers to use the "30% at 6 months" stopping rule in their base-case, as the 25% at 3 months stopping rule was not appropriately justified and likely not in line with clinical practice. The EAG notes, however, that the stopping rule at 6 months seems to be inaccurately implemented in the model for all treatment arms. In case of the 6 month stopping rule, all patients were removed from health state 0 (less than 25% reduction in DSF) every 6 months, instead of only the patients that were in health state 0 for 6 months. In this way, also patients that were in health state 0 for only 3 months are discontinued. The company's implementation of the stopping rule likely underestimated the treatment costs for patients that stop treatment as a proportion of patients will stop treatment at 6 months but is already discontinued at 3 months.
e) In order to inform resource use, utility values and mortality, the absolute number of drop seizures per health state were calculated. As a consequence of the model structure based on reductions in DSF, a conversion from relative to absolute numbers was needed for which the company used two different methods. For health states 0 and 3 the average absolute number of drop seizures was directly sourced from Study 1601,[2] while for health states 1 and 2 this was based on a midpoint approach by Neuberger et al.[29] According to the company, this combination of approaches was chosen because *"utilising direct evidence for midpoints for all states reveals that the median number of DSF is higher in state 2 compared to state 1 (38.16 vs. 34.86), as indicated in Table above. To align with the definition of health states and maintain consistency, we have employed different approaches in the base case for midpoint definition.*" The company modelled this as a scenario in response to clarification question B14d, which showed only a slight decrease in the ICER (£16) for fenfluramine + SoC compared to cannabidiol + clobazam + SoC, indicating that this approach has limited impact on the results[3].
f) Only Study 1601[2] and GWPCARE 3 and 4 were included in the NMA by the company, as the OLE studies for fenfluramine and cannabidiol had no placebo group to anchor the NMA. As a consequence, only cycle 1 in the model makes use of adjusted results based on the NMA, while unadjusted results directly derived from the OLE studies were used for the other cycles. Although patient characteristics seemed comparable between the OLE studies for fenfluramine and cannabidiol, the EAG wants to note that the effectiveness measures are unadjusted and

might be over or underestimating the treatment effectiveness for fenfluramine. The impact on the ICER is unknown.

4.2.7 AEs

The economic model included the most commonly reported TEAEs of special interest in the fenfluramine and cannabidiol trials (i.e., diarrhoea, somnolence, pyrexia, decreased appetite and vomiting), and were assumed to occur in cycle 1. The AE rates for fenfluramine + SoC and SoC were based on the safety data from Study 1601,[2] whereas AE rates for cannabidiol + clobazam + SoC were sourced from the safety data from the GWPCARE4 trial.

EAG comment: The main concern of the EAG relates to the selection of TEAEs that were used in the economic model. In the CS[1], the company stated that TEAEs that were most commonly reported in the pivotal trials of fenfluramine and cannabidiol were included in their economic model. In response to clarification question B21, the company further explained that this included those TEAEs with an occurrence of at least 10% of patients, or those leading to withdrawals from treatment. However, the EAG noted that the company's application of selecting TEAEs seems inconsistent. Fatigue was not modelled as a TEAE despite the pivotal trial of fenfluramine reporting fatigue in 14% of patients that received fenfluramine. Furthermore, the pivotal trial of cannabidiol reported several TEAEs leading to withdrawal from treatment that were not included in the economic model. Hence, the EAG would like to see a scenario analysis in which the company applies the TEAEs in their economic model consistent with the defined selection criteria (i.e., occurrence of at least 10% or leading to withdrawal from treatment).

4.2.8 HRQoL

4.2.8.1 HRQoL data identified in the review

According to the CS[1], the SLR identified two studies reporting UK relevant utility values. Both studies (Lo et al. and Auvin et al.[41, 42]) were used in scenario analyses to inform the economic model. An abstract of Verdian et al.[43] was identified after additional searches within the papers retrieved in the SLR, which was used to inform the company's base-case.

4.2.8.2 Health state utility values

Health-related quality of life data in Study 1601[2] and the OLE study[27] were collected using QOLCE-16. The company did not use these data to inform the economic model, because the QOLCE-16 is a disease-specific measure and long-term data were not yet available. Instead, health state utility values to inform the economic model were derived from the literature.

The study by Auvin et al.[42] that was identified in the SLR did not align with the patient population mentioned in the decision problem, as it included patients with various types of epilepsies (including DS and others). The other study that resulted from the SLR by Lo et al.[41] provided time trade-off (TTO) and visual analogue scale (VAS) ratings based on vignettes evaluated via interviews from the general population in the UK and Sweden. The vignettes described health states based on the total number of drop seizures per month rather than treatment response as structured in the modelling approach. Therefore, the company conducted additional searches and identified a conference abstract by Verdian et al. This abstract reported utilities using EQ-5D, TTO and VAS measures for four LGS health states, categorised by the percentage reduction in seizures (ranging from <25% reduction in DSF to ≥75% reduction response). These measures were conducted with 119 members of the general public of whom 48% were caregivers/parents of children aged 4 to 18.

The company preferred to use the EQ-5D utilities from Verdian et al. to inform their base-case, as these closely matched the EQ-5D reporting requirements as per NICE guidelines, were used in similar cost effectiveness studies in LGS[44, 45], and were aligned with the model's relative health state structure (Table 4.11. The company matched the anchor state from Verdian et al. (21-28 drop seizures per week) to health state 0 in the economic model, as this state was considered to be similar to the median number of seizures in the economic model (70.5 per 28 days). The other health states used in Verdian et al. were matched with the same level of seizure reduction categories in the economic model (i.e., ≥25 - <50%, ≥50 - <75% and ≥75% reductions).

The company also included caregiver utilities in the economic model and assumed 1.8 caregivers per LGS patient (in line with NICE TA615). As no specific utilities for caregivers were provided by Verdian et al. the same utility values were assumed for both patients and caregivers.

4.2.8.3 Disutility values

In the absence of disutility data available directly from Study 1601,[2] the fatigue disutility of -0.060 from Matza et al.[46] was applied to all TEAEs. The TEAEs were assumed to occur once in the initial cycle after the Titration period only and would not occur in any subsequent cycles.

Table 4.11: Health state utility values

Health state	Utility value (for patients and caregivers)	Reference	Justification
State 0: (<25% reduction)	0.020	Verdian et al. 2008[43]	LGS patients within Study 1601[2] have similar baseline characteristics as those quoted within the clinical paper. Anchor point for drop seizures of 17.6 per week is close to the 21-28 range for the patients of the present analysis. EQ-5D scores are requested to be reported as per NICE guidelines. Utilities and health states are aligned with the current CEA in this dossier and used in previous similar studies.
State 1: 25% to <50% reduction	0.100		
State 2: 50% to <75% reduction	0.500		
State 3: ≥75% response	0.596		
TEAE (all)	-0.060 (for patients only)	Matza et al. 2019	Fatigue disutility was the only TEAEs of special interest to be found in Matza et al. 2019. In the absence of other TEAEs of special interest fatigue disutility was applied to all TEAEs in the model in the first cycle after the Titration period.
Based on CS Table 54			

Health state	Utility value (for patients and caregivers)	Reference	Justification
CEA = cost-effectiveness analysis; CS = company submission; EQ-5D = EuroQol-5-Dimensions; LGS – Lennox-Gastaut syndrome; NICE = National Institute for Health and Care Excellence; TEAE = treatment emergent adverse event			

EAG comment: The main concerns of the EAG relate to: a) the modelling of patient HRQoL; b) the approach for the modelling of caregiver HRQoL; c) the lack of modelling the impact of institutionalisation on caregiver HRQoL; d) the lack of modelling the potential impact of non-drop seizures on HRQoL; and d) the modelling a single fatigue disutility for all TEAEs.

a) The company used utility scores from a conference abstract of Verdian et al. to inform health state utilities in the economic model. This involved a vignette study focussing on DSF in which LGS health states were rated using the VAS and EQ-5D. The EAG was concerned about 1) the use of vignette studies to estimate patient utility values and 2) the face validity of the resulting utility values.
    1) Next to a transparency issue resulting from the unavailability of a full text publication of Verdian et al. the vignette study suffered from the limitation that EQ-5D health states were not directly provided by patients living with the condition and utility values may therefore differ from the health status of actual LGS patients. In addition, the approach was condition-oriented and hence does likely not appropriately capture other aspects known to influence health-related quality of life. In response to clarification question B22, the company acknowledged the potential limitations of vignette studies, but also argued that vignette-based utility values may be useful in situations where patients are difficult to access (such as patients with LGS). The two other studies reporting UK relevant utility values that were identified by the company in its SLR were also not ideal for informing the health state utility values in the economic model. The study by Auvin et al.[42] did not align with the patient population mentioned in the decision problem, as it included patients with various types of epilepsies (including DS and others). Health states in the study of Lo et al.[41] were based on the total number of drop seizures per month rather than treatment response as structured in the company's modelling approach. Although the EAG understands the difficulties mentioned by the company, the limitations of their current approach persist. Scenario analyses conducted by the company indicated that the source and method of eliciting patient utility values to inform the economic model substantially impact the cost-effectiveness results, and the EAG therefore considers this a key issue for the committee to consider.
    2) Although the disease burden of LGS patients is high, the EAG considers the health state utility values from Verdian et al. that were used to inform the economic model to be relatively low, especially the utility values of health states 0 (0.020) and 1 (0.100) which are on the end of the scale. As highlighted in the CS, HRQoL in Study 1601[2] and the OLE study[27] were measured using the disease-specific QOLCE-16 instrument. Despite the fact that the HRQoL data resulting from this instrument may not be suitable to estimate health state utility values in the economic model, the EAG used these to check the face validity of the currently used health state utility values from Verdian et al. The mean baseline scores of the QOLCE-16 overall quality of life domain in the placebo and two fenfluramine arms of Study 1601[2] were around 40 (SD±13) on a scale of 0 (worst overall QoL) to 100 (best overall QoL), indicating that patient HRQoL in

the economic model is currently potentially underestimated. In addition, the overall QoL domain and most other domains of the QOLCE-16 show hardly any clinically relevant change at visit 12 compared to baseline, indicating that the patient's HRQoL may not be very sensitive to improvements in DSF. Therefore, the large differences in utility values between the health states in the economic model, especially between the worse (0 and 1) and better (2 and 3) health states, seems to lack face validity. The EAG would like the company to justify these differences and explore the potential impact of assuming utility values for health states 0 and 1 that are close to the utility values of health states 1 and 2.

Overall, the EAG considers the use of vignette studies to inform HRQoL a violation of good practice. The EAG is concerned that none of the utility values presented in the CS[1] are ideal for informing patient HRQoL in the economic model, as all HRQoL studies identified in the SLR (and explored in the economic model) suffer from limitations as discussed above. Nevertheless, the EAG acknowledges the challenges related to estimating HRQoL in rare and severe diseases such as LGS and appreciates the company's numerous scenario analyses in which different assumptions related to the source and elicitation methods were explored.

b) In addition to patient utilities, the company included caregiver utilities in its base-case by applying the same health utility values from Verdian et al. to 1.8 caregivers per patient. The EAG questions the plausibility of this approach. Firstly, the EAG considers the assumption that the HRQoL of the caregivers equals the HRQoL of the LGS patient to be unrealistic. Although the burden of LGS caregivers may be high, the EAG would expect their HRQoL to be higher than the patient living with the disease. The results of the studies of Auvin et al.[42] and Lo et al.[41], in which both patient utilities and caregiver utilities were estimated, also indicate this by reporting higher utility values for caregivers compared to patients. Next to that, the mean baselines scores of the Zarit Caregiver Burden Inventory in the placebo and the two fenfluramine arms of Study 1601[2] were approximately 30 (SD± 16), representing a mild to moderate caregiver burden which indicates that the low caregiver utilities in the company's base-case potentially overestimate the caregiver burden. Notably, the mean Zarit Caregiver Burden Inventory scores at visit 12 in Study 1601[2] were similar to these baseline scores, suggesting that caregiver burden may not be sensitive to changes in seizure frequency. Secondly, the company's approach of modelling caregiver HRQoL entailed that when a patient in the economic model died, the corresponding carer utility was also set to zero. This overestimates the impact of mortality, given that the caregiver does not die together with the patient and its assumed utility value of 0 hence is an underestimation of reality. The EAG, therefore, in line with TA614, requested a caregiver disutility approach to incorporate caregiver HRQoL in its request for clarification. In response to clarification question B23, the company provided a scenario analysis in which caregiver disutilities for each health state were calculated by finding the difference between the UK VAS norm and the UK caregiver utility scores for LGS estimated in Auvin et al.[42, 47] These caregiver disutilities were applied until a patient died. Although there is no clear guidance as to how best to incorporate carer utilities, the EAG considers the disutility approach to be more appropriate than the company's approach and therefore adopted it in the EAG base-case. Moreover, the company did not justify why the study of Auvin et al.[42] was used for the calculation of the caregiver disutilities, and it was noted in the CS[1] that the various types of epilepsies in this study did not align with the patient population in the NICE scope. The EAG preferred using the TTO-based caregiver utilities from Lo et al.[41] for the calculation of caregiver disutilities in its base-case, because 1) the TTO approach from

Lo et al.[41] is better aligned with the NICE reference case (stating that a choice-based method should be used) than the VAS approach by Auvin et al.[42], 2) the sample size of Lo et al.[41] (n=150) was larger than the sample size of Auvin et al.[42] (n=30), and 3) the DSF categories of Lo et al.[41] (≤45, >45–≤110, >110) better aligned with the DSF categories in the current STA compared to Auvin et al.[42] (0, 80, 130).

c) Although it was stated in the CS[1] that "*outcomes for patients with LGS are typically very poor; the majority of patients will require home care or institutionalisation*", the company did not initially model the impact of institutionalisation in its submission. In response to clarification question B24, the company included the costs of institutionalisation in a scenario analysis, assuming that 10% of LGS patients would be institutionalised when reaching the age of 18 years old. However, unlike costs, the company did not adjust caregiver (dis)utilities for the fact that a proportion of patients will be institutionalised. Although the EAG expects institutionalisation of the patient to substantially reduce the caregiver burden, it is also aware of the remaining caregiver burden resulting from travelling long distances for visits and patients returning to their home in weekends and holiday periods. Therefore, the EAG in its base-case assumed an alternative number of caregivers for the 10% of patients that was institutionalised at the age of 18 years: first, the number of days per year that institutionalised patients are expected to be home based on weekend days (105.25), days of annual leave (28) and bank holidays (eight) was calculated. Together these days (141.25) represented the number of days caregivers would have full responsibility, while on the other days the caregivers would have no responsibilities. Then, the total number (141.25 days) was converted to a proportion per year (0.39), which was subsequently applied to the modelled 1.8 caregivers that were assumed for non-institutionalised patients. This resulted in an average number of 0.7 caregivers for the 10% of patients that was institutionalised at the age of 18 years in the EAG base-case.

d) As discussed in Section 4.2.2, health states in the company's economic model were based on drop seizures only, while clinical trial data also reported a significant number of non-drop seizures in LGS patients. The EAG is concerned that this assumption potentially underestimated HRQoL, especially in health states for patients with lower numbers of drop seizures as the non-drop seizure frequency in these patients is not necessarily also low.

e) In the absence of disutility data available directly from Study 1601,[2] the company applied the fatigue disutility of -0.060 from Matza et al.[46] for patients on oral antiepileptic medications in the general population to all TEAEs. In response to clarification question B21, the company argued that the AEs reported in Matza et al.[46] did not align with the TEAEs in the LGS population, and hence it was assumed that TEAEs would have similar decrement in utility as those experiencing fatigue in the general population taking oral antileptic medications. Although the EAG considers the impact on the cost effectiveness results likely to be very minor, it would like to see a scenario analysis in which the company applies TEAE-specific disutilities sourced from the literature (e.g., the abstract by Verdian et al.).

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, subsequent treatment costs, health state costs, monitoring costs, costs of managing AEs and mortality costs. Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), and Personal Social Services Research Unit (PSSRU).

4.2.9.1 Resource use and costs data identified in the review

The SLR identified eight unique publications that reported data on the health care resource use (HCRU) and costs for LGS patients from publications globally, of which three were conducted in

Europe (Netherlands, Germany, and the UK). In addition, an HTA review of previous submissions was conducted to supplement the HCRU database search, which identified primary care resource use data from NICE TA615[30] that was used in the economic model. Two further studies were identified through a desk search on general epilepsy (Tobochnik et al. and Kurth et al.[48, 49]), which were used to estimate HCRU for GTC versus other types of seizures.

4.2.9.2 Treatment acquisition costs (with PAS)

Drug acquisition costs were age-dependent, and the average dose was calculated using the proportion of patients across age groups. For the dosing of weight-dependent drugs, the model considered a fixed weight approach, based on inputted patients' mean weight by age group based on Study 1601[2] (CS[1] Table 55).

A discount of [redacted] was applied to the list price of fenfluramine, resulting in a cost per milligram of [redacted]. Average Titration and Maintenance doses of 0.3 mg/kg/day and 0.413 mg/kg/day (the initial average Maintenance dose of 0.5 mg/kg/day was reduced by the company in its clarification response) were in implemented in the economic model, respectively.

Cannabidiol was modelled at a list price of £0.085 per mg, and average Titration dose implemented in the economic model was 5 mg/kg/day.

The model assumed the Maintenance dose of cannabidiol in the initial Maintenance cycle to be 12 mg/kg/day to align with NICE TA615 submission, and 16 mg/kg/day thereafter (the initial average Maintenance dose of 14 mg/kg/day was increased by the company in its clarification response).

The SoC included a basket of ASMs according to baseline distribution observed in Study 1601[2] (CS[1] Table 60). As SoC drugs were available in different formulations, a weighted average price per milligram was calculated based on prescribing percentages obtained from the Prescription Cost Analysis (PCA)– England – 2022 shares of each formulation in England (CS Table 59). The total costs in the first year included the cost of the Titration period and the Maintenance period, whereas the costs of subsequent years only accounted for the cost of the Maintenance period.

Costs were sourced from BNF 2023. As all drugs were administered orally, it was assumed that no cost would be associated with administration.

4.2.9.3 Subsequent treatment costs

A basket of subsequent treatment lines was modelled for patients on fenfluramine or cannabidiol that discontinued treatment. The distribution of treatments within the basket was assumed to be the same as the SoC arm of the Study 1601[2] (CS[1] Table 61).

4.2.9.4 Health state costs

The CS distinguished between primary care (i.e., LGS routine care) and secondary care (i.e., seizure associated care) costs. Resource use for primary care was 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 (0, <45, 45-110 and >110) based on the midpoint approach by Neuberger et al.[29] Resource use for secondary care was estimated separately for GTC and other drop seizure types (based on the observed GTC seizure reduction in the Study 1601[2]).

Primary care

Primary care HCRU inputs (CS[1] Table 63) were separately modelled for patients <12 years and ≥ 12 years and included nurse visits, specialists visits, paediatrician/general practitioner visits, phone call follow-ups and number of rescue medication per intake (sourced from UK clinical experts and obtained from NICE TA615). All primary care unit costs were sourced from the NHS reference costs for the year 2021-22 and PSSRU 2022 (CS[1] Table 64)[50, 51]. The average cost per patient per cycle for each health state was then calculated by weighting the costs and HCRU to the baseline age distribution found in the fenfluramine trial (Table 4.12).

Secondary care

The HCRU costs for secondary care were based on HCRU hospitalisations and emergency department visits to calculate per patient per cycle costs of secondary care for each seizure type. HCRU for LGS patients was first adjusted for age (using Chin et al.[52]), and then the HCRU for each seizure type (GTC and other seizures) was estimated based on Kurth et al.[49] The final HCRU adjusted by seizure type were reported in CS[1] Table 70. Secondary care unit costs were based on NHS reference costs for the year 2023. The total secondary care costs per patient per cycle is reported in Table 4.12 below.

Table 4.12: Health state costs

	≤45 drop seizures	**>45 to ≤110 drop seizures**	**>110 drop seizures**
Primary care			
Nurse visit	£57.00	£87.47	£171.00
Specialist visit	£105.83	£176.94	£317.50
Paediatrician/GP visit	£93.69	£187.38	£281.06
Phone call follow-up	£14.58	£36.46	£87.50
Rescue medication (per number of medicine intake)	£2.64	£6.59	£10.54
Secondary care			
Hospitalisation GTC seizures	£292.17	£292.17	£292.17
Hospitalisation other seizures	£97.08	£97.08	£97.08
ED visits GTC seizures	£87.87	£87.87	£87.87
ED visits other seizures	£45.09	£45.09	£45.09

Based on CS Tables 67 and 72
CS = company submission; ED = Emergency Department; GP = General Practitioner; GTC = generalised tonic-clonic

4.2.9.5 Monitoring costs

Patients on fenfluramine were modelled to have an echocardiogram every 6 months for the first 2 years and annually thereafter. A final ECG is performed upon treatment discontinuation. The cost associated with an ECG was sourced from the 2022/23 National Tariff Payment system (CS[1] Table 73).

4.2.9.6 Adverse event costs

In line with NICE TA615, AE costs were assumed to be equal to one specialised nurse visit (£57.00, sourced from PSSRU 2022), and applied as a one-off cost in the first cycle when patients start treatment.

4.2.9.7 Mortality costs

In line with the NICE TA615, mortality costs were assumed to be one Emergency Department (ED) visit and one Intensive Care Unit (ICU) visit (CS[1] Table 75), which was applied as a one-off terminal care cost to patients at time of death (Table 75).

EAG comment: The main concerns of the EAG relate to: a) modelling of institutionalisation; b) the lack of modelling the potential impact of non-drop seizures on costs and resource use; and c) modelling the costs of managing TEAEs.

a) It was stated in the CS[1] that "*outcomes for patients with LGS are typically very poor; the majority of patients will require home care or institutionalisation*". However, costs of institutionalisation were initially not included in the company's economic model. In response to clarification question B24, the company provided a scenario analysis including a per cycle institutionalisation cost of £1,594 that was applied to 10% of LGS patients being institutionalised when reaching the age of 18 years old. Assuming an institutionalisation rate of 10% was based on NICE TA615 and adopted by the EAG in its base-case. Nevertheless, it is unclear to the EAG whether this percentage is representative of UK clinical practice, and further justification and evidence should be provided to support this assumption.
b) As discussed in section 4.2.2, health states in the company's economic model were based on drop seizures only, while clinical trial data also reported a significant number of non-drop seizures in LGS patients. The EAG is concerned that this assumption potentially underestimated costs and resource use, especially in health states for patients with lower numbers of drop seizures as the non-DSF in these patients is not necessarily also low.
c) In its economic model, the company assumed that the cost of managing TEAEs was equivalent to that of a single visit to a specialised nurse. While a cost of £57 was reported in the CS[1], a cost of £52 was used in the economic model. In response to clarification question B21, the company acknowledged this was an error and adjusted the modelled cost to £57 per TEAE. Despite the company's adjustments, the EAG noted in the updated economic model that the cost correction was implemented for all TEAEs except diarrhoea. The EAG therefore adjusted this costing error in its base-case, which very minorly impacted the cost effectiveness results. The company further argued that their approach of assuming a single visit to a specialised nurse was chosen in line with NICE TA615 as the majority of AEs were typically mild to moderate, occurred during the initiation of treatment, were transient, and resolved within 4 weeks of onset. However, the pivotal trial of fenfluramine reported that 11% of patients receiving fenfluramine at a dose of 0.7 mg/kg/day experienced at least one serious TEAE, which required hospitalisation (as stated by the company in response to clarification question B21b). As a result, the costs of managing TEAEs in the economic model are currently likely underestimated and the company should provide a scenario analysis including TEAE-specific costs that are in line with clinical practice.

4.2.10 Severity

The company identified no QALY shortfall calculations for previous NICE appraisals within the relevant indication. The QALY shortfall calculator by Schneider et al.[53] was utilised using the tool's reference case scenario by Hernandez Alava et al.[54] to generate absolute and proportional QALY

shortfall estimates. The informing sex distribution, starting age and discount rate were consistent with the company's base-case. As the QALY shortfall calculator only allows for integers, sex distribution and starting age were rounded. A severity modifier of x1.7 was applied to both patient and caregiver QALYs.

Table 4.13: QALY shortfall analysis

	Input/output
QALY shortfall analysis: input factors	
Sex distribution	55.5% male, 44.5% female*
Starting age	13.7 years*
Selected scenario	Reference case: measurement and value of health value set + health survey for England 2014 adjusted limited dependant variable mixture mode model
Discount rate	3.5%
Total (discounted) QALYs for general population	23.55
QALY shortfall analysis: summary outputs	
Absolute QALY shortfall	22.97
Proportional QALY shortfall	0.98
QALY weight	x1.7
Based on CS[1] Tables 78 and 80 *The calculator only allows integers, so the percentage of females was rounded to 45% and starting age was rounded to 14 CS = company submission; QALY = quality-adjusted life year	

EAG comment: The main concern of the EAG relates to the application of the severity modifier to caregiver QALYs. In the CS[1], the severity modifier was applied to both patient and caregiver QALYs. clarification question B27 requested justification for additionally applying the x1.7 severity modifier to caregiver QALYs, rather than solely to patient QALYs. As a result of the significant impact on caregivers, the company's response indicates that they consider LGS caregivers to fit the NICE guidance definition of severity which specifies the "*future health lost by people living with the condition with standard care in the NHS*". Whilst the EAG recognises the potential for multiple interpretations, it is the understanding of the EAG that the severity modifier should be applied solely to the patient QALYs, consistent with the patient population utilised when calculating the QALY shortfall.

4.2.11 Uncertainty

The company considers as the key areas of uncertainty:

- Heterogeneity:
    - Heterogeneity in the clinical presentation of LGS.
    - Variation in the management of patients in clinical practice.
    - Heterogeneity among LGS patients limits the predictability of clinical effectiveness studies. Addressing this heterogeneity through collecting data is difficult to practically conduct due to the rarity of LGS, and the nature of diagnosing LGS in clinical practice not being straightforward.

- Lack of head-to-head clinical trial between fenfluramine and cannabidiol + clobazam. This results in the need for efficacy data to be derived from an ITC which involves assumptions surrounding the transitivity and homogeneity of patients compared across trials.

EAG comment: The EAG largely agrees with the company's assessment of the key areas of uncertainty. In addition to the company's appraisal, the EAG highlights uncertainty surrounding the approach to model drop seizures only. The directional impact on the results of excluding non-drop seizures remains uncertain and potentially underestimates costs and effects.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The updated company base-case cost effectiveness results (probabilistic [95% CI]), in response to the request for clarification, indicated that fenfluramine + SoC is both more effective (incremental QALYs including severity modifier of 1.39 [0.61-2.31]) and more costly (incremental costs of [redacted]) than cannabidiol + clobazam + SoC, amounting to an ICER including the severity modifier of [redacted]. This result includes the application of a x1.7 QALY weight to both patient and caregiver QALYs. With the applied x1.7 QALY weight to patient and caregiver QALYs, the probability of fenfluramine + SoC being cost-effective, at threshold of £30,000 per QALY gained, compared to cannabidiol + clobazam + SoC is [redacted].

The deterministic ICER for fenfluramine and SoC versus cannabidiol + clobazam and SoC (with severity modifier) was [redacted]. The discrepancy between the probabilistic and deterministic ICERs is explained by the application of a dose cap to fenfluramine, which distorts the distribution for fenfluramine dosing.

Table 5.1: Probabilistic company base-case results, following clarification response

Intervention	Total QALYs	Total QALYs (incl. SM)	Total Costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	Incr. Costs	ICER (£/QALY)	ICER (£/QALY, incl. SM)
Fenfluramine + SoC	3.68	6.26	[redacted]					
Cannabidiol + clobazam + SoC	2.86	4.87	[redacted]	0.82	1.39	[redacted]	[redacted]	[redacted]
SoC alone	1.66	1.66	[redacted]	2.02	3.44	[redacted]	[redacted]	[redacted]
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care; SM = severity modifier								

Overall, the technology is modelled to affect QALYs (including the severity modifier) by:

- Reduction in the frequency of drop seizures. Incremental QALYs for fenfluramine + SoC (total for patients and caregivers [proportion of total incremental QALYs]) in health states 2 and 3 were 0.64 (45%) and 0.74 (53%) compared with cannabidiol + clobazam and SoC and 1.33 (38%) and 2.13 (61%) compared to SoC alone.
- Reduction in caregiver burden. The incremental caregiver QALYs (proportion of total QALY increment) for fenfluramine + SoC were 0.91 (65%) compared with cannabidiol + clobazam + SoC, and 2.25 (65%) compared with SoC alone.

Overall, the technology is modelled to affect costs by:

- The higher treatment costs for fenfluramine. Incremental treatment costs (proportion of total incremental costs) for fenfluramine + SoC were [redacted] ([redacted]) compared to cannabidiol + clobazam + SoC and [redacted] ([redacted]) compared to SoC alone.

EAG comment: The main concerns of the EAG relate to: a) observed versus extrapolated QALYs for fenfluramine and SoC versus cannabidiol + clobazam and SoC; and b) reporting error in the clarification response.

a) In the economic model, the QALYs accumulated during the observed trial period were higher for cannabidiol + clobazam + SoC than for fenfluramine + SoC, i.e., total fenfluramine + SoC QALY gains equal 0.73 in the first year and total cannabidiol + clobazam + SoC QALY gains equal 0.75 (Table 5.2). Contrastingly, the total observed and extrapolated QALYs for fenfluramine + SoC were 3.68 and 2.86 for cannabidiol + clobazam + SoC. Hence, the incremental QALYs of fenfluramine + SoC versus cannabidiol + clobazam + SoC over the lifetime time horizon of the economic model were obtained in the unobserved period. The EAG is concerned about the uncertainty regarding the extrapolation of the fenfluramine + SoC treatment effect and its impact on the cost effectiveness results. The extrapolation of the fenfluramine + SoC treatment effect and its subsequent impact on the relative cost effectiveness is discussed in more detail in Section 4.2.6 (EAG comment a). The EAG would like further justification regarding the plausibility of an increasing treatment effect of fenfluramine after the observed period.

b) In Table 10 of the clarification response, the company provided the updated deterministic company base-case with the severity modifier applied, with a reported ICER of [redacted] per QALY gained for fenfluramine + SoC versus cannabidiol + clobazam + SoC. This ICER differs from the [redacted] per QALY gained reported in the model and the ICER later reported as base-case ICER for the scenario analyses (also [redacted]). Therefore, the EAG assumes that the [redacted] is a reporting error. The EAG has displayed results as reported in the updated economic model as provided by the company.

Table 5.2: Observed versus extrapolated QALYs (excluding severity modifier)

	Fenfluramine + SoC	CBD + CLB + SoC	SoC alone
	Observed (at cycle 5, 12, 5 months)		
% on treatment	[redacted]	[redacted]	N/A
Costs	[redacted]	[redacted]	[redacted]
Life years gained	1.28	1.28	1.28
Patient QALYs gained	0.25	0.26	0.16
Caregiver QALYs gained	0.47	0.48	0.31
Total QALYs gained	0.73	0.75	0.47
	Total (observed + extrapolated)		
Costs	[redacted]	[redacted]	[redacted]
Life years gained	20.45	20.33	20.15
Patient QALYs gained	1.30	1.01	0.57
Caregiver QALYs gained	2.39	1.85	1.06
Total QALYs gained	3.68	2.86	1.63

CBD + CLB = cannabidiol + clobazam; N/A = not applicable; SoC = standard of care; QALY = quality-adjusted life year

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic (one-way) sensitivity analyses (DSA) as well as scenario analyses.

The parameters that have the greatest effect on the ICER (based on the company's DSA) are:

- Fenfluramine cost per mg
- Cannabidiol cost per mg
- The relative risk of treatment discontinuation for fenfluramine + SoC in the Titration and Maintenance period
- Weight (12-17 years and 18-35 years)
- Discount rate (benefits and costs)
- Number of caregivers
- The relative risk of treatment discontinuation for cannabidiol + clobazam + SoC in the Titration and Maintenance period

Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following CS[1] scenarios that have a substantial impact on the ICER:

- Varying the stopping rule (discontinuation if response is <50%, compared with <25% in the base-case)
- Increasing the percentage of cannabidiol + clobazam + SoC patients that undergo treatment waning (from 5.2% to 19.60% of patients)
- Drug Maintenance dosage (varying fenfluramine and cannabidiol dose both separately and simultaneously)
- Utility source

EAG comment: The main concern of the EAG relates to the substantial difference between the company's deterministic and probabilistic base-case ICER. The probabilistic base-case ICER for fenfluramine + SoC versus cannabidiol + clobazam + SoC was significantly lower than the deterministic ICER. This was explained by the application of a dose cap of 26 mg/day to fenfluramine with no dose cap applied to cannabidiol. The dose cap for cannabidiol is 20 mg/kg/day, which is above the 16mg/kg/day utilised in the model. Within the PSA, dosage was held fixed, with only cost per mg and average weight parameters varied probabilistically. Given the uncertainty surrounding the utilised maintenance dose for both fenfluramine and cannabidiol and dosage heterogeneity between patients, the EAG believe that dosage parameters should be included in the PSA, with a cap of 20mg/kg/day applied to cannabidiol. Further, the parameters for cost per mg, currently included in the PSA, should simultaneously be held fixed provided that this is based on a set cost per pack.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

To assess face validity, the problem formulation, model structure, clinical assumptions and data sources were examined by UK clinical experts in an advisory board meeting with UK clinical experts.

5.3.2 Technical verification

As per the CS[1], quality-control procedures for coding, inputs and model assumptions were performed by an independent senior health economist not involved in the development of the model. The utilised

checklist was provided in Table 96 of the CS[1]; however, procedures and outputs of the independent review were not detailed.

5.3.3 Comparisons with other technology appraisals

The CS indicated that model comparability, costs and QALYs were examined in relation to the NICE cannabidiol submission (NICE TA615). The company noted the current submission differed from NICE TA615 in that health states were based on the percentage of reduction in drop seizures (as opposed to seizure frequency). In the initial CS[1], incremental costs for cannabidiol + clobazam + SoC compared with SoC alone were similar between the current Technology Assessment and NICE TA615. Incremental (deterministic) costs were estimated to be [redacted] for the current Technology Assessment, compared with £48,907 in NICE TA615 over 15 years. However, in the company base-case after clarification response, incremental costs for cannabidiol + clobazam + SoC compared with SoC alone were substantially higher at £62,011, mainly relating to the higher dose used for cannabidiol. The company base-case utilised a cannabidiol dose of 16 mg/kg/day (14 mg/kg/day in the initial CS[1]) which differs from the 10 mg/kg/day utilised in the company base-case in NICE TA615. Differences also existed in the estimation of life years (LYs) and QALYs. The current Technology Assessment incorporated caregiver utilities separately, whilst NICE TA615 assigned a disutility to incorporate caregivers, resulting in a lower incremental QALY gain for cannabidiol + clobazam + SoC compared to SoC alone in the current Technology Assessment (1.22 without the severity modifier compared with 1.58 in NICE TA615). No further detail was provided in Section B.3.14.1 as to the outcome of the comparison.

5.3.4 Comparison with external data used to develop the economic model

In relation to comparisons with external data, the company only discuss comparisons of mortality rates with those reported in Chin et al.[52] which estimated disease-specific LGS mortality to be 6.12 per 1,000 person-years. The current Technology Assessment, utilising an area under the curve approach, estimated deaths in the SoC arm to be 7.17 per 1,000 person-years which the company considers to be relatively close.

5.3.5 Comparison with external data not used to develop the economic model

The company does not discuss any comparisons with external data not used to develop the economic model in the CS.[1]

EAG comment: The main concerns of the EAG relate to: a) use of DS data as a proxy for LGS (non-) SUDEP rates; b) transparency of the advisory board meeting; and c) transparency of the externally conducted technical verification.

a) In the CS,[1] the company used DS data as a proxy for (non-)SUDEP rates for LGS patients. In clarification question B31, the EAG requested justification as to the plausibility and appropriateness of using DS data as a proxy for LGS (non-)SUDEP rates. In response, the company pointed towards epilepsy-related deaths being related to frequency rather than underlying condition, with mortality rates thought to be higher in DS than LGS. The company further justified the approach with reference to SUDEP mortality rates derived from DS data being aligned with the approach taken in NICE TA615 where its plausibility in light of lacking LGS SUDEP mortality was validated by clinical experts. Furthermore, the company suggested that uncertainty in mortality rates does not translate into model uncertainty provided mortality is not a major driver within the economic model. The advisory board meeting report provided by the company states than clinicians advised the use of long-term DS data to confirm long-

term efficacy, safety and tolerability for fenfluramine. The company state that UK clinicians were asked to clarify how assumptions of mortality in DS can be applied in LGS. However, this was not clear within the advisory board report. The EAG recognises the lack of alternative sources of data to inform (non-)SUDEP rates for LGS patients, however, also highlights the outstanding uncertainty resulting from the paucity of available data. The directional impact of using DS data as a proxy remains unclear to the EAG.

b) In response to a request for advisory board meeting minutes, the company provided a report containing an executive summary suggesting the full meeting minutes or a recording were unable to obtain due to the vendor not being commissioned to produce this. For transparency purposes and to allow for a better understanding of uncertainty, the EAG would like to highlight the preference of NICE submissions to provide clear reporting for expert elicitation or expert opinion from study planning to conduct and should, where possible, follow existing reporting guidelines.

c) Details of the technical verification conducted by an independent senior health economist were not provided in the CS.[1] Clarification question B32 requested detail regarding this assessment but were not provided by the company without explanation. For transparency and completeness, the EAG would like to see a completed assessment consistent with the model checklist parameters as provided in Table 96 of the CS.[1]

6. EAGs ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al.[55]:

- Transparency (e.g., lack of clarity in presentation, description, or justification).
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case).
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data).
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered).
- Unavailability (e.g., lack of data or insight).

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler et al.)[56]:

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS[1] base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

1. AE management cost of £57 for diarrhoea (Section 4.2.9)
   The EAG corrected the TEAE management cost for diarrhoea from £52 to £57.

6.1.1.2 Fixing violations

The EAG was unable to make adjustments for the violations that were identified.

6.1.1.3 Matters of judgement

2. Modelling an average Maintenance dose of 0.5 mg/kg/day for fenfluramine (Section 4.2.4)

The EAG modelled an average Maintenance dose of 0.5 mg/kg/day for fenfluramine instead of 0.413 mg/kg/day.

3. Modelling an average Maintenance dose of 12 mg/kg/day for cannabidiol (Section 4.2.4)
   The EAG modelled an average Maintenance dose of 12 mg/kg/day for cannabidiol instead of 16 mg/kg/day.
4. Informing health state occupancies for fenfluramine based on clinical trial data in the first year (Section 4.2.6).
   The EAG informed health state occupancy in the first year of the economic model based on the observed clinical trial data rather than the modelled transition probabilities.
5. Maintained treatment effect for fenfluramine after the observed period (Section 4.2.6).
   The EAG assumed that the fenfluramine treatment effect is maintained instead of increased after the observed period.
6. Deteriorating transition probability to model treatment effect waning based on all patients still on treatment in months 9 to 12 (Section 4.2.6).
   The EAG applied a deteriorating transition probability based on all patients still on treatment in months 9 to 12 to model treatment effect waning instead of only including the patients that stayed in their health state or deteriorated in that period.
7. Modelling the fenfluramine stopping rule in line with NICE TA615 (Section 4.2.6).
   The EAG applied a fenfluramine stopping rule where patients stopped treatment if they had less than 30% reduction in DSF over a period of 6 months instead of less than 25% reduction in DSF over a period of 3 months.
8. Applying a caregiver disutility approach to reflect caregiver HRQoL in the economic model (Section 4.2.8).
   The EAG applied a caregiver disutility approach to model the impact of caregiver HRQoL instead of assuming similar health state utility values for patients and their caregivers.
9. Modelling the impact of institutionalisation on caregiver HRQoL (Section 4.2.8).
   The EAG modelled the impact of institutionalisation on caregiver HRQoL by assuming 0.7 instead of 1.8 caregivers for institutionalised patients.
10. Including the cost of institutionalisation as part of the base-case analysis (Section 4.2.9).
    The EAG included the costs of institutionalisation in its base-case, whereas the company included it as a scenario analysis.
11. Applying the severity modifier (x1.7) to patient QALYs only (Section 4.2.10).
    The EAG applied the severity modifier (x1.7) to patient QALYs only instead of also applying it to caregiver QALYs.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

12. Applying treatment effect waning to 80% of patients (Section 4.2.6).
    The EAG applied treatment effect waning to 80% of patients instead of 5.2% of patients in both the fenfluramine + SoC and cannabidiol + clobazam + SoC arms.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on FE highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Model structure based on relative reductions in drop-seizures instead of absolute seizure frequency.	4.2.2	Methods	An updated economic model and scenario analysis using health states which are categorised by absolute seizure frequency instead of relative reduction in seizure frequency.	+/-	No	An updated economic model and scenario analysis using health states which are categorized by absolute seizure frequency instead of relative reduction in seizure frequency.
Uncertainty regarding the Maintenance dose of fenfluramine and cannabidiol.	4.2.4	Bias and indirectness	The EAG preferred Maintenance doses of 0.5 and 12 mg/kg/day for fenfluramine and cannabidiol, respectively.	+	Partly	Supporting clinical evidence and expert opinion on the appropriate recommended dose for LGS patients in the UK.
Uncertainty regarding the extrapolation of the fenfluramine + SoC treatment effect.	4.2.6	Methods	The EAG preferred to use a stable treatment effectiveness after the observed period (as for cannabidiol + clobazam + SoC).	+	Partly	The treatment effect of fenfluramine + SoC should be observed over a longer time period.
Discrepancy between clinical trial state occupancy and model state occupancy for fenfluramine + SoC.	4.2.6	Methods	Use state occupancies for fenfluramine + SoC directly derived from clinical trial state occupancies, in line with the comparators.	-	Partly	Provide exact patient numbers per health state to accurately model probabilistic outcomes.
Uncertainty in the modelling of patient HRQoL.	4.2.8	Bias and indirectness	Further justification on whether the study of Verdian et al. incorporated all relevant domains of generic HRQoL. Informing health state utilities based on the QOLCE-16 data from Study 1601[2] and the OLE study.[27]	+/-	No	Further justification regarding the face validity of the relatively low health state utilities currently used compared to the scores from the QOLCE-16 instrument.

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Plausibility of the approach for the modelling of caregiver HRQoL.	4.2.8	Methods	A caregiver disutility approach, in line with TA614, to model caregiver HRQoL.	+	Partly	Justification regarding why Auvin et al.[42] was used for the calculation of the caregiver disutilities in the company's scenario analysis.
Uncertainty in the proportion of institutionalised patients and the lack of modelling its impact on caregiver HRQoL.	4.2.8 and 4.2.9	Bias and indirectness	Further justification and evidence to support the assumption that 10% of LGS patients would be institutionalised when reaching the age of 18 years old. The EAG assumed 1.8 caregivers for the 90% of patients not institutionalised and 0.7 caregivers for the 10 % of institutionalised patients.	+	Partly	Further justification and evidence to support the assumption that 10% of LGS patients would be institutionalised when reaching the age of 18 years old.
Application of severity modifier to caregiver QALYs	4.2.10	Methods	Apply severity modifier to patient QALYs only.	+	Yes	N/A

[a]Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored

EAG = Evidence Assessment Group; FE = fixing errors; FV = fixing violations; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; kg = kilogram; LGS = Lennox-Gastaut syndrome; mg = milligram; MJ = matters of judgement; N/A = not applicable; OLE = open label extension; QOLCE = quality of life in childhood epilepsy; SoC = standard of care; TA = Technical Assessment; UK = United Kingdom

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 (DSA) and Table 6.3 (PSA) show how individual changes impact the results, the combined effect of all changes simultaneously, and the exploratory scenario analyses. The submitted model file contains technical details on the analyses performed by the EAG (e.g., the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic EAG base-case – pairwise results

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incr. costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
Company base-case												
Fenfluramine + SoC	[redacted]	1.30	2.39	3.68	6.26							
CBD + CLB + SoC	[redacted]	1.01	1.85	2.86	4.86	[redacted]	0.82	1.40	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.78	[redacted]	2.05	3.48	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 1. Fixing error - Diarrhoea AE cost												
Fenfluramine + SoC	[redacted]	1.30	2.39	3.68	6.26							
CBD + CLB + SoC	[redacted]	1.01	1.85	2.86	4.86	[redacted]	0.82	1.40	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.78	[redacted]	2.05	3.48	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 2. Matter of Judgement - 0.5 mg/kg/day average fenfluramine Maintenance dosage												
Fenfluramine + SoC	[redacted]	1.30	2.39	3.68	6.26							
CBD + CLB + SoC	[redacted]	1.01	1.85	2.86	4.86	[redacted]	0.82	1.40	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.78	[redacted]	2.05	3.48	[redacted]	[redacted]	[redacted]	[redacted]

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incr. costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
EAG Analysis 3. Matter of Judgement – 12 mg/kg/day average cannabidiol Maintenance dosage												
Fenfluramine + SoC	[redacted]	1.30	2.39	3.68	6.26							
CBD + CLB + SoC	[redacted]	1.01	1.85	2.86	4.86	[redacted]	0.82	1.40	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.78	[redacted]	2.05	3.48	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 4. Matter of Judgement – Fenfluramine state occupancies from trial data in first year												
Fenfluramine + SoC	[redacted]	1.21	2.24	3.45	5.86							
CBD + CLB + SoC	[redacted]	1.01	1.85	2.86	4.86	[redacted]	0.59	1.00	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.78	[redacted]	1.82	3.09	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 5. Matter of Judgement - Maintained fenfluramine treatment effect after observed period												
Fenfluramine + SoC	[redacted]	0.98	1.82	2.80	4.76							
CBD + CLB + SoC	[redacted]	1.01	1.85	2.86	4.86	[redacted]	-0.06	-0.10	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.78	[redacted]	1.17	1.98	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 6. Matter of Judgement - Treatment waning using deteriorating transition probabilities based on all patients on treatment												
Fenfluramine + SoC	[redacted]	1.33	2.45	3.78	6.43							
CBD + CLB + SoC	[redacted]	1.02	1.87	2.89	4.92	[redacted]	0.89	1.52	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.78	[redacted]	2.15	3.66	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 7. Matter of Judgement - Stopping rule 30% at 6 months												
Fenfluramine + SoC	[redacted]	1.61	2.95	4.56	7.76							

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incr. costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
CBD + CLB + SoC	[redacted]	1.21	2.22	3.43	5.83	[redacted]	1.13	1.93	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.60	1.13	1.73	2.94	[redacted]	2.83	4.82	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 8. Caregiver disutility approach based on Lo et al.[41]												
Fenfluramine + SoC	[redacted]	1.30	-21.08	-19.78	-33.63							
CBD + CLB + SoC	[redacted]	1.01	-21.36	-20.36	-34.60	[redacted]	0.57	0.97	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	-21.72	-21.15	-35.95	[redacted]	1.36	2.32	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 9. Matter of Judgement - Lower caregiver (dis)utility in case of institutionalisation												
Fenfluramine + SoC	[redacted]	1.30	2.06	3.36	5.71							
CBD + CLB + SoC	[redacted]	1.01	1.68	2.69	4.57	[redacted]	0.67	1.13	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.01	1.58	2.69	[redacted]	1.78	3.02	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 10. Matter of Judgement – Inclusion of institutionalisation costs												
Fenfluramine + SoC	[redacted]	1.30	2.39	3.68	6.26							
CBD + CLB + SoC	[redacted]	1.01	1.85	2.86	4.86	[redacted]	0.82	1.40	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.78	[redacted]	2.05	3.48	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 11. Matter of Judgement - Severity modifier applied to patients only												
Fenfluramine + SoC	[redacted]	1.30	2.39	3.68	4.59							
CBD + CLB + SoC	[redacted]	1.01	1.85	2.86	3.56	[redacted]	0.82	1.03	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.06	1.63	2.03	[redacted]	2.05	2.56	[redacted]	[redacted]	[redacted]	[redacted]

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incr. costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
EAG base-case analysis												
Fenfluramine + SoC	[redacted]	1.16	-19.94	-18.78	-17.97							
CBD + CLB + SoC	[redacted]	1.23	-19.94	-18.71	-17.85	[redacted]	-0.07	-0.11	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.60	-20.57	-19.96	-19.54	[redacted]	1.18	1.57	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 12. Exploratory Scenario - Treatment waning applied to 80% of patients												
Fenfluramine + SoC	[redacted]	0.87	-20.34	-19.48	-18.87							
CBD + CLB + SoC	[redacted]	0.91	-20.33	-19.42	-18.78	[redacted]	-0.06	-0.09	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.60	-20.57	-19.96	-19.54	[redacted]	0.49	0.67	[redacted]	[redacted]	[redacted]	[redacted]

AEs = adverse events; CBD + CLB = cannabidiol + clobazam; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Incr = incremental; kg = kilogram; mg = milligram; NHB = net health benefit; QALY = quality-adjusted life year; SoC = standard of care; SM = severity modifier

Table 6.3: Probabilistic EAG base-case – pairwise results

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incr. costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
Company base-case												
Fenfluramine + SoC	[redacted]	1.29	2.39	3.68	6.26							
CBD + CLB + SoC	[redacted]	1.00	1.86	2.86	4.87	[redacted]	0.817	1.39	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.08	1.66	2.82	[redacted]	2.023	3.44	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 1. Fixing error - Diarrhoea AE cost												
Fenfluramine + SoC	[redacted]	1.29	2.40	3.69	6.27							
CBD + CLB + SoC	[redacted]	1.00	1.87	2.87	4.89	[redacted]	0.812	1.38	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.09	1.66	2.82	[redacted]	2.026	3.44	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 2. Matter of Judgement - 0.5 mg/kg/day average fenfluramine Maintenance dosage												
Fenfluramine + SoC	[redacted]	1.29	2.40	3.69	6.27							
CBD + CLB + SoC	[redacted]	1.00	1.87	2.87	4.89	[redacted]	0.812	1.38	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.09	1.66	2.82	[redacted]	2.026	3.44	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 3. Matter of Judgement – 12 mg/kg/day average cannabidiol Maintenance dosage												
Fenfluramine + SoC	[redacted]	1.29	2.40	3.69	6.27							
CBD + CLB + SoC	[redacted]	1.00	1.87	2.87	4.88	[redacted]	0.812	1.38	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.09	1.66	2.82	[redacted]	2.026	3.44	[redacted]	[redacted]	[redacted]	[redacted]

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incr. costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
EAG Analysis 4. Matter of Judgement – Fenfluramine state occupancies from trial data in first year												
Fenfluramine + SoC	[redacted]	1.20	2.24	3.44	5.84							
CBD + CLB + SoC	[redacted]	1.00	1.87	2.87	4.89	[redacted]	0.561	0.95	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.09	1.66	2.82	[redacted]	1.775	3.02	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 5. Matter of Judgement – Maintained fenfluramine treatment effect after observed period												
Fenfluramine + SoC	[redacted]	0.99	1.85	2.84	4.82							
CBD + CLB + SoC	[redacted]	1.00	1.87	2.87	4.89	[redacted]	-0.04	-0.06	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.09	1.66	2.82	[redacted]	1.18	2.00	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 6. Matter of Judgement - Treatment waning using deteriorating transition probabilities based on all patients												
Fenfluramine + SoC	[redacted]	1.36	2.52	3.88	6.59							
CBD + CLB + SoC	[redacted]	1.03	1.91	2.94	5.00	[redacted]	0.938	1.60	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.09	1.66	2.82	[redacted]	2.217	3.77	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 7. Matter of Judgement - Stopping rule 30% at 6 months												
Fenfluramine + SoC	[redacted]	1.59	2.95	4.54	7.72							
CBD + CLB + SoC	[redacted]	1.20	2.24	3.44	5.85	[redacted]	1.102	1.87	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.61	1.15	1.76	3.00	[redacted]	2.779	4.73	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 8. Caregiver disutility approach based on Lo et al.[41]												
Fenfluramine + SoC	[redacted]	1.29	-21.44	-20.15	-34.25							

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incr. costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
CBD + CLB + SoC	[redacted]	1.00	-21.72	-20.72	-35.22	[redacted]	0.569	0.97	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	-22.08	-21.51	-36.56	[redacted]	1.358	2.31	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 9. Matter of Judgement - Lower caregiver (dis)utility in case of institutionalisation												
Fenfluramine + SoC	[redacted]	1.29	2.08	3.37	5.73							
CBD + CLB + SoC	[redacted]	1.00	1.70	2.71	4.60	[redacted]	0.66	1.13	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.03	1.61	2.73	[redacted]	1.76	3.00	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 10. Matter of Judgement – Inclusion of institutionalisation costs												
Fenfluramine + SoC	[redacted]	1.29	2.40	3.69	6.27							
CBD + CLB + SoC	[redacted]	1.00	1.87	2.87	4.89	[redacted]	0.81	1.38	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.09	1.66	2.82	[redacted]	2.03	3.44	[redacted]	[redacted]	[redacted]	[redacted]
EAG Analysis 11. Matter of Judgement - Severity modifier applied to patients only												
Fenfluramine + SoC	[redacted]	1.29	2.40	3.69	4.59							
CBD + CLB + SoC	[redacted]	1.00	1.87	2.87	3.58	[redacted]	0.81	1.01	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.57	1.09	1.66	2.06	[redacted]	2.03	2.53	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case analysis												
Fenfluramine + SoC	[redacted]	1.18	-20.27	-19.09	-18.27							
CBD + CLB + SoC	[redacted]	1.24	-20.26	-19.02	-18.16	[redacted]	-0.07	-0.11	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.61	-20.91	-20.30	-19.87	[redacted]	1.21	1.60	[redacted]	[redacted]	[redacted]	[redacted]

Technology	Total costs (£)	Patient QALYs	Caregiver QALYs	Total QALYs	Total QALYs (incl. SM)	Incr. costs (£)	Incr. QALYs	Incr. QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)	NHB (£30,000 threshold)	NHB (£30,000 threshold) with SM
EAG Analysis 12. Exploratory Scenario - Treatment waning applied to 80% of patients												
Fenfluramine + SoC	[redacted]	0.88	-20.68	-19.80	-19.18							
CBD + CLB + SoC	[redacted]	0.93	-20.66	-19.74	-19.09	[redacted]	-0.06	-0.09	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	0.61	-20.91	-20.30	-19.87	[redacted]	0.50	0.69	[redacted]	[redacted]	[redacted]	[redacted]

AEs = adverse events; CBD + CLB = cannabidiol + clobazam; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; kg = kilogram; mg = milligram; NHB = net health benefit; QALY = quality-adjusted life year; SoC = standard of care; SM = severity modifier

6.3 EAG's preferred assumptions

The estimated EAG base-case ICERs (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, were [redacted] (versus cannabidiol + clobazam + SoC) and [redacted] (versus SoC) per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities for fenfluramine + SoC versus cannabidiol + clobazam + SoC of [redacted] at willingness to pay (WTP) thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were assuming a maintained instead of increasing fenfluramine treatment effect after the observed period, and assuming different average Maintenance doses for fenfluramine and cannabidiol. The ICER increased most in the scenario analysis with alternative assumptions regarding the proportion of patients experiencing waning of the fenfluramine treatment effect.

6.4 Conclusions of the cost effectiveness section

The company's cost effectiveness model largely complied with the NICE reference case. The only deviation from the NICE reference case related to the fact that the EQ-5D health state descriptions in the Verdian et al. vignette study were not directly provided by patients living with the condition and utility values may therefore differ from the health status of actual LGS patients. The most prominent issues highlighted by the EAG are shown in the key issue tables in Section 1.5.

The first important limitation was that the Markov model developed by the company was structured based on the percentage reduction in DSF rather than on the absolute number of seizures. This likely resulted in patients 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. Second, there was uncertainty regarding the average fenfluramine and cannabidiol Maintenance doses, which are key model drivers. Doses in the fenfluramine and cannabidiol trials varied, and the company's modelled doses were not in line with the suggested doses by UK clinical experts during an advisory board meeting, nor in line with the SmPC recommended doses. In addition, the company's assumption of an increased treatment effect for fenfluramine plus SoC after the observed study period (i.e., from cycle 5 to 9) while assuming a stable treatment effect for cannabidiol + clobazam plus SoC was considered questionable. Next to that, the fenfluramine plus SoC treatment effect during the observed study period was overestimated due to a discrepancy between the clinical trial versus modelled health state occupancy. Regarding HRQoL, there were concerns about the suitability of the patient utility values presented in the CS[1] due to limitations related to the use of vignette studies. In addition, the company's approach of modelling caregiver HRQoL (assuming that the HRQoL of caregivers equals the HRQoL of the LGS patient) seemed unrealistic and overestimated the impact of mortality. Related to that, caregiver burden was expected to reduce for patients that are institutionalised, but the company neglected the impact of institutionalisation on caregiver HRQoL and only modelled the impact on costs. The company assumed an institutionalisation rate of 10% based on NICE TA615, but it was unclear whether this percentage was representative of UK clinical practice and should hence be further justified and supported by evidence. Finally, the company's application of the severity modifier to both patient and caregiver QALYs contradicted the EAGs understanding that the severity modifier should be applied solely to the patient QALYs, consistent with the patient population utilised when calculating the QALY shortfall.

The CS[1] base-case ICERs (probabilistic) were [redacted] (versus cannabidiol + clobazam + SoC) and [redacted] (versus SoC). The estimated EAG base-case ICERs (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, were [redacted] (versus cannabidiol + clobazam + SoC) and [redacted] (versus SoC) per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities for fenfluramine + SoC versus cannabidiol + clobazam + SoC of [redacted] at

WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were assuming a maintained instead of increasing fenfluramine treatment effect after the observed period, and assuming different average Maintenance doses for fenfluramine and cannabidiol. The ICER increased most in the scenario analysis with alternative assumptions regarding the proportion of patients experiencing waning of the fenfluramine treatment effect.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of fenfluramine + SoC, which can be partly resolved by the company by conducting further analyses. This includes providing a model structure based on absolute seizure frequencies, supporting clinical evidence on the appropriate average fenfluramine and cannabidiol Maintenance doses for LGS patients in the UK, clinical evidence of the fenfluramine + SoC treatment effect over a longer observed time period, further justification regarding the face validity of the health state utilities currently used compared to the scores from the QOLCE-16 instrument, and further justification and evidence to support the assumption that 10% of LGS patients would be institutionalised when reaching the age of 18 years old. Therefore, the EAG believes that the CS[1] nor the EAG report contains an unbiased ICER of fenfluramine + SoC compared with the relevant comparators.

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Single Technology Appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 1 November 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 EAG report's Key issue 1: The comparator definition in the decision problem is too narrow

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 15, Table 1.2, first row: *"The company restricted their specific comparator to CBD + CLB + SoC on the premise that only CBD + CLB + SoC has been evaluated in an STA by NICE as a 3rd line therapy"*	The company highlighted that this was the premise upon which CBD+CLB+SoC has been evaluated in NICE TA615, but this was not the only reason, as detailed in the answer of the clarification questions **A6.** The company suggests the following amendment: *"The company restricted their specific comparator to CBD + CLB + SoC on the premise that only CBD + CLB + SoC has been evaluated in an STA by NICE as a 3rd line therapy, and it is also the only therapy with sufficient trial data to permit a robust comparison. The other ASMs and the non-pharmaceutical treatments are not considered as comparators but constitute the SoC 'basket.' "*	The statement implies that the company purposefully restricted the specific comparator and did not consider 3rd line therapies for LGS. However, this is inaccurate as the 3rd line therapies have been included in the model within the SoC arm, and evidence has been provided regarding the inability to include trials for the clobazam, rufinamide, and topiramate based on NICE methodological specifications for conducting indirect treatment comparison (ITC). Further reasons to include are: - The fact that alternative 3rd line therapies: clobazam, rufinamide and topiramate are indeed evaluated as SoC within the ASM basket of treatments; we could not compare these 3rd line options separately in the CEM as specific data from their trials	Not a factual inaccuracy as the EAG were (at this point in the report) referring only to the inclusion of the alternative treatment comparators in the decision problem, and were not referring to the additional issue of their inclusion into the NMA. Therefore, the company's arguments explaining why the alternative treatments were not included in the NMA are not relevant at this point in the report. What is proposed in the decision problem should not pre-suppose the evidence. The decision problem should define the evidence that is to be systematically reviewed, rather than the decision problem being defined by a review that has already

		such as standard errors, reporting all outcome measures relevant to the model are not available. For example, incorporating rufinamide NMA results into the model would mean only having a comparison vs fenfluramine for the 50% reduction in drop seizure frequency measure in a patient population for rufinamide with missing information on baseline seizure frequency and number of prior ASMs used within its trial. This would introduce multiple levels of implausible conclusions on the cost-effectiveness of fenfluramine - What are considered as separate third line treatment options are not what are used as specific third line treatment options in clinical practice. As eluded by clincians in the advisory board, patients have tried many of the treatments considered as 3rd line	taken place. Therefore, regardless of whether the company justifications for the omission of the other 3rd line comparators from the NMA are correct, these other 3rd line comparators should still have been fully considered and proposed in the decision problem. In addition, the fact that the other 3rd line comparators were part of the SoC basket does not compensate for the lack of a proper comparison between alternative treatments. This is because the existence of these treatments within the SoC baskets will provide little or no information that informs their relative efficacy: in each of the double blinded randomised studies that constitute the evidence for fenfluramine and the other treatments, it is to be expected that the SoC baskets in each arm will be

		(rufinamide, topiramate and clobazam) even before a diagnosis of LGS has been made. They also have been tried on patients before considering fenfluramine as a treatment option. This is evident from fenfluramine's pivotal trial, as the median number of ASMs used previously was 7 (range 1-20). The most common ASMs included topiramate (57%), clobazam (47%) and rufinamide (44%). It is evident that approximately half of all patients have already tried these treatment options prior to the introduction of fenfluramine, therefore on this basis alone, considering each as separate comparators would not apply to half of the LGS patient population, raising further concerns on the plausbility of making these comparisons. - Unlike any of the trials for rufinamide, topiramde and	highly comparable. Therefore, no useful conclusions will be able to be drawn about the relative efficacy of the treatments contained within the SoC baskets. Please see the KSR comments to issue 4, for further discussion on the issue of whether the NMA should have been restricted or extended to all 9 RCTs.

		clobazam, the patient characteristics, concomitant ASMs used, prior therapies are most closely aligned for fenfluramines postioning with cannabidiol plus clobazam, as per the NMA feasibility assessment. There are also further core reasons why rufinamide, clobazam and topiramte were excluded at the NMA feasibility stage. For example, Rufinamide (via Arzimanoglou et al, 2016) had outcomes only reported at 26 weeks, and its open label study only reported outcomes in paediatric populations aged 1 to <4 years old. For clobazam (via Conry et al, 2009) outcomes were only reported at 7 weeks and placebo response rates observed were substantially higher across efficacy endpoints compared to other trials. - Trials for rufinamide, clobazam and topiramate did not report	

		any important patient characteristics elements including: baseline seizure frequency, number of prior ASMs used, and for clobazam and topiramate, the number of concomitant ASM use. Hence their exclusion from the NMA is valid due to comparability issues. - In Cannabidiol's appraisal for LGS in TA615, this same issue was raised by the EAG. However the EAG specifically agreed as written within committee papers that ",it is unlikely that data would be available to support indirect treatment comparisons or mixed treatment comparisons of cannabidiol versus individual AEDs or specific combinations of AEDs". Given the same level of information is available in fenfluramine's submission for LGS, it would be discriminative and unfair to request these comparisons to be made when previously the	

		3rd line treatments in question were considered to be appropriate within the 'basket' of usual care and NMAs were not considered. The correct level of data is still unavailable to make these comparisons.	

Issue 2 EAG report's Key issue 1: The comparator definition in the decision problem is too narrow

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 15, Table 1.2, third row: "NMA demonstrated that some of these alternative treatments may have greater efficacy than fenfluramine"	The company suggests the following amendment: *"The extended NMA analysis which has failed the feasibility assessment due to failure to report important patient characteristics such as baseline seizure frequency, the number of prior ASMs and the number of concomitant ASM and failed to report all targeted outcomes for alternative treatments, have shown that some of these alternative treatments may have marginally better results than fenfluramine in some of the NMA outcomes".*	Stating that the NMA demonstrated that some of the alternative treatments may have greater efficacy than fenfluramine is factually incorrect as it ignores the fact that this extended NMA included studies that failed the feasibility assessment. Additionally, it ignores the fact that this was not true for all outcomes. For instance median percentage reduction in frequency of GTC seizures were not available for rufinamide nor topiramate. Fenfluramine showed best	Not a factual inaccuracy. The NMA results showed that for some outcomes alternative treatments demonstrated better efficacy than fenfluramine. To allow for any uncertainties (including those arising from other outcomes producing the opposite direction of effect) the EAG appropriately used the word 'may'. The issue of whether the NMA should have included those extra

		results of all treatments for ≥50% reduction in drop seizure frequency and for discontinuation due to AE, fenfluramine showed better results than rufinamide, whereas topiramte trial did not report this outcome. Furthermore, it ignores the fact that studies constituting the NMA analysis cannot be deemed comparable, hence results are not indicative of their greater efficacy when taking the incomparability issue into consideration. To emphasise, patient characteristics were not sufficiently reported to deem these studies comparable according to transitivity principle of conducting a NMA. For instance, baseline seizure frequency may alter the results if they are lower than what is considered for fenfluramine. Additionally, the number of prior ASMs used and number of concomitant	studies does not affect the validity of the EAG statement, as the EAG is simply stating what the company's NMA demonstrated.

		ASM used were not reported. Considering that the practice of management of LGS using ASMs has changed drastically in the last few decades since some of these trials were conducted, we cannot assess comparability by omitting these important elements of patient characteristics. This also contributes to the incomparability issue of these studies.	

Issue 3 EAG report's key issue 7: Not all relevant comparisons in the ITC

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 19, Table 1.8, first row: *"The results from this extended NMA (including all nine RCTs) show that for >25% reduction in frequency of drop seizures, rufinamide and lamotrigine were likely to be superior to fenfluramine. Similarly, for >75% reduction in frequency*	The company suggests the following amendment: *"The results from this extended NMA (including eight RCTs, five of which has failed the feasibility assessment) show that for >25% reduction in frequency of drop seizures,* [redacted]	The extended NMA analysis includes eight studies and not nine. Jensen et al 1994 was excluded in both the base case NMA analysis and the extended NMA analysis. This was done due to high baseline seizure frequency (all seizures) reported in this study which may have had a	Not a factual inaccuracy. The EAG reference to 9 RCTs was not a factual inaccuracy at the time of writing, as in the company response to clarification a clear reference was made to 9 RCTs by the company:

of drop seizures, clobazam (1 mg/kg), rufinamide, cannabidiol (20 mg/kg) and topiramate were more likely than fenfluramine to be the best treatments. For all cause discontinuation, lamotrigine, felbamate, clobazam (1 mg/kg), clobazam (0.5 mg/kg), clobazam (0.25 mg/kg) and cannabidiol (10 mg/kg) were all likely to be superior to fenfluramine"	[redacted]. *For the >75% reduction in frequency of drop seizure* [redacted] *and* [redacted]*".*	major impact on treatment outcomes in the NMA analysis. It is also important to note the incomparable studies included in this analysis and the fact that they did not pass the feasibility assessment. All cause discontinuation was not an outcome in the base case analysis NMA nor the model, only discontinuation due to AE, so it is not accurate to cite this outcome in this context. Cannabidiol is already considered in the base case analysis, so it is misleading to mention it here as it may imply that it was not considered. Regarding the >25% reduction in frequency of drop seizures outcome, [redacted]	"*The NMA report provided in the reference pack (UCB data on file NMA report) included the extended (broader) network analysis in Appendix F (including data from 9 RCTs)*." All cause discontinuation is an important outcome in the context of evaluating the adverse effects of fenfluramine (which is a decision problem outcome), and therefore it was appropriate for the EAG to discuss this outcome in the clinical efficacy section of the report, regardless of whether it was used in the base case analysis. Including cannabidiol in the discussion does not constitute a factual inaccuracy – it is, in fact,

		Regarding the >75% reduction in frequency of drop seizure outcome, [redacted]	factually correct to do so. Conclusions reached by the EAG on relative efficacy were based on the NMA 'probability of being the best', and not through comparison of RRs. The EAG conclusions relating to the >25% and 75% reduction in frequency of drop seizures are therefore not a factual inaccuracy, given that it was made clear that 'probability of being the best treatment' was the measure being discussed.

Issue 4 EAG report's key issue 7: Not all relevant comparisons in the ITC

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 19, Table 1.8, first row: *"Overall, the fuller (nine RCTs) NMA provides information suggesting that the clinical benefits of other 3rd line ASMs may be superior to those of fenfluramine, an extremely important piece of information that appears to have not been discussed or considered in the CS"*	The company suggests the following amendment: *"Overall, the extended (eight RCTs) NMA provides information suggesting that* [redacted] *to those of fenfluramine, however it should be noted t that this NMA includes additional 5 RCTs that failed the feasibility assessment as they did not report patient characteristics nor all relevant outcomes. This important piece of information has been discussed in the CS feasibility assessment section 2.9.2 and its associated subsections".*	The extended NMA analysis includes eight studies and not nine (see issue 3). The full results of the feasibility assessment which provided reasons for excluding the additional RCTs were discussed at length in the CS submission and in the EAG clarification questions. Major concerns were raised in the feasibility assessment, as the 5 excluded trials did not report key patient characteristics including: baseline seizure frequency, number of prior ASMs used, and number of concomitant ASMs used (see Table 16 in the CS Document B) and most of these excluded studies were dated from 20-30 years old.	Please see the EAG comments in the section above for the issue of whether we should have written 8 or 9 RCTs. The EAG do not consider the rationale provided (in the CS or the response to clarification) for the omission of the other 3rd line comparators from the NMA to be sufficient. This is explained in the report, section 3.3, as follows: "*The rationale given for the six additional exclusions was that these excluded RCTs did not report all outcomes of interest or "most characteristics relevant to the disease". It was also implied that the data from the*

			excluded trials were outdated. The final explanation for the inclusion of only three RCTs was that "cannabidiol is the most recently approved LGS medication and is a main comparator to fenfluramine". These explanations for the dramatic reduction of the scope of the NMA appear weak. A separate NMA is carried out for each outcome of interest and so each RCT should have been allowed to contribute to the NMA for any relevant outcome that it covered; excluding an RCT because it did not cover all of the relevant outcomes appears wasteful. Furthermore, the reasons related to patient characteristics and recency require considerable

			strengthening before they can adequately explain the six exclusions. Finally, the fact that cannabidiol has been most recently approved and is a common comparator to fenfluramine does not in any way justify the exclusion of other comparators." However, we have removed the section "*an extremely important piece of information that appears to have not been discussed or considered in the CS"* from Table 1.8 in the report.

Issue 5 EAG's report key issue 8: Model structure based on relative reductions in drop-seizures instead of absolute seizure frequency

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 20, Table 1.9, second row: *"A model structure based on absolute seizure frequency"*	The company suggests the following amendment: *"A model structure based on absolute seizure frequency would have been better in theory, but given the available clinical trial material and data available it was considered unviable to be developed".*	We have considered and discussed the possibility of having a model based on absolute seizure frequency but after careful study of available material this approach was not possible to implement. Reasons were provided in the CS and the EAG clarification questions as follows: Using absolute DSF values directly as health states in the model was not feasible in the current model due to the existence of comparators (CBD with clobazam +SoC) for which data was not publicly available (please see detailed discussion in Question B8). Indeed, in all pivotal trials, including the fenfluramine and CBD trials, the established primary	Not a factual inaccuracy.

		clinical endpoint is the percentage reduction in DSF. In addition, the primary rationale for using absolute drop seizures in previous NICE submissions, rather than percentages of decreases, lies in the associations between QoL and absolute DSF in conjunction with seizure-free days. It was possible in the CBD submission as no ITC was used, the only comparator being SoC (+placebo).	

Issue 6 Matter of Judgement no. 5 - Maintained treatment effect for fenfluramine after the observed period

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
There is a discrepancy between the EAG report ‘s description of the model modification due to matter of judgement no. 5, and the	We propose the EAG model is implemented as described in the report, by modifying cells 'Calc - TP - FFA'!E20:H23 to reflect the same methodology used in the cannabidiol treatment arm of the	How the EAG has implemented this change, currently results in waning starting at cycle 6 for fenfluramine and cycle 10 for cannabidiol and SoC. This results in an unrealistic advantage to the cannabidiol	The EAG agrees and amended the EAG model as proposed by the company.

actual changes done in the model shared by the EAG. The EAG report states the intention of implementing maintained efficacy in the fenfluramine arm as was done by the company in the cannabidiol arm, however, the implementation made by the EAG to the model sets waning of efficacy in the fenfluramine arm to start immediately after the observation period, whereas in the cannabidiol and SoC arms, waning starts 12 months (or 4 cycles) after the observation period. This modification in the EAG model does not simulate a maintenance of the treatment effect for fenfluramine, it simulates a decrease of treatment effect for fenfluramine due to waning in cycles where treatment effect is maintained for cannabidiol and SoC.	model, instead of modifying cell "Calc - TP - FFA E6".	treatment arm by maintaining treatment effect for cycles 6-9 while fenfluramine treated patients experience waning of efficacy much earlier, from cycle 6. Implementing this correction outlined by the company would result in the incremental QALYs changing from -0.16 to -0.11 (when considering the EAGs current preferred base-case assumptions). The Company acknowledges the rationale behind matter of judgement no. 5, which intends to uniformize the methodologies used in both the fenfluramine and cannabidiol treatment arms to model treatment effect after the observed period. The EAG proposed to achieve this by using cycle 5 state occupancy data in cycles 6-9. This was the approach used by the company in the cannabidiol arm of the	

This inaccuracy can be found on: 1. Page 145*: "Therefore, the EAG prefers a base-case analysis where the treatment effect for fenfluramine is maintained instead of increased after the observed period (i.e., in line with what was assumed for cannabidiol + clobazam + SoC)."* 2. Page 163: *"Maintained treatment effect for fenfluramine after the observed period (Section 4.2.6). The EAG assumed that the fenfluramine treatment effect is maintained instead of increased after the observed period."* 3. Page 167: Table 6.2: Deterministic EAG		trial given the absence of publicly available transition probability data that could be used to inform the model. However, the implementation of this point in the model provided by the EAG does not reflect the description provided in the report. In the model the efficacy duration of fenfluramine (cell "Calc - TP - FFA E6") has been modified from 27.5 to 15.5 months, while both cannabidiol and standard of care (SoC) treatment arms are assumed to remain at 27.5 months of efficacy. As a result, fenfluramine treated patients start experiencing treatment waning of efficacy at cycle 6, i.e., 4 cycles or 12 months before cannabidiol and SoC arms experience the same effect. From cycle 6 to 9 both cannabidiol and SoC experience maintained treatment effect, observed as equal state occupancies in	

base-case – pairwise results 4. Page 171: Table 6.3: Probabilistic EAG base-case – pairwise results 5. Any additional results that may be impacted by this modification, including the EAG base-case analysis.		cycles 6-9 as in cycle 5, while fenfluramine experiences waning of efficacy in cycles 6-9 and not maintained treatment effect as described in the report. Implementation of matter of judgement no. 5 provided in the EAG model results in an unrealistic advantage to the cannabidiol treatment arm by maintaining treatment effect for cycles 6-9 while fenfluramine treated patients experience waning of efficacy from cycle 6.	

Issue 7 Section 5.2 – Company's sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Inaccuracy in section 5.2, page 159: "*This was explained by the application of a dose cap of 26 mg/day to fenfluramine with no dose cap applied to cannabidiol. The dose cap for*	The transcribed section should be amended to clarify that the company took into consideration the cap of 20mg/kg/day in cannabidiol's daily dose in all the proposed analysis and that implementation of both cannabidiol and fenfluramine dosing caps follow	When discussing the results of the probabilistic sensitivity analysis cost-effectiveness plane, the company mentioned there is no maximum dose per day for cannabidiol, as the cap of	The EAG agrees that the current PSA does not exceed the cannabidiol dose cap as described in the SmPC, provided that the included dose of 16 mg/kg/day is held

cannabidiol is 20 mg/kg/day, which the company suggest could not be incorporated within the model. Failing to incorporate a dose cap in for cannabidiol and including one for fenfluramine is likely to underestimate the relative difference in treatment costs for fenfluramine + SoC versus cannabidiol + clobazam + SoC and subsequently bias the ICER in favour of fenfluramine + SoC.".	the guidance provided in the respective SmPCs. Thus, any indication of bias in the company's submission in relation to treatment costs and/or ICER should also be amended. The company suggests the following amendment: "*This was explained by the application of a dose cap of 26 mg/day to fenfluramine with no dose cap applied to cannabidiol as the daily cap of 20mg/kg/day described in the SmPC is above the dose used to treat patients in the model (16mg/kg/day). In the cannabidiol SmPC there is no reference to a daily cap independent on weight. On the other hand, fenfluramine has a daily cap of 26mg/day, independent of the weight of the patient. Both these caps are explicitly described in the respective SmPCs and have been respected in the implementation of the model".*	20mg/kg/day is dependent on weight and thus the daily dose increases exponentially with weight. On the other hand, fenfluramine has a daily cap of 26mg/day which is independent of the weight of the patient, meaning that beyond a certain number, the daily dose will not increase exponentially with weight. Both these caps are explicitly described in the respective SmPCs and have been respected in the implementation of the model, which should clear the company's methodology of any bias. The error implies bias in the company's submission, when all the guidelines for drug dosing and capping were implemented in the model and company's submission according to the respective SmPCs data.	fixed. The EAG believes that dose parameters should be incorporated into the PSA and varied probabilistically, with a dose cap of 20 mg/kg/day being applied to cannabidiol and maintaining the dose cap for fenfluramine of 26 mg/day, as already incorporated. Further, the cost per mg parameters currently included in the PSA would preferably be held fixed. As such, the EAG have amended section 5.2 of the EAG report.

Issue 8 Section 2. Critique of company's definition of decision problem – intervention

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 26, Table 2.1, second row 5th column: *"No justification is currently given of the dosages chosen for evaluation"*	The company suggests the following amendment: *"Justification for the dosages chosen for evaluation were provided by the company."*	This statement is inaccurate. Whenever a dosage for fenfluramine was chosen, a justification for that dose was provided whether within the CS or clarification questions. Justification for the fenfluramine dosage chosen has been provided in the addendum clarification answers provided on 21st of September 2023 (see page 17). The following information were provided: *Given new evidence that we have obtained on the actual average dose for fenfluramine in the OLE study, we would like to use maintenance dose of [redacted] mg/kg/day within the base case of the model*	Not a factual inaccuracy. The EAG was referring to the doses used in the fenfluramine RCT trial (0.2 and 0.7 mg/kg), which were not justified in the CS as far as can be seen. To clarify that the comment is related to the RCT (and not the economic evaluation) the EAG have amended the statement to: "*No justification is currently given of the dosages chosen for RCT evaluation*"

		instead of 0.5mg/kg/day suggested in the original CS base case. This was done for several reasons. First, *According to the fenfluramine OLE study, efficacy continued to improve at lower average doses of fenfluramine than what was used in study 1601, which justifies the use of a lower dose within the model. Furthermore, in the fenfluramine OLE study, doses were titrated based on tolerability and safety, which is more reflective of clinical practice. Finally, the company sought further insight from UK clinical experts, they advised that the dosing and efficacy seen within Dravet Syndrome is likely to be reflected in the LGS indication (10). A dose of [redacted] mg/kg/day is comparable to the average dose of patients in Dravet Syndrome that are not on stiripentol (0.44mg/kg/day) . Therefore, the dose of [redacted]*	

		mg/kg/day was used in the new base case to closely reflect the dose that is expected to be utilised in practice. *Please note: average doses from the fenfluramine OLE study were accepted for use within the economic model within NICE's appraisal of Fenfluramine for use in Dravet Syndrome (TA808).*	

Issue 9 Section 2. Critique of company's definition of decision problem - Special considerations including issues related to equity or equality

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 28, table 2.1, last row, 5th column: "*No comments were made by the company in this respect"*	The company suggests the following amendment: *"The Comment provided by the company noted that there were no issues to highlight regarding special considerations related to equity or equality".*	The company did provide a comment on the equity issue by stating that there were no special considerations regarding equity or equality to be emphasised within the decision problem.	Thank you for highlighting this error, which we have amended.

Issue 10 Section 2. Critique of company's definition of decision problem - Special considerations including issues related to equity or equality

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 28, table 2.1, last row, 5th column: *"The assumption that efficacy in reducing severe seizures automatically implies efficacy in reducing less severe seizures may not necessarily hold"*	The company suggests the following amendment: to consider removing this statement as we did not make this assumption and did not state this in the CS.	This assumption is not accurate and was not stated by the company. The company did not state that efficacy seen in reducing severe seizures implies less severe seizures are also reduced. We only provided rationale for not capturing less severe seizures in the model, as it is difficult to measure less severe seizures and hence, we could not incorporate it in the CE analysis. Non-drop seizure outcomes were considered part of these less severe seizures and in this outcome fenfluramine trial showed positive results. For that specific reason, we mentioned that we are being conservative by not	[Please note that the statement referred to did not occur in Table 2.1, but in Table 2.4 and in the text on page 32.] The EAG does not see the statement as a factual inaccuracy. The EAG did not mean to imply that this assumption would necessarily be made by company. However, it was felt important to pre-emptively raise arguments against what could be seen to be a potential assumption in some readers, which might otherwise serve to falsely counteract the disadvantages of not

		considering less severe seizures in the model.	recording other seizure outcomes.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
ID1651 Fenfluramine EAG report 24102023MT [CON], page 86, second bullet point	*"non-pharmacological therapies (≥15% of patients overall) included the following: vagus nerve stimulation (VNS) (82 patients [31.2%]), paracetamol (57 patients (21.7%]), and melatonin (51 patients [19.4%]). It is noted in the trial that no patients received concomitant stiripentol (STP)".*	*"non-pharmacological therapies [redacted] of patients overall) included the following: vagus nerve stimulation (VNS) ([redacted] patients [redacted]), paracetamol ([redacted] patients ([redacted] and melatonin ([redacted] patients [redacted]). It is noted in the trial that no patients received concomitant stiripentol (STP)".*	Thank you – this has been amended
ID1651 Fenfluramine EAG report 24102023MT [CON], page 140, point a) (multiple mentions), **Page 139; page 153; page 164**	*"however, the justification for the decrease in dose from 0.5 mg/kg/day to 0.413 mg/kg /day for fenfluramine was insufficient and seemed to contradict to the statement of clinical experts originally provided by the company, in which they stated that "0.5 mg/kg/day of FFA [fenfluramine] on average is realistic".*	*"however, the justification for the decrease in dose from 0.5 mg/kg/day to [redacted] mg/kg /day for fenfluramine was insufficient and seemed to contradict to the statement of clinical experts originally provided by the company, in which they stated that "0.5 mg/kg/day of FFA*	Thank you – this has been amended

Please note: anywhere there is mention of the actual average dose for fenfluramine should be highlighted for confidential information as this information is not in the public domain and there is no intention to publish this information in the near future.		*[fenfluramine] on average is realistic".*	
ID1651 Fenfluramine EAG report 24102023MT [CON], **page 19, Table 1.8, first row, second column (multiple mentions);** **page 24, section 1.7, third paragraph;** **page 104;** **page 127, 4th paragraph.** *Please note: anywhere there are descriptions or interpretations from the extended NMA are considered as confidential as this information is not in*	*"The results from this extended NMA (including all nine RCTs) show that for >25% reduction in frequency of drop seizures, rufinamide and lamotrigine were likely to be superior to fenfluramine. Similarly, for >75% reduction in frequency of drop seizures, clobazam (1 mg/kg), rufinamide, cannabidiol (20 mg/kg) and topiramate were more likely than fenfluramine to be the best treatments. For all cause discontinuation, lamotrigine, felbamate, clobazam (1 mg/kg), clobazam (0.5 mg/kg), clobazam (0.25 mg/kg) and cannabidiol (10 mg/kg) were all likely to be superior to fenfluramine".*	*"The results from this extended NMA (including all nine RCTs) show [redacted], rufinamide and lamotrigine were [redacted] to fenfluramine. Similarly [redacted], clobazam (1 mg/kg), rufinamide, cannabidiol (20 mg/kg) and topiramate were [redacted] fenfluramine to be [redacted], lamotrigine, felbamate, clobazam (1 mg/kg), clobazam (0.5 mg/kg), clobazam (0.25*	Thank you – this has been amended

the public domain and there is no intention to publish this information in the near future.		*mg/kg) and cannabidiol (10 mg/kg) were [redacted]”.*	

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fenfluramine hydrochloride for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Additional scenarios post-EAG report

Scenarios run by NICE technical team and checked by EAG (KSR)

Contains redacted data

Table 1: Company's preferred assumptions applied to EAG base case

Scenario	Technology	Total costs (£)	Total QALYs	Total QALYs (inc. SM)	Incremental costs (£)	Incremental QALYs	Incremental QALYs (incl. SM)	ICER (£/QALY)	ICER (£/QALY) (incl. SM)
EAG base case	Fenfluramine +SoC	[redacted]	-18.78	-17.97	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-18.71	-17.85	[redacted]	-0.07	-0.11	[redacted]	[redacted]
	SoC	[redacted]	-19.96	-19.54	[redacted]	1.18	1.57	[redacted]	[redacted]
Analysis 1– 0.413 mg/kg/day average fenfluramine maintenance dosage	Fenfluramine +SoC	[redacted]	-18.78	-17.97	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-18.71	-17.85	[redacted]	-0.07	-0.11	[redacted]	[redacted]
	SoC	[redacted]	-19.96	-19.54	[redacted]	1.18	1.57	[redacted]	[redacted]
Analysis 2 – 16mg/kg/day average cannabidiol maintenance dosage	Fenfluramine +SoC	[redacted]	-18.78	-17.97	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-18.71	-17.85	[redacted]	-0.07	-0.11	[redacted]	[redacted]
	SoC	[redacted]	-19.96	-19.54	[redacted]	1.18	1.57	[redacted]	[redacted]

Analysis 3 – Calculated TPs between states based on study 1601 OLE	Fenfluramine +SoC	[redacted]	-18.70	-17.85	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-18.71	-17.85	[redacted]	0.02	0.00	[redacted]	[redacted]
	SoC	[redacted]	-19.96	-19.54	[redacted]	1.27	1.69	[redacted]	[redacted]
Analysis 4 – Fenfluramine treatment effect assumed to increase after observed period	Fenfluramine +SoC	[redacted]	-17.99	-16.91	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-18.71	-17.85	[redacted]	0.73	0.94	[redacted]	[redacted]
	SoC	[redacted]	-19.96	-19.54	[redacted]	1.98	2.63	[redacted]	[redacted]
Analysis 5 – Treatment waning TPs calculated only using patients that stayed in health state or deteriorated from month 9 to 12	Fenfluramine +SoC	[redacted]	-18.85	-18.05	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-18.78	-17.93	[redacted]	-0.07	-0.12	[redacted]	[redacted]
	SoC	[redacted]	-19.96	-19.54	[redacted]	1.12	1.49	[redacted]	[redacted]
Analysis 6 – Stopping rule 25% at 3 months	Fenfluramine +SoC	[redacted]	-19.24	-18.57	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-19.18	-18.47	[redacted]	-0.06	-0.10	[redacted]	[redacted]

	SoC	[redacted]	-20.07	-19.67	[redacted]	0.82	1.10	[redacted]	[redacted]
Analysis 7 – Caregiver utility approach based on Verdian et al.	Fenfluramine +SoC	[redacted]	3.01	3.83	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	3.20	4.06	[redacted]	-0.19	-0.23	[redacted]	[redacted]
	SoC	[redacted]	1.67	2.09	[redacted]	1.34	1.73	[redacted]	[redacted]
Analysis 8 – No impact of institutionalisation on caregiver disutility	Fenfluramine +SoC	[redacted]	-19.97	-19.16	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-19.90	-19.04	[redacted]	-0.08	-0.12	[redacted]	[redacted]
	SoC	[redacted]	-21.05	-20.63	[redacted]	1.07	1.46	[redacted]	[redacted]
Analysis 9 – Exclusion of institutionalisation costs	Fenfluramine +SoC	[redacted]	-18.78	-17.97	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-18.71	-17.85	[redacted]	-0.07	-0.11	[redacted]	[redacted]
	SoC	[redacted]	-19.96	-19.54	[redacted]	1.18	1.57	[redacted]	[redacted]
Analysis 10 – Severity modifier applied to patients and caregivers	Fenfluramine +SoC	[redacted]	-18.78	-31.93	-	-	-	-	-
	Cannabidiol with clobazam + SoC	[redacted]	-18.71	-31.81	[redacted]	-0.07	-0.12	[redacted]	[redacted]
	SoC	[redacted]	-19.96	-33.94	[redacted]	1.18	2.01	[redacted]	[redacted]