Fenfluramine for treating seizures associated with Lennox–Gastaut syndrome in people 2 years and over (ID1651)

For zoom – redacted

Technology appraisal committee D [6 March 2024]

Chair: Raju Reddy

External assessment group: Kleijnen Systematic Reviews (KSR)

Technical team: Dilan Savani, Lizzie Walker, Linda Landells

Company: UCB

Background on Lennox-Gastaut syndrome

RECAP

Symptoms and prognosis

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

Epidemiology

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

Diagnosis

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

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

RECAP

Fenfluramine (Fintepla, UCB)

Table: Fenfluramine key information

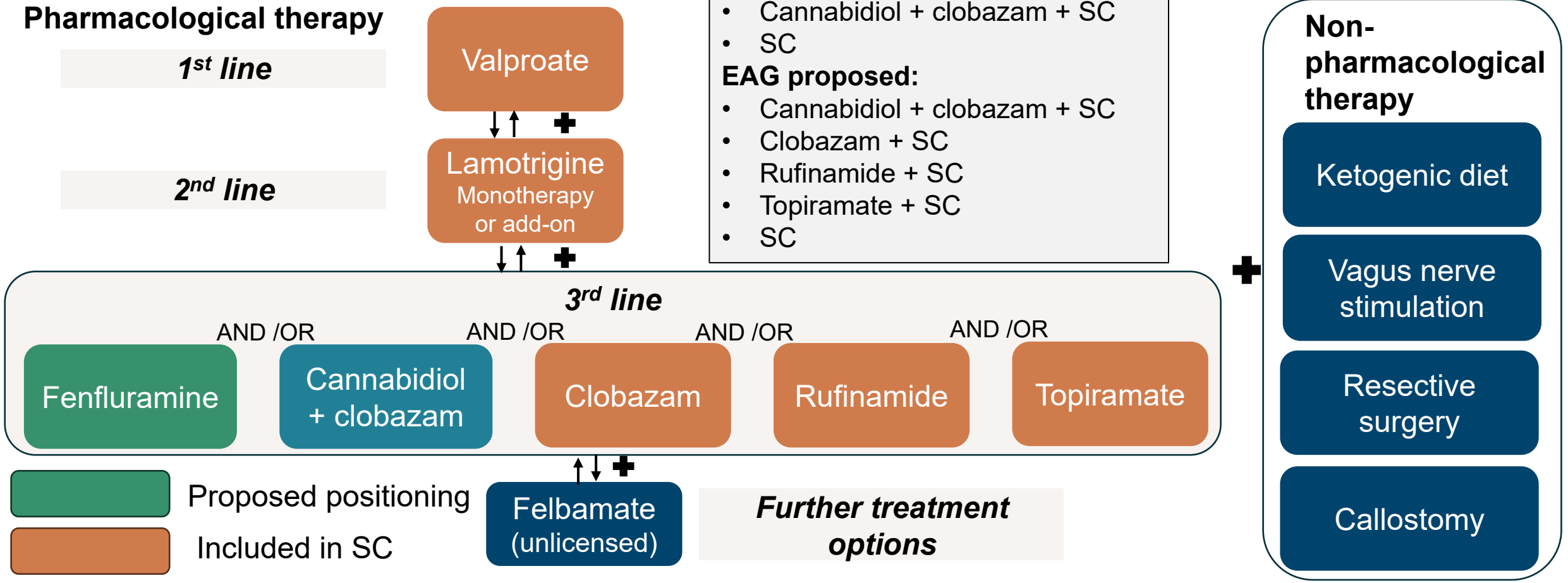
Marketing authorisation	• Indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome as an add-on therapy to other antiepileptic medicines for patients aged 2 years and older • GB marketing authorisation: July 2023
Mechanism of action	• Precise anticonvulsant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

Treatment pathway

RECAP

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

Figure: LGS treatment pathway



Relevant comparators:

Company:

- Cannabidiol + clobazam + SC
- SC

EAG proposed:

- Cannabidiol + clobazam + SC
- Clobazam + SC
- Rufinamide + SC
- Topiramate + SC
- SC

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

Has committee heard anything that would alter the appropriate comparators identified at ACM1?

NICE SC, Standard care

Key clinical trials

RECAP

Table: Study 1601 RCT and OLE key trial information

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

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

Key issues from ACM1 (1)

Recommendation after ACM 1

Fenfluramine is not recommended, within its marketing authorisation, for treating seizures associated with Lennox-Gastaut syndrome (LGS) as an add-on to other antiseizure medicines for people 2 years and over.

Table: Key issues

Issue	Resolved?	Notes	ICER impact
Modelling fenfluramine treatment effect during OLE	No, to discuss	Imputation analysis required	Potentially large
Extrapolation of fenfluramine treatment effect	No, to discuss	Imputation analysis required	Potentially large
Treatment waning	No, to discuss	Additional evidence requested	Potentially large
Maintenance doses and wastage	No, to discuss	Requested additional scenarios	Moderate
Plausibility of approach for modelling caregiver HRQoL	Partially, see appendix	Committee preferred carer disutility approach using values from Lo et al. applied in manner that did not result in negative QALYs	-

See appendix for full list of ACM1 committee considerations

ACM, Appraisal committee meeting; ICER, Incremental cost-effectiveness ratio; LGS, Lennox-Gastaut syndrome; QALY, quality-adjusted life year

Key issues from ACM1 (2)

Table: Key issues

Issue	Resolved?	Notes
Relevant comparators	Yes	Cannabidiol plus clobazam plus SC and SC alone are appropriate comparators
Appropriateness of model structure based on relative reduction in drop seizures	Yes	Uncertain but acceptable for decision making
Utility values		
• Uncertainty in the modelling of patient HRQoL	Yes	Uncertain but acceptable for decision making
• Application of severity modifier to caregiver QALYs	Yes	Company accepted committee's assumptions
Modelling residential care		
• Impact of residential care on caregiver HRQoL	Yes	Company accepted committee's assumptions
• Inclusion of residential care costs	Yes	Company accepted committee's assumptions

ACM, Appraisal committee meeting; HRQoL, Health-related quality of life; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Key issues from ACM1 (3)

Table: Key issues

Issue	Resolved?	Notes
Inclusion of seizure frequency and seizure severity	Yes	Uncertain but acceptable for decision making
Study validity		
• Measurement validity of eDiary	Yes	Uncertain but acceptable for decision making
• External validity of trial – age, gender, ethnicity	Yes	Uncertain but acceptable for decision making
• Internal and external validity of trial – concomitant treatments	Yes	Uncertain but acceptable for decision making

ACM, Appraisal committee meeting; ICER, Incremental cost-effectiveness ratio; SC, Standard care

Consultation responses to draft guidance summary (1)

Unmet need

TSA, clinical expert and patient expert:

- Standard treatments provide long term seizure control in ~0.7% people with LGS → people often increase dosage and/or increase number of medications to try to achieve seizure control
- Fenfluramine would particularly benefit people who develop tolerance to antiepileptic medication
- Many unable to receive cannabidiol plus clobazam due to previous adverse reaction to clobazam
- Research by PHE shows:
  - Number of annual deaths of epilepsy patients increased by 70% between 2001 to 2014
  - Mortality rate in people with epilepsy correlated to deprivation
  - With right treatment, over 60% of people with epilepsy could stop having seizures altogether

Modelling assumptions/parameters

Company (UCB):

- Provides updated base case incorporating several of committee's preferred assumptions following ACM1 and various scenario analyses requested by committee
- Used alternative method to implement stopping rule– see appendix for further details

Jazz Pharma (manufacturer of cannabidiol):

- Questions company's modelling approach for cycle 6-9
- Comments on dosage considerations for fenfluramine and cannabidiol, including wastage assumptions

See appendix for further responses

Consultation responses to draft guidance summary (2)

Uncaptured benefits in model

Company (UCB)

States there are several uncaptured benefits in model:

- Reduction in duration of drop and non-drop seizures
- Benefits of treatment on the quality of life of siblings and other family members of people with LGS
- Improvements in child's intellectual development due to fewer seizures
- Motor function and executive function improvements
- Work productivity loss may be reduced with treatment, also providing wider societal benefit

Clinical evidence

Company (UCB)

- Unable to provide estimate of:
  - People ineligible for cannabidiol plus clobazam
  - Proportions of people using clobazam, rufinamide and topiramate for LGS in NHS clinical practice
- Provides data on the per-arm use of non-pharmacological treatments in Study 1601
- Study validity:
  - Provided more evidence on validity of the eDiary
  - No evidence that age, gender and/or ethnicity may be treatment effect modifiers
- Conducted imputation analyses based on all people who received open-label fenfluramine and used resulting data to perform additional ITC

See appendix for further responses

Consultation responses to draft guidance summary (3)

Carer impact

TSA, patient expert and web comment:

- Substantial impact on carers' physical and mental health, as well as secondary challenges in employment, financial security, social interactions and wider family unit
- Seizure reduction reduces burden on carer
- Patient death has substantial impact on carers
- Early access programme to fenfluramine in Dravet syndrome shows improvement in several outcomes for carers following fenfluramine treatment
- Residential care:
  - If people with LGS are in residential care, the number of hours of care required would remain the same (just different people providing care)
  - Percentage of people requiring residential care would increase over time as carers become older

NICE comment

- At ACM1, committee concluded that LGS severely affects the quality of life of people with the condition, their families and carers→ committee agreed that it is appropriate to include impact of carers in modelling

See appendix for further responses

Consultation responses to draft guidance summary (4)

Wording

Jazz Pharma (manufacturer of cannabidiol):

- ITC results should be interpreted with caution due to heterogeneity
- Lack of statistical significance in comparisons between fenfluramine and cannabidiol plus clobazam

Equality

Clinical expert

- Fenfluramine is available in other countries so inequality issue if not available in NHS

See appendix for further responses

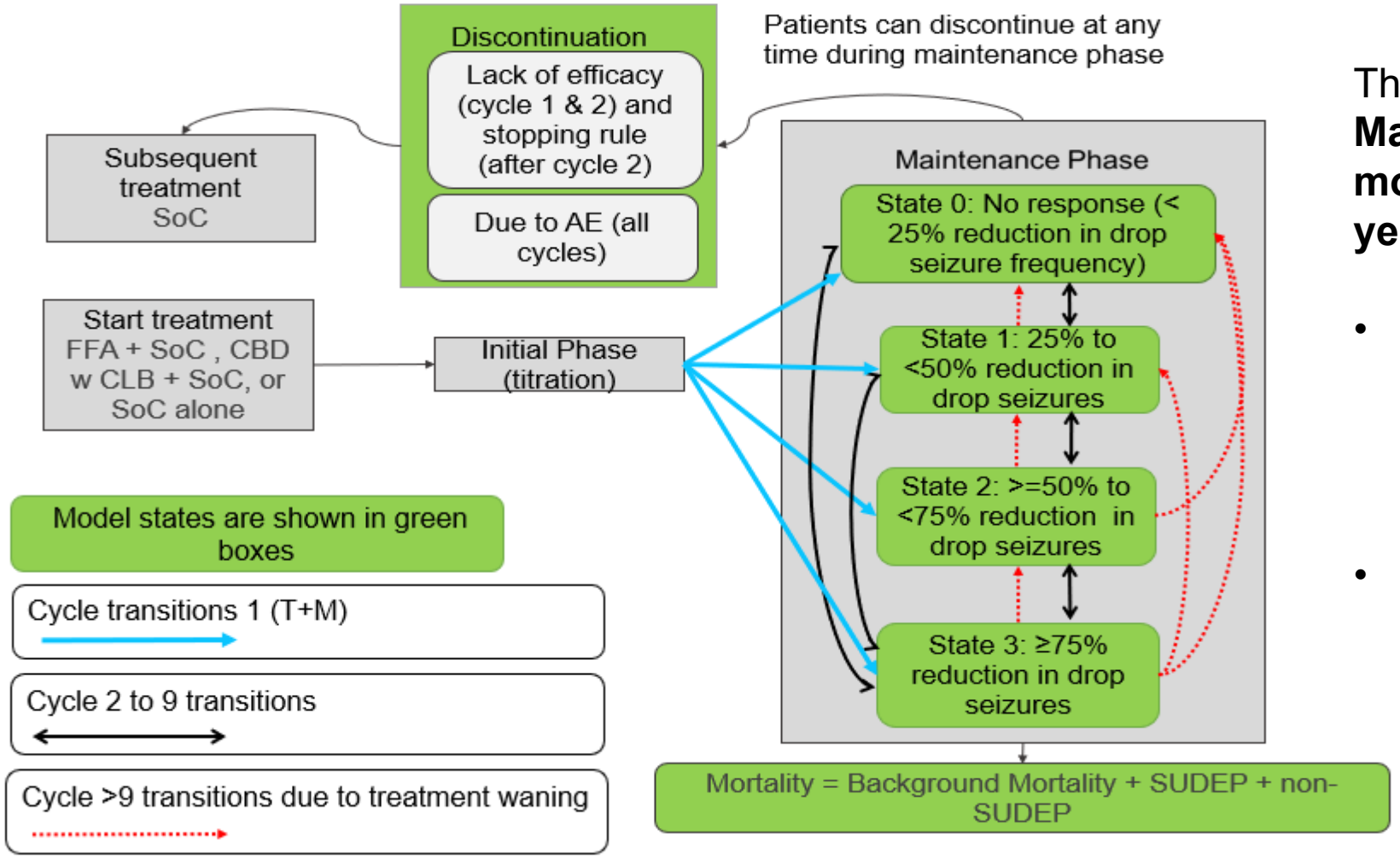
Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

RECAP

Figure: Company's model structure



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

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

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

Summary of changes to efficacy assumptions (1)

Red = changes from original company base case

FFA + SC efficacy	Original company base case	Company base case after ACM1	EAG base case after ACM1
Cycle 1	TPs based on RR from NMA	TPs based on RR from NMA	TPs based on RR from NMA
Cycles 2-5	TPs based on Study 1601 OLE	State occupancies from updated NMA of OLEs	State occupancies based on treated population of OLEs
Cycles 6-9	TPs assumed to equal TPs observed in cycle 4-5	State occupancies assumed to equal those observed in cycle 4-5	State occupancies assumed to equal those observed in cycle 4-5
Cycles 10+	Change in state occupancy based on treatment waning, discontinuation and death	Change in state occupancy based on treatment waning, discontinuation and death	Change in state occupancy based on treatment waning, discontinuation and death

ACM, Appraisal committee meeting; FFA, Fenfluramine; LGS, Lennox-Gastaut syndrome; NMA, Network meta-analysis; OLE, Open-label extension; RR, Risk ratio; SC, Standard care; TP, Transition probability

Summary of changes to efficacy assumptions (2)

Red = changes from original company base case

CBD + CLB + SC efficacy	Original company base case	Company base case after ACM1	EAG base case after ACM1
Cycle 1	TPs based on a RR from NMA results (weighted average of 10 and 20 mg/kg/day subgroups)	TPs based on a RR from NMA results (weighted average of 10 and 20 mg/kg/day subgroups)	TPs based on RR from NMA
Cycles 2-5	State occupancy based on CBD + CLB + SC trial OLE	State occupancies from updated NMA of OLEs	State occupancies based on treated population of OLEs
Cycles 6-9	State occupancies assumed to equal those observed in cycle 4-5	State occupancies assumed to equal those observed in cycle 4-5	State occupancies assumed to equal those observed in cycle 4-5
Cycles 10+	Change in state occupancy based on treatment waning, discontinuation and death	Change in state occupancy based on treatment waning, discontinuation and death	Change in state occupancy based on treatment waning, discontinuation and death

ACM, Appraisal committee meeting; CBD, Cannabidiol; CLB, Clobazam; LGS, Lennox-Gastaut syndrome; NMA, Network meta-analysis; OLE, Open-label extension; RR, Risk ratio; SC, Standard care; TP, Transition probability

Key issue: Modelling fenfluramine treatment effect during OLE (1)

Company did NMA based on safety population from fenfluramine OLE and ITT population from cannabidiol OLE

Recap

- At ACM1, committee concerned that state occupancy data for fenfluramine was only available for people who had a report measured at each time point and the potential bias this introduced
- Committee would like to see an analysis that includes all 247 people that entered Study 1601 OLE that accounts for missing data points (i.e. attrition) and an analysis using the same methodology and assumptions to account for missing data points in cannabidiol OLE

Company

- Identified cannabidiol OLE data for ITT population based on LOCF analyses within Thiele et al. 2019
- Conducted imputation analyses (LOCF method) using Study 1601 OLE safety population
- Updated base case using the results of the ITC to model fenfluramine (plus SC) and cannabidiol plus clobazam (plus SC) treatment effect for cycles 2-5 - see appendix for methods overview
- ITC results summary: fenfluramine ranked 1st for ≥25%, and ≥50% reduction in DSF; cannabidiol ranked 1st for ≥75% reduction in DSF. Credible intervals overlap for fenfluramine and cannabidiol - see appendix for results
- Fenfluramine effectiveness in clinical practice likely to be similar to RCT data (based on RWE in Spain), whereas cannabidiol effectiveness likely to be lower than in RCTs (based on clinical expert opinion)

ACM, Appraisal committee meeting; DSF, Drop seizure frequency; ITC, Indirect treatment comparison; ITT, Intention-to-treat; LOCF, Last observation carried forward; OLE, Open-label extension; RCT, Randomised controlled trial; SC, Supportive care

Key issue: Modelling fenfluramine treatment effect during OLE (2)

Company did NMA based on safety population from fenfluramine OLE and ITT population from cannabidiol OLE

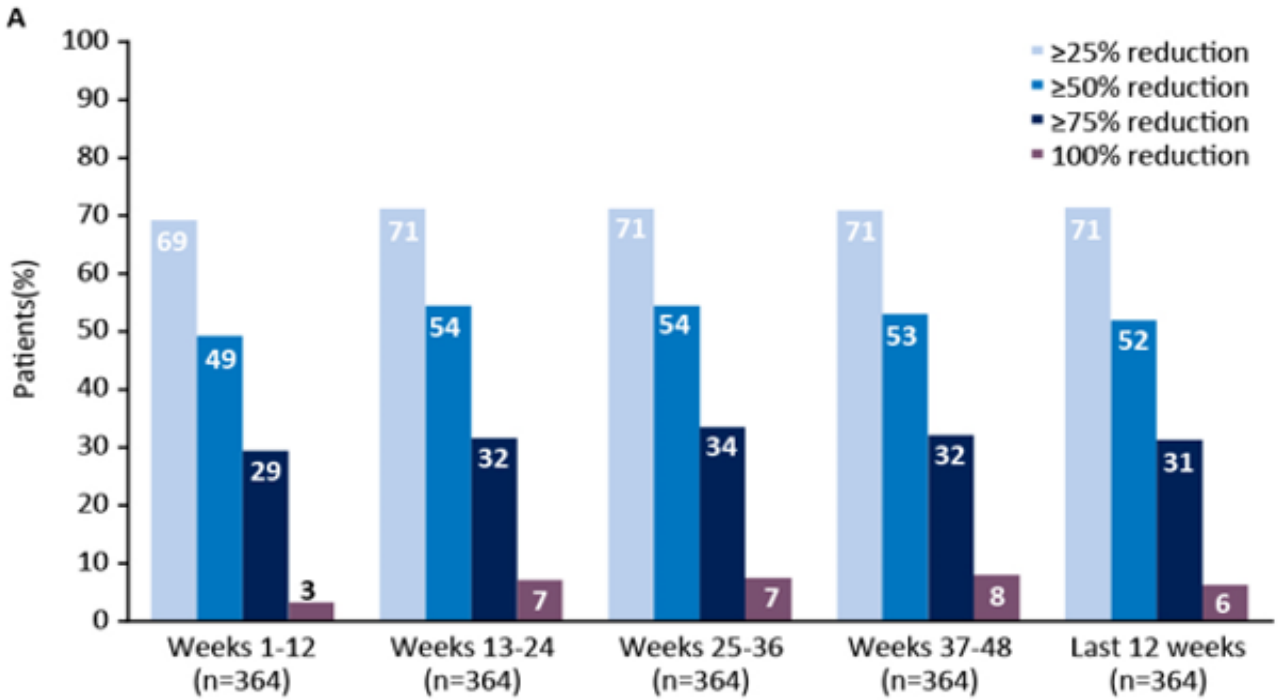
Figure: OLE data for safety population based on LOCF analyses for fenfluramine

Fenfluramine

[redacted]

Figure: OLE data for ITT population based on LOCF analyses for cannabidiol

Cannabidiol



NICE

ITT, Intention-to-treat; LOCF, Last observation carried forward; OLE, Open-label extension

Key issue: Modelling fenfluramine treatment effect during OLE (3)

Company did NMA based on safety population from fenfluramine OLE and ITT population from cannabidiol OLE

EAG comments

- Company included cannabidiol alone rather than cannabidiol + clobazam as comparator in NMA
- Company have presented results for each treatment against placebo, rather than an indirect comparison of cannabidiol + clobazam + SC vs fenfluramine + SC
- No meta-regression so analysis provides limited information → direct estimates similar to company's NMA results
- Company assumes that the placebo value for both trials remains unchanged after 12 weeks
  - Purpose of placebo arm is to determine true treatment effect
  - EAG cannot reach a conclusion as to the pattern of change in placebo effect given that it has not been observed→ potential for bias
- Reiterates that clobazam alone, rufinamide and topiramate should be included in ITC (NMA)
- Clinical heterogeneity between populations does not appear to have been properly investigated
- Notes company's initial modelling approach resulted in higher total patient and carer QALYs gained in the observed period (cycles 2-5) for cannabidiol + clobazam + SC compared to fenfluramine + SC. Updated approach using OLE ITC data favours fenfluramine + SC
- Given limitations with ITC, prefers to retain original base case in which health state occupancies are based on treated population state occupancy data from OLEs

EAG, External assessment group; ITC, Indirect treatment comparison; ITT, Intention-to-treat; NMA, Network meta-analysis; OLE, Open-label extension

Key issue: Modelling fenfluramine treatment effect during OLE (4)

Company did NMA based on safety population from fenfluramine OLE and ITT population from cannabidiol OLE

Other considerations

Jazz Pharma:

- Cannabidiol was a concomitant medication in 4.9% (n=12) of people at baseline in Study 1601 OLE. Questions if this has been accounted for

Is the company's approach using the OLE ITC (NMA) results to model health state occupancy for cycles 2-5 for both treatment arms appropriate?

EAG, External assessment group; ITC, Indirect treatment comparison; ITT, Intention-to-treat; NMA, Network meta-analysis; OLE, Open-label extension

Key issue: Extrapolation of fenfluramine treatment effect (1)

Company updated base case to maintained treatment effect for both fenfluramine + SC and cannabidiol + clobazam + SC in cycles 6 to 9

Recap

- Observed period data (15 months) extrapolated out to 86-year modelled time horizon
- In CS, treatment effectiveness for fenfluramine + SC was assumed to increase after observed study period (cycles 6-9), while the treatment effectiveness for cannabidiol + clobazam + SC was assumed to be stable
- At ACM1, committee concluded that:
  - neither company's preferred assumption of increasing treatment effect, nor EAG's preferred assumption of maintained treatment effect, were consistent with Study 1601 OLE data when accounting for attrition
  - an analysis of Study 1601 OLE (n=247) accounting for missing data points was needed to inform the treatment effect for fenfluramine plus SC for cycles 6-9

Company

- Conducted imputation analyses (LOCF method) using Study 1601 OLE safety population
- Updated base case assumes treatment effect is maintained from cycles 6-9 (i.e. people stay in same health state as cycle 5 for cycles 6-9), for both fenfluramine + SC and cannabidiol + clobazam + SC.
- Provided 2 alternative scenarios:
  - assuming treatment maintained at average effect observed in cycles 2-5 in both treatment arms
  - assuming treatment effect maintained only until cycle 5 (and waning start at cycle 6) in both treatment arms

ACM, Appraisal committee meeting; EAG, External assessment group; ITC, Indirect treatment comparison; ITT, Intention-to-treat; LOCF, Last observation carried forward; NMA, Network meta-analysis; OLE, Open-label extension; SC, Supportive care

Key issue: Extrapolation of fenfluramine treatment effect (2)

Company updated base case to maintained treatment effect for both fenfluramine + SC and cannabidiol + clobazam + SC in cycles 6 to 9

EAG comments

- Agrees with assuming a maintained treatment effect for both arms
- However, all new analyses for the treatment effect of fenfluramine + SC and cannabidiol + clobazam + SC are conditional on modelling in cycles 2-5, which is informed by OLE ITC and is subject to limitations→ adds to uncertainty of extrapolation of treatment effect in cycles 6-9
- Prefers to retain original assumption of maintained treatment effect for both treatments in cycles 6-9 but based on preferred method for calculating treatment effect for cycles 2-5 (as outlined in 'Modelling fenfluramine treatment effect during OLE' slide)

Other considerations

Jazz Pharma:

- Questions company's original modelling approach in which transition probabilities for cycle 6-9 were based on last 3 months of Study 1601 OLE (cycles 4-5). Notes people were able to add concomitant treatments at this stage

What is the committee's preferred assumption for treatment effect extrapolation after the OLE period? Is it appropriate to assume people stay in the same health state as cycle 5 for cycles 6-9 in both treatment arms?

OLE, Open-label extension; SC, Supportive care

Key issue: Treatment waning

Company base case assumes 5.2% of people experience treatment waning from cycle 10 onwards in fenfluramine + SC and cannabidiol + clobazam + SC arms

Recap

- At ACM1, company and EAG differed in approach to calculating treatment waning transition probabilities
- Committee requested additional evidence to support company's assumption of 5.2% of people experiencing waning and concluded any analysis of OLE data to inform waning assumptions should account for data attrition

Company

- Updated base case method for calculating treatment waning probabilities to align with EAG's (calculated using all people on treatment from month 9-12, rather than only those that stayed in same health state or deteriorated)
- 5.2% based on % of people discontinuing due to lack of efficacy in the last cycle of fenfluramine OLE
- Observational study: people with LGS discontinue fenfluramine due to lack of efficacy at rate of 6.8%
- Lack of data to support waning assumptions→ conservative to assume equal waning for both to reduce bias
- Provided 2 scenarios assuming 19.6% and 30% of people experience waning and 3rd scenario in which 10% of people discontinue treatment every cycle from cycle 2

EAG comments

- Considers the company's assumption of 5.2% treatment waning implausibly low → translates 0.58% and 0.48% of people experiencing treatment waning in cycle 10 for fenfluramine and cannabidiol, respectively
- Retains assumption of 5.2% in base case but suggests that higher % waning may be more realistic

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

ACM, Appraisal committee meeting; EAG, External assessment group; NMA, Network meta-analysis; OLE, Open-label extension; SC, Supportive care

Key issue: Maintenance doses and wastage (1)

Company base case assumes maintenance dosage of 0.413mg/kg/day for fenfluramine and 14mg/kg/day for cannabidiol

Recap

- At ACM1, committee preferred to use mean dose from the Study 1601 OLE for fenfluramine maintenance dose and considered cannabidiol maintenance dosage for model was likely between 12 and 16 mg/kg/day
- Requested scenarios exploring wastage associated with both cannabidiol and fenfluramine treatment

Company

Fenfluramine maintenance dose

- 0.413 mg/kg/day is exact average dose (excluding people who received >0.7 mg/kg/day)
- Provided scenario in which dose of 0.7mg/kg/day assumed for cycle 1 of model but highlights that in clinical practice doses are gradually increased to the maximum tolerated dose, opposed to starting with maximum dose

Cannabidiol maintenance dose

- Updated base case to dose of 14 mg/kg/day but considers that average dose in clinical practice is closer to 16mg/kg/day given mean modal dose within cannabidiol OLE study (24 mg/kg/day) and clinical expert opinion
- Provided scenario analyses exploring cannabidiol maintenance doses of 12, 13, 15 and 16 mg/kg/day

Treatment wastage

- Provided 3 scenarios incorporating wastage: 1) assuming 5% wastage for fenfluramine and cannabidiol; 2) 5% wastage for fenfluramine and 10% for cannabidiol; 3) 0% wastage for fenfluramine and 10% for cannabidiol
- Appropriate to assume 0% wastage for fenfluramine and 10% for cannabidiol because cannabidiol is an oily liquid presented in a glass bottle (states fenfluramine is not oily and presented in plastic bottle)

ACM, Appraisal committee meeting; OLE, Open-label extension

Key issue: Maintenance doses and wastage (2)

Company base case assumes maintenance dosage of 0.413mg/kg/day for fenfluramine and 14mg/kg/day for cannabidiol

EAG comments

Fenfluramine maintenance dose

- People who received >0.7 mg/kg/day excluded from average maintenance dose used by company in revised model, because clinicians say people will not exceed the maximum stated dose in clinical practice. However:
  - people with mean daily dose lower than initial titration dose (0.2 mg/kg/day) included in company's calculation
  - people that received >0.7 mg/kg/day included in treatment effectiveness estimates
- So prefer to use average maintenance fenfluramine maintenance dose from Study 1601 OLE, including people who received >0.7 mg/kg/day ([redacted] mg/kg/day)

Cannabidiol maintenance dose

- Agrees that based on expert opinion the likely cannabidiol maintenance dose is between 12 and 16 mg/kg/day
- For base case, prefers to use maintenance dose of 12mg/kg/day to align with NICE TA615

Wastage

- Notes that assumed wastage percentages provided by company were not justified→ unsure whether any of the provided scenarios are reflective of clinical practice
- Assumes no wastage for fenfluramine or cannabidiol in base case

EAG, External assessment group; OLE, Open label extension; RCT, Randomised controlled trial

Key issue: Maintenance doses and wastage (3)

Company base case assumes maintenance dosage of 0.413mg/kg/day for fenfluramine and 14mg/kg/day for cannabidiol

Jazz Pharma:

- Cannabidiol RCTs show statistically significant reduction in number of drop/non-drop seizures at 10 mg/kg/day
- Maintenance dosage for cannabidiol should reflect dosage used in TA615 (12mg/kg/day)
- Similar containers for fenfluramine and cannabidiol and considers bottle breakage an isolated incident → unlikely any difference in wastage

What maintenance doses for fenfluramine and cannabidiol should be used in model and which wastage assumptions are most appropriate?

Summary of company and EAG base case assumptions (1)

Table: Assumptions in company and EAG base case

Assumption	Company updated base case	EAG base case
Fenfluramine model state occupancy cycles 2-5	State occupancies based on results of OLE ITC	Based on state occupancies in treated population of Study 1601 OLE
Fenfluramine treatment effect extrapolation (cycles 6-9)	Assumes people stay in same health state as cycle 5 for cycles 6-9	Assumes people stay in same health state as cycle 5 for cycles 6-9
Patient utility	Verdian et al.	Verdian et al.
Carer (dis)utility approach	Disutility approach using Lo et al.	Disutility approach using Lo et al.
Application of severity modifier	Modifier of 1.7 applied to only patient QALYs	Modifier of 1.7 applied to only patient QALYs
Fenfluramine maintenance dose	0.413 mg/kg/day	[redacted] mg/kg/day
Cannabidiol maintenance dose	14 mg/kg/day	12 mg/kg/day
Wastage	No wastage for fenfluramine or cannabidiol	No wastage for fenfluramine or cannabidiol

NICE EAG, Evidence Assessment Group; ITC, Indirect treatment comparison; OLE, Open-label extension; QALY, Quality-adjusted life year

Summary of company and EAG base case assumptions (2)

Table: Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Impact of residential care on caregiver dis(utility)	Reduced carer disutility – 0.7 carers for people requiring residential care	Reduced carer disutility – 0.7 carers for people requiring residential care
Residential care costs	Included	Included
Stopping rule	<30% reduction in DSF assessed every 6 months (updated implementation at draft guidance consultation- see appendix)	<30% reduction in DSF assessed every 6 months (prefers implementation as per original company model- see appendix)
Treatment waning transition probabilities	Calculated using all patients on treatment from month 9 to 12	Calculated using all patients on treatment from month 9 to 12
% of people experiencing treatment waning per year	5.2% for cycle 10 onwards	5.2% for cycle 10 onwards

NICE

DSF, Drop seizure frequency; EAG, Evidence Assessment Group; ITT, Intention to treat

Cost-effectiveness results

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

Results presented in part 2:

- Deterministic company base case* – above the threshold usually considered an acceptable use of NHS resources vs cannabidiol + clobazam + SC and vs SC
- Deterministic EAG base case – dominated versus cannabidiol + clobazam + SC; above the threshold usually considered an acceptable use of NHS resources versus SC

Scenarios requested by committee in draft guidance document will also be considered

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

EAG, Evidence Assessment Group; ICER, Incremental cost-effectiveness ratio; PAS, Patient access scheme; SC, Supportive care

NICE National Institute for Health and Care Excellence

Supplementary Appendix

Summary of appraisal to date (1)

Table: Committee considerations from ACM1

Issue	Committee's considerations	Updated/ provided?
Treatment options	Requested data on the proportion of people ineligible for cannabidiol plus clobazam	No
	Requested data on the proportion of people with LGS using clobazam, rufinamide and topiramate in NHS clinical practice	No
Proposed positioning and comparators	Positioning of fenfluramine plus SC in the treatment pathway in line with cannabidiol plus clobazam plus SC was appropriate	N/A
	Cannabidiol plus clobazam plus SC and SC alone are appropriate comparators	N/A
	Requested scenarios that considered clobazam, rufinamide and topiramate as separate comparators	No
NMA	Company's base case NMA suggests that fenfluramine plus SC demonstrates superior efficacy to cannabidiol plus clobazam plus SC and SC alone for outcomes except the ≥75% reduction in DSF outcome	N/A

ACM, Appraisal committee meeting; DSF, Drop seizure frequency; LGS, Lennox-Gastaut syndrome; NMA, Network meta-analysis; SC, Standard care

Summary of appraisal to date (2)

Table: Committee considerations from ACM1

Issue	Committee's considerations	Updated/ provided?
Study 1601 validity	Per-arm use of non-pharmacological treatments, validity of e-diary and lack of sub-group analysis on age, gender and ethnicity may add uncertainty	Yes
Model structure	Accepted company's modelling approach but model structure added uncertainty to cost-effectiveness estimates	N/A
	Absence of non-drop seizures from the model adds to the uncertainty around the economic analysis	N/A
Modelling treatment effect in OLE period (cycles 2 to 5)	Would like clarification on data used to populate cannabidiol plus clobazam plus SC health states for cycles 2 to 5	Yes
	Would like to see imputation analyses that include all 247 people that entered study 1601 OLE which account for attrition, and imputation analyses using the same methodology and assumptions used to account for missing data points applied to the cannabidiol OLE data as well	Partially*

*Used LOCF method for imputation rather than approach requested by committee

ACM, Appraisal committee meeting; ITT, Intention to treat; OLE, Open-label extension; SC, Standard care

Summary of appraisal to date (3)

Table: Committee considerations from ACM1

Issue	Committee's considerations	Updated/ provided?
Extrapolation of fenfluramine treatment effect	Imputation analyses of Study 1601 OLE data needed to inform treatment effect for fenfluramine plus SC for cycle 6 to cycle 9	Partially*
Treatment waning	Would like to see additional data or evidence to support the company's assumption of 5.2% of people experiencing treatment waning after cycle 9	Partially
	Any analysis of OLE data to inform treatment waning assumptions should account for data attrition as opposed to assuming data are missing at random	N/A
	Requested additional scenarios exploring different proportions of people experiencing treatment waning and a scenario with 10% of people per year discontinuing treatment	Yes
Patient utility values	Verdian et al. utility values are associated with substantial uncertainty but are likely the best available source of utility values given model structure	N/A
Carer utility values	Preferred carer disutility approach using carer utility values from Lo et al. but applied in a manner that did not result in negative QALYs	Partially

*Used LOCF method for imputation rather than approach requested by committee

ACM, Appraisal committee meeting; OLE, Open-label extension; QALY, Quality-adjusted life year; SC, Standard care

Summary of appraisal to date (4)

Table: Committee considerations from ACM1

Issue	Committee's considerations	Updated/ provided?
Fenfluramine maintenance dose	Would like clarification on how the 0.5 mg/kg/day dosage and the updated 0.413 mg/kg/day dosage were calculated	Yes
	Minded to prefer the use of the mean dose from the Study 1601 OLE but would also like to see a scenario in which the dose in cycle 1 reflects the mean dose in the 0.7mg/kg/day arm in Study 1601	Yes
Cannabidiol maintenance dose	The appropriate cannabidiol maintenance dosage for the model was likely between 12 and 16 mg/kg/day →would like to see scenario analyses exploring range of cannabidiol maintenance dosages	Yes
	Requested further data on the average maintenance dosage of cannabidiol used in NHS clinical practice	Partially
Wastage	Would like to see scenarios which account for expected wastage costs associated with both cannabidiol and fenfluramine treatment	Yes
Residential care	It was appropriate to include residential-care costs and to assume 0.7 carers for people needing residential care	Yes

ACM, Appraisal committee meeting; OLE, Open-label extension

Summary of appraisal to date (5)

Table: Committee considerations from ACM1

Issue	Committee's considerations	Updated/ provided?
Stopping rule	Stopping rule whereby fenfluramine is stopped if the DSF has not reduced by at least 30% from baseline, assessed every 6 months is reasonable	Yes
Pulmonary hypertension	It is appropriate not to model the cost of treatment for pulmonary arterial hypertension	N/A
Severity modifier	Only applying the severity weight of 1.7 to the patient QALYs was appropriate	Yes

ACM, Appraisal committee meeting; DSF, Drop seizure frequency; QALY, Quality-adjusted life year

Further consultation responses to draft guidance summary (1)

Recommendation

Clinical expert:

- Recommendation 'would not appear sound' - given uncertainties in economic modelling and request for further data, appropriate to re-examine recommendations prior to final guidance

Web comment:

- Disagrees with current recommendation given pharmacoresistant nature of LGS and limited treatment options. Highlights FDA and EMA have approved use of fenfluramine in LGS.

Clinical evidence

Web comment

- Additional sources of evidence for fenfluramine:
  - **Bishop et al. 2023:** fenfluramine associated with clinically meaningful improvements in everyday executive in adults with LGS
  - **Jensen at al. 2023:** data from early access programme to fenfluramine in Dravet Syndrome showing caregiver and clinician reported non-seizure related improvement for various outcomes

EMA; European Medicines Agency; FDA, Food and Drug Administration; LGS, Lennox-Gastaut syndrome

Further consultation responses to draft guidance summary (2)

Wording

Jazz Pharma (manufacturer of cannabidiol):

- Provides various comments requesting updates to wording in draft guidance

Clinical expert:

- States that all people with LGS have moderate to severe learning difficulties (contrasting with statement in guidance that people 'may' have learning difficulties).

OLE NMA summary

Methodology overview

- Following ACM1, company conducted an additional analyses based on ITT population from cannabidiol OLE and safety population from Study 1601 OLE corresponding to cycles 2-5 in the cost-effectiveness model
- Outcomes assessed were: ≥25% / ≥50% / ≥75% reduction in DSF
- Network consisted of fenfluramine, cannabidiol (with or without clobazam) and placebo from the OLE studies
- As OLE studies did not contain placebo control arms, company assumed that placebo rates in the key studies remained same during OLE period
- Both fixed-effects and random-effects models were assessed, but in line with the original NMA, the fixed effects model was selected
- Company confirmed safety population equivalent to OLE ITT population (all people who received open-label fenfluramine)

Base case NMA analysis results overview

- Fenfluramine ranked 1st for ≥25%, and ≥50% reduction in DSF
- Cannabidiol ranked 1st for ≥75% reduction in DSF
- Credible intervals overlap for fenfluramine and cannabidiol

ACM, Appraisal committee meeting; DSF, Drop seizure frequency; ITT, Intention to treat; NMA, Network meta-analysis; OLE, Open-label extension

Summary of efficacy results comparing fenfluramine and cannabidiol with placebo, fixed effects, all time points

	Treatment Arm	
Health State	**RR FFA versus Placebo (95% CrI)**	**RR CBD versus Placebo (95% CrI)**
Timepoint: After 3 months in OLE study (weeks 1-12)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 6 months in OLE study (weeks 13-24)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 9 months in OLE study (weeks 25-36)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]
Timepoint: After 12 months in OLE study (weeks 37-48)		
>= 25% response	[redacted]	[redacted]
>= 50% response	[redacted]	[redacted]
>= 75% response	[redacted]	[redacted]

CBD, Cannabidiol; CrI, Credible interval; FFA, Fenfluramine; LGS, Lennox-Gastaut syndrome; NMA, Network meta-analysis; OLE, Open-label extension; RR, Risk ratio

Stopping rule implementation

Draft guidance:

- Committee concluded a stopping rule whereby fenfluramine is stopped if DSF has not reduced
- by at least 30% from baseline, assessed every 6 months is reasonable
- EAG noted that stopping rule at 6 months appeared to be incorrectly implemented in model→ all people from health state 0 discontinued every 6 months, instead of only the people that were in health state 0 for 6 months
- Committee requested that company resolve this issue in the model

Company:

- Tracking of patients in the model not possible for cannabidiol as would require transition probabilities. So estimated proportion of people remaining in health state 0 and health state 1 from transition probabilities of people treated with fenfluramine during OLE study
- On average, 61.2% of people in health state 0 remain in health state 0, while 37.9% of patients in health state 1 remains in health state 1 following cycle
- As cycle length in model is 3 months, probability of remaining in health state 0 and health state 1 for 6 months is 37.5% (61.2%*61.2%) and 14.3% (37.9%*37.9%), respectively→ these probabilities are applied every cycle to both fenfluramine (plus SC) and cannabidiol plus clobazam (plus SC) arms to determine discontinuation rate due to lack of efficacy

EAG:

- Limitations with company's updated approach→ although sub-optimal EAG prefer using company's initial approach of modelling 6 month stopping rule

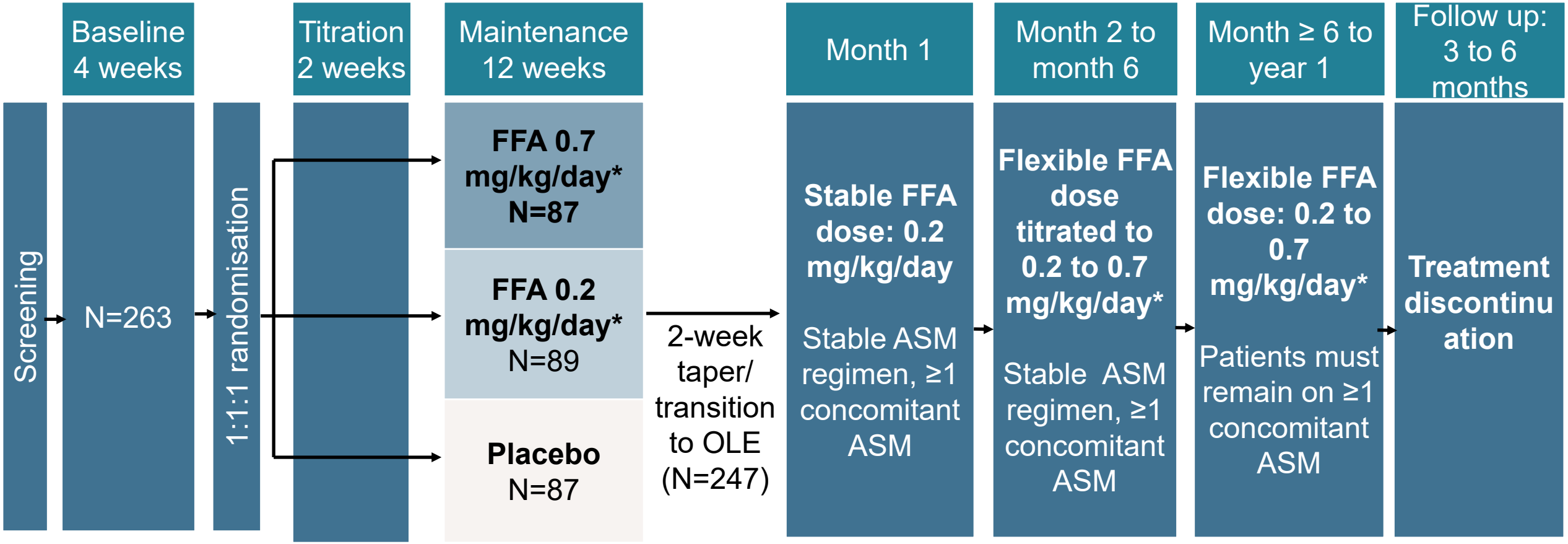
ACM, Appraisal committee meeting; DSF, Drop seizure frequency; EAG, Evidence assessment group; OLE, Open-label extension; SC, Standard care

RECAP

Study 1601 RCT and OLE design

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

Figure: Study 1601 and OLE design



* Maximum daily dose: 26 mg fenfluramine. Mean maintenance dose in OLE: 0.413 mg/kg/day

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

Study 1601 and OLE key results

RECAP

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

Table: Study 1601 key results

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

OLE

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

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

How company incorporated evidence into model at ACM1

RECAP

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

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

NMA, Network meta-analysis; OLE, Open label extension; RR, Risk ratio; SC, Standard of care; TP, Transition probability

Key issue: Caregiver utilities

Company: total negative QALYs are inherent to disutility approach in this case

Recap

- At ACM1, committee preferred a carer disutility approach using the Lo et al. carer utility values, but applied in a manner that does not result in negative QALYs

Company

- Updated base case using a carer disutility approach with Lo et al. values. Calculated difference between carer utility values and UK VAS norm value (0.828) to derive disutility values (resulting in negative QALYs)
- Negative QALYs inherent to disutility approach in this case, considering that people with LGS have very low QALYs and require more than 1 carer resulting in high disutilities
  - Negative QALYs were also observed in TA615 (company's base case after draft guidance consultation)
- Provides scenario analysis using baseline value of 0.78 (rather than 0.828) associated with the least severe health state from Auvin. et al 2021 to calculate disutility values

EAG comments

- Company's method of incorporating carer disutility values aligns with EAG's preferred approach. EAG's method also results in overall negative QALYs

Are committee satisfied with the company's application of carer disutility values using Lo et al.?

ACM, Appraisal committee meeting; EAG, External assessment group; LGS, Lennox-Gastaut syndrome QALY, Quality-adjusted life year; VAS, Visual analogue scale

Key issue: Caregiver utilities

RECAP

Table: Lo et al. caregiver utility values

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

Table: Lo et al. calculated caregiver TTO disutility values

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

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

LOCF imputation for cannabidiol and fenfluramine

LOCF imputation for cannabidiol: If a patient had valid data for ≥1 consecutive periods from and inclusive of the first period but only missing periods thereafter, then imputation of the missing period(s) was carried out using the last 12 weeks of valid data

LOCF imputation for fenfluramine: if a patient had valid data for ≥1 consecutive periods from and inclusive of the first period, the periods with any non-missing data were considered to have valid data and the seizure frequency for that period was calculated based on the available data. For any periods with only missing data, imputation of the missing period(s) was carried out using the seizure frequency from the last 12-week period that had (any non-missing) valid data. In other terms, if a patient dropped out during a given period, the seizure rate for the period was calculated based on the available data in the period, and then was carried forward to the following periods.

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

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