Ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over [ID3988]

For public – contains no confidential information

Technology appraisal committee B [06 July 2023]

Chair: Baljit Singh

Lead team: Nigel Westwood, Alistair Patton, Peter Wheatley Price

External assessment group: Peninsula Technology Assessment Group (PenTAG)

Technical team: Summaya Mohammad, Adam Brooke, Ian Watson

Company: Orion Pharma

Background: Seizures caused by CDKL5 deficiency disorder

Causes of CDD (cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

- Mutations in CDKL5 gene (X-chromosome): less proteins for brain and neurone development
- Most CDKL5 mutations are not inherited

Epidemiology – rare condition (also compared to other DEEs including DS and LGS)

- 11-17 people born with CDD a year in England and Wales (1 in 40,000-60,000 live births)
- Prevalence: 50-60 in England and Wales
- Long-term prognosis and survival not available – genetic cause of CDD first identified in 2004
- 4x more common in females than males – but males may have more severe disease
- Some adults diagnosed with CDD in 40s and 50s

Symptoms and diagnosis

- Seizures within the first months of life (often first symptom); followed by CDKL5 genetic test
- Most children have multiple seizures a day, hypotonia (low muscle tone), sleeping and nutrition problems, cortical visual impairment, learning and motor disabilities

Abbreviations: DEE: Developmental epileptic encephalopathy; DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome

Patient and carer perspectives (1)

Submission from CDKL5 UK

High unmet need – only symptomatic treatment:

- Multiple seizures daily, with additional co-morbidities and learning difficulties → significant pain, recurrent infections, poor quality of life
- Impact on quality of life for people with the condition and their carers

Current service provision:

- Need for improved service, coordination of care, and support for people with CDD and carers
- Experience of condition varies with location
- Education on CDKL5 should be promoted across NHS through professional organisations

"It's scary. As you never know what's going to hit you next. Even during a period of calm, you're always acutely aware there's a storm coming…The needs are constant AND constantly evolving"

"Sometimes you get sleep, sometimes you don't…"

"We have just completed the trial, it has definitely reduced the severity of A's seizure as we haven't had to use emergency medicine since been on it . It also has reduced the qty of seizures . She seems brighter also…"

"There's so much joy to be had when your child is well, seizure are minimal…"

"Exhausting. All encompassing. Unpredictable. Poor sleep, poor quality of life. Constant juggling"

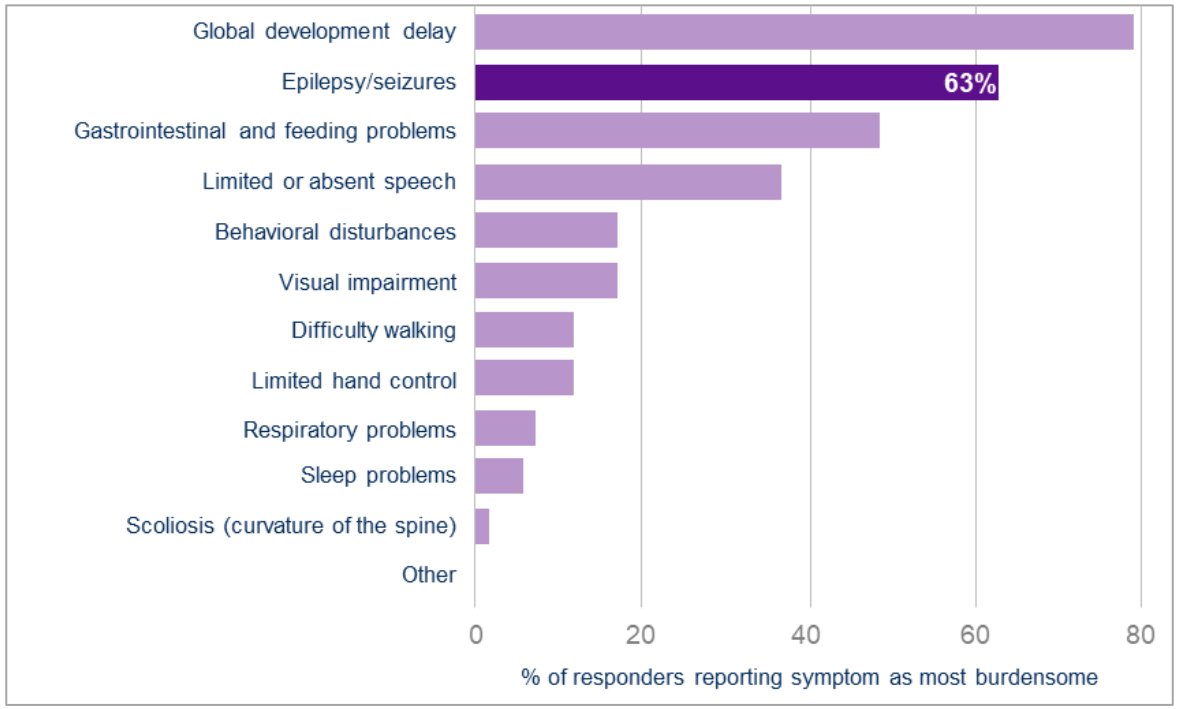
"Boys seemed to have experienced more side effects of these drugs…"

"It feels like we live in a constant state of 'anxiety' …Every little twitch could mean a new seizure type…"

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Patient and carer perspectives (2)

Most burdensome symptoms of CDD on patient (reported by caregivers in US)



How do seizures in CDKL5 deficiency affect patients and their carers?

Company:

Impact on patient (52 caregivers in US):

- Multisystem complications of CDD have large devastating impact on family life
- Sleep disturbances among most burdensome and frequent symptom in children with CDD

Caregivers (192 primary caregivers):

- Impaired emotional wellbeing
  - Associated with increased severity of child sleep problems and family financial difficulties
- Sleep problems for patient and families may worsen with high seizure frequency (increased risk of nocturnal seizures)
- Mental impact on caregivers
- Children dependent on enteral nutrition had poorer physical health

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Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Clinical perspectives (1)

Submission from Association of British Neurologists (ABN)

- Unmet need – many with CDD do not become seizure-free with current ASMs
  - Comorbidities include motor delay, intellectual disabilities, sleep disturbance
- Treatment aim
  - Prevent seizures and their consequences – to improve quality of life
  - Refractory epilepsy: risk of injury and sudden unexpected death in epilepsy
- Increased support and systems for prescribing in hospitals needed
  - Blood monitoring may be required
- Adverse effects of ganaxolone
  - Upper respiratory infection, fatigue, drowsiness

How do CDD, Dravet syndrome and Lennox-Gastaut syndrome compare?

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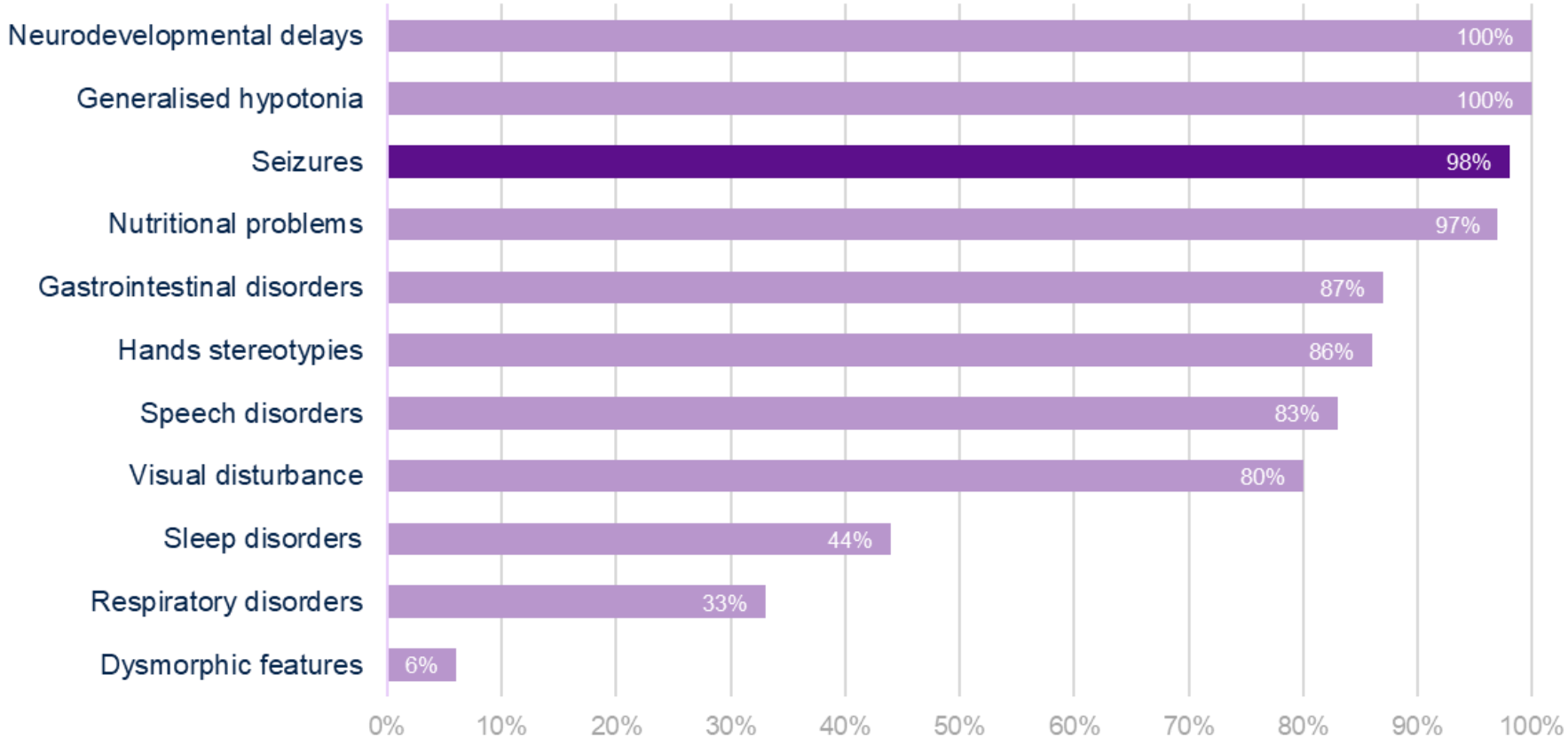
Abbreviations: ASM: anti-seizure medication; CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Clinical perspectives (2)

Common clinical characteristics of CDD affecting multiple organ systems



To what extent is quality of life driven by seizure frequency compared with comorbidities?

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Equality considerations

No equality issues raised by the company or stakeholders

Treatment pathway

*some people with CDD also diagnosed with Lennox-Gastaut syndrome so eligible for epidiolex

Symptom management – no current treatments for seizures caused by CDD

Pharmacological treatment:
- Anti-seizure medications (not CDD specific)

Non-pharmacological treatment:
- Ketogenic diet
- Vagus nerve stimulation
- Surgery

NG217 for epilepsies in children, young people and adults (not CDD-specific)

Anti-seizure medications (first-line often sodium valproate, lamotrigine, levetiracetam monotherapy or combination with other treatments)

Guidance on assessment and management of CDD from international panel of clinical experts (2022):

Treatment option	Clinical expert consensus
Combination therapy with steroids and vigabatrin	1st-line (n=15, 37.5%)
Steroids monotherapy	1st-line (n=14, 25%)
Vigabatrin monotherapy	1st-line (n=11, 27.5%)
Ketogenic diet	2nd-line (n=9, 23.1%); 3rd-line (n=15, 54.8%); 4th-line (n=10, 41.7%)

n=25 (92.6%) epidiolex for epilepsy in CDD (not licensed)*

Company position ganaxolone as add-on treatment to anti-seizure medications for CDD in people 2 years of age and older

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Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; NG: NICE guideline

NICE Guidelines 217 – epilepsies in children, young people and adults*

Symptom management – individualised treatment and no current options for seizures caused by CDD:

First-line:
- Sodium valproate
- Lamotrigine
- Levetiracetam

Second-line:
- Carbamazepine
- Clobazam
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Rufinamide
- Topiramate
- Zonisamide

Third-line:
- Clobazam
- Lacosamide
- Perampanel
- Rufinamide
- Topiramate

Add-on:
- Brivaracetam
- Carbamazepine
- Cenobamate
- Clobazam
- Eslicarbazepine
- Felbamate
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Perampanel
- Phenobarbital
- Phenytoin
- Pregabalin
- Primidone
- Sodium valproate
- Tigabine
- Topiramate
- Vigabatrin
- Zonisamide

Non-pharmacological:
- Ketogenic diet

*For generalised tonic-clonic seizures, focal seizures with or without evolution to bilateral tonic-clonic seizures, tonic or atonic seizures, idiopathic generalised epilepsies

Are there any special considerations for choice of ASMs for people with CDKL5 deficiency? Are unlicensed treatments for adults used in younger populations?

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Key issues

Issue	ICER impact
Marigold Open-label extension • Uncertainty in long-term treatment effect	Unknown
Model structure • Highly simplified model atypical for genetic epileptic syndrome appraisals	Unknown
Stopping rule • Clinical justification of stopping rule and likely adherence in NHS practice • Implementation in the model	Increase
Utility values for people with CDD and their caregivers • Lo et al. (2022) vs Auvin et al. (2021) proxy utility sources • Incorporating seizure-free days in the model	Increase/decrease
Wastage • If wastage is likely during treatment	Increase
Health state resource costs • Effect of reduction in seizure frequency on hospital admissions and A&E	Increase
Severity modifier • Calculating severity modifier and if it should be applied to people with CDD, their caregivers or both	Increase/decrease

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Ganaxolone (Ztalmy, Orion)

Marketing authorisation	• "For the adjunctive treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 to 17 years of age. Ztalmy may be continued in patients 18 years of age and older." • CHMP positive opinion (May 2023)
Mechanism of action	• Binding and enhancing certain GABAa receptor activity located within and on the surface of nerve cells that control excessive activity in the brain (resulting in seizures)
Administration	• Oral suspension – total daily dose recommended in 3 equal parts • Recommended dose: 63 mg/kg/day (weighing ≤28 kg); 1800 mg/day (weighing >28 kg) • Minimum dose: 33 mg/kg/day or 900 mg/day • Diagnosis of CDD needs genetic testing for CDKL5 mutations

Price	• Indicative list price per 50mg/ml oral suspension pack: [redacted] per 110 ml pack (50 mg/ml)
	  • Average weekly cost: [redacted]
	  • Average annual cost: [redacted]
	• Patient access scheme is applicable

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Abbreviations: GABAa: γ-aminobutyric acid type A

Decision problem

	Final scope	Company	EAG comments
Population	People 2 years of age or older with seizures caused by CDD		
Intervention	Ganaxolone plus ECM (ASMs, steroids, non-pharmacological treatments e.g. ketogenic diet and vagus nerve stimulation)		
Comparators	ECM without ganaxolone	ECM but restrictions on cannabidiol	Trial excludes cannabidiol (except epidiolex) – may not reflect clinical practice
Outcomes	Seizure frequency (overall and type), proportion seizure-free (overall and type), seizure severity, adverse effects, HRQoL	Consistent with clinical evidence but model did not consider seizure severity or differences in adverse effects between arms	• Seizure frequency as primary outcome may not entirely represent disease severity • Drug-related adverse events higher for ganaxolone but no evidence of significant resource implications

Abbreviations: ASM: anti-seizure medication; CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; ECM: established clinical management; HRQoL: health-related quality of life

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Clinical evidence for ganaxolone

Double-blind randomised controlled trial (Marigold):
- Phase 3 (completed May 2021)
- Open-label extension (ongoing)

Open-label proof-of-concept trial with 52-week extension (completed Jan 2019):
- Phase 2a
- Population: People between 2 to 18 years of age with PCDH19; CDKL5; Dravet Syndrome; Lennox Gastaut Syndrome; Continuous Spikes and Waves during Sleep

→ **Key clinical evidence**

→ **Used as supportive evidence; does not inform the model**
- 7 (out of 30) people enrolled with CDD; 4 in open-label extension
- Criteria to enter extension phase: Minimum 35% improvement in mean seizure frequency per 28 days vs baseline over 28-day period before study entry

Double-blind randomised controlled trial (Not started; estimated completion Dec 2024):
- Phase 3
- Population: Adjunctive ganaxolone in people with CDD between 6 months to <2 years of age

→ Possible extension of license population (outside current marketing authorisation population)

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Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Key clinical trial – Marigold (used in model)

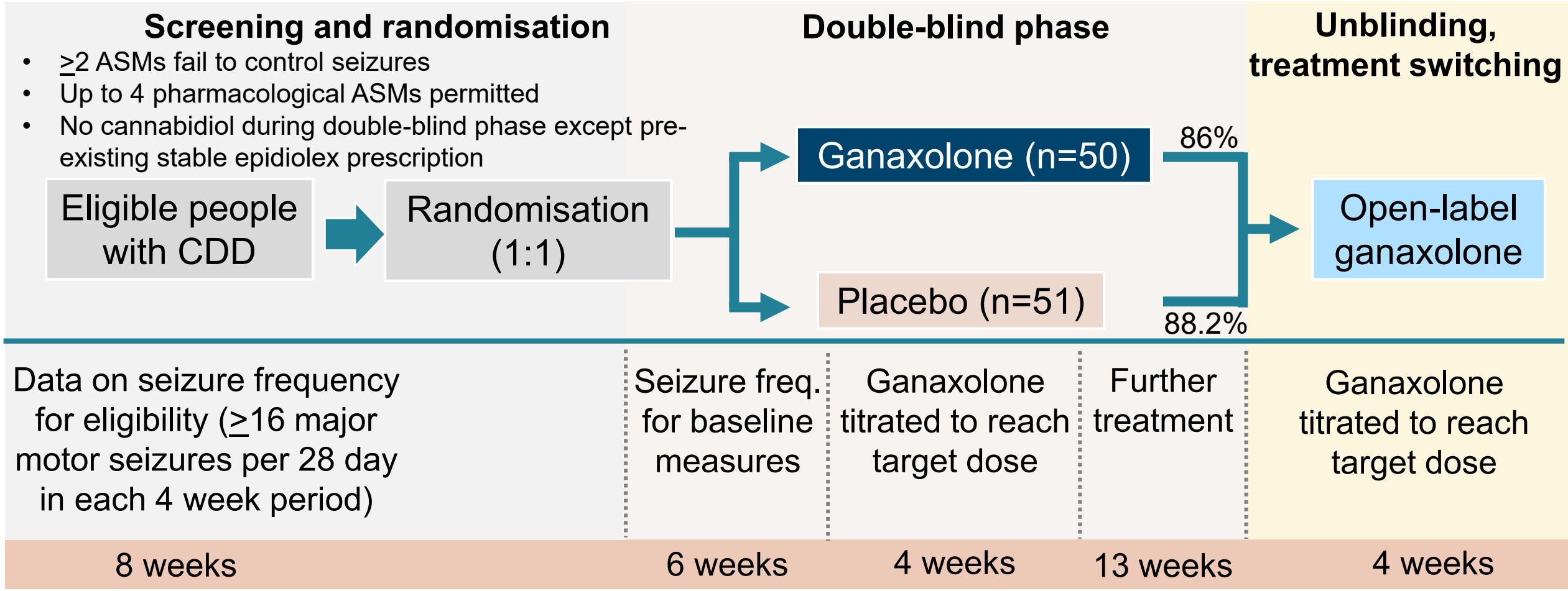
	Marigold (n=101)	Marigold extension (n=88)
Design	Phase 3, double-blind, randomised, placebo-controlled	Phase 3, open-label
Population	2 to 21 years of age with pathogenic or probably pathogenic CDKL5 variant and ≥16 major motor seizures* per 28 days in each 4-week period of an 8-week historical period	
Intervention	Ganaxolone, 3 times daily plus other ASMs (up to 4)	
Comparator	Placebo plus other ASMs	None
Duration	17 weeks follow-up	Latest data cut: June 2022 (2 year)
Primary outcome	% change from baseline in 28-day major motor seizure frequency during 17-week double-blind phase	
Key secondary outcomes	% people with ≥50% reduction from baseline in major motor seizure frequency	
Locations	Multi-site in 8 countries (Australia, Asia, Europe, North America); 8 centres in UK (n=7, 6.9%)	

*major motor seizures defined as: bilateral tonic, generalised tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic)

Abbreviations: ASM: anti-seizure medication; CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Marigold study design

- Primary analyses (17-week period)
- Sensitivity analyses: Full target dose only



Discontinuation (double-blind)	Ganaxolone	Placebo
Adverse event	1	4
Withdrawal	1	0

$$= \frac{\text{total seizures in 17 week double blind phase}}{\text{number of days with seizure data in phase}} \times 28$$

Abbreviations: ASM: anti-seizure medication; CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Seizure frequency outcome

Used in model | Used in scenario (all seizure types)

*i.e., major motor seizures in Marigold

Company: Primary seizures* represent majority in Marigold (uncertainty using low incidence numbers); form primary outcome; considered most impactful in terms of resource use & HRQoL

Primary seizures	Secondary seizures	Tertiary seizures
Bilateral tonic	Motor with intact or altered awareness	Non-motor with intact awareness
Generalised tonic-clonic	Non-motor with altered awareness	Absence
Atonic/drop		Myoclonic
Bilateral clonic		Epileptic spasms
Focal to bilateral tonic-clonic		

Seizures (often combinations):
- Primary: Major motor
- Secondary: Countable focal-onset
- Tertiary: Hard to count

Focal (1 side brain) | **Generalised** (both sides brain)

EAG: Issues using seizure outcomes in Marigold

- Treatment effect may differ by type – ICER may be between primary and all seizures scenarios
- Seizure frequency assessed using daily diary – less reliable for less visible seizures – generalised clonic seizures may be most reliable
- Difficulty capturing full impact of seizures including clusters (company define as 1 seizure – underestimating count), small changes in severity, duration of seizure and after-effects
- Variation in seizure frequency rate may not be captured in trial follow-up
- Capturing exacerbations in seizure frequency – regression to mean effect

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Abbreviations: ICER: incremental cost-effectiveness ratio; HRQoL: health-related quality of life

Marigold primary results – seizure frequency

Primary efficacy endpoint: % change from baseline in 28-day major motor seizure frequency during 17-week double-blind treatment phase (including 4-week dose titration period)

Major motor seizures per 28 days (intention-to-treat)	Baseline		17-week post-baseline		% change	
	GNX	PBO	GNX	PBO	GNX	PBO
Patients, n	49	51	50	51	49	51
Mean (SD)	115 (138)	104 (173)	94 (134)	151 (470)	-14 (65)	64.6 (273)
Median (95% distribution-free CI)	54 (38, 107)	49 (32, 61)	45 (32, 76)	55.5 (36, 80)	-31 (-36, -12)	-7 (-17, 15)
Hodges-Lehmann estimate of location shift (95% CI)		12 (-8, 32)		-4 (-25, 14)		-27 (-48, -10)
Wilcoxon test p-value / Z-value		0.238		-		0.004 / -2.910

Hodges-Lehmann test: Estimate of how far the responses in ganaxolone group are shifted from placebo (median difference between arms) – see next slide

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Abbreviations: CI: confidence interval; GNX: ganaxolone; PBO: placebo; SD: standard deviation

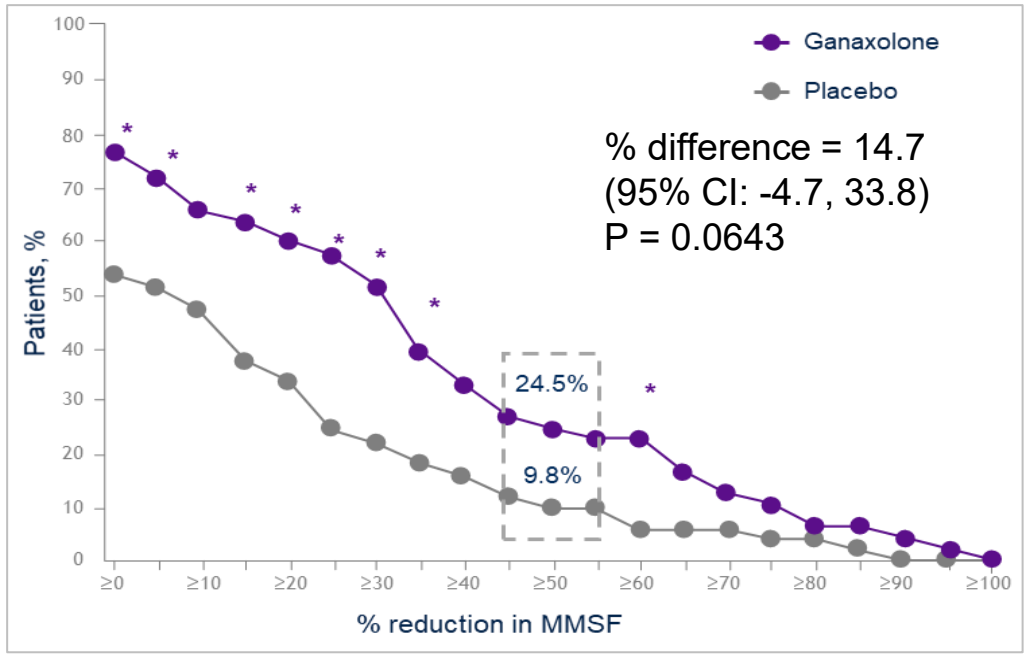
Seizure frequency in the model

Company: Apply Hodges-Lehmann estimated difference to mean of baseline seizure frequency distribution for better approximation of distribution parameters

Marigold key secondary results – response rate

Secondary endpoint: % people with ≥50% reduction from baseline in major motor seizure frequency (MMSF)

≥50% response against cumulative response curve (week 17)



Major motor seizures per 28 days (intention-to-treat)	Ganaxolone	Placebo
≥50% reduction from baseline, n (%)	12 (24.5)	5 (9.8)
Fisher's Exact test p-value	0.064	

	Cumulative % change in MMSF							
	-80%	-60%	-40%	-20%	+20%	+40%	+60%	+80%
GNX	7%	22%	32%	60%	[redacted]	[redacted]	[redacted]	[redacted]
PBO	5%	6%	16%	33%	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; GNX: ganaxolone; PBO: placebo

Treatment effects – regression to mean effect

Background: Uncertainty in clinical effects from Marigold OLE (>17 weeks treatment data)

- Risk of regression to mean after treatment initiation

Company: Any regression to mean effect should be balanced between arms

- Trial recruitment used same criteria for both arms – difference in relative efficacy between arms should not by default be driven by regression to mean
- Baseline period = 6 weeks, mitigating risk of sudden increase in seizure frequency (no further information on historical seizure data frequency before trial)
- People switching from placebo to ganaxolone after 17 weeks showed similar pattern in seizure frequency reduction – supporting absence of regression to mean effect
- OLE suggest ganaxolone effect increases beyond double-blind phase but model does not assume increase or decreasing effect after 17-weeks period to avoid bias

EAG: Consider unresolved with currently available data

- Duration of exacerbations in seizures may vary – 6-week baseline period may not be sufficient
- Regression to mean effect timing linked to typical duration of seizure frequency exacerbations (unknown)
- OLE has no control arm – unknown if proportion of reduction in MMSF from factors other than treatment effect (inc. regression to mean effect)

Abbreviations: MMSF: major motor seizure frequency; OLE: open-label extension

Treatment effects – uncertainty in OLE data

Background: Uncertainty in clinical effects from Marigold OLE → High rate of missing data

Company after TE: Analyses on full 2-year OLE data and MMSF reduction in responders

- Imputation of missing data for full cohort – show ganaxolone maintenance of treatment effect rather than increase in difference in 28-day MMSF between arms
  - Double-blind phase: -27.1% to >50% reduction from baseline after 12 months in OLE
- Imputation of missing data using last observation carried forward method*:
  - Difference in seizure frequency did not increase and consistent as 17-weeks (-29.3%)
- Median reduction in MMSF at 17-weeks could be maintained up to 2-years

EAG: Missing data analysis show OLE outcomes affected by attrition bias

- Likely all outcomes affected
- Imputation of missing data method may be optimistic – last reported treatment effect may not reflect reality
  - Any treatment effect waning not evident in last observation or if there's benefit of treatment but discontinue for other reasons (e.g. toxicity)

*Last observation carried forward: Last available measure of seizure frequency assessed before discontinuing used at all subsequent timepoints

Maintenance phase difference of ganaxolone vs placebo in median 28-day MMSF reduction	
Overall population	29.31%
≥30% responders	[redacted]%

(No variance measures reported)

Consistent difference in seizure frequency at 17-weeks – suggest this reduction could be maintained up to 2 years

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Abbreviations: MMSF: major motor seizure frequency; OLE: open-label extension

Cost effectiveness

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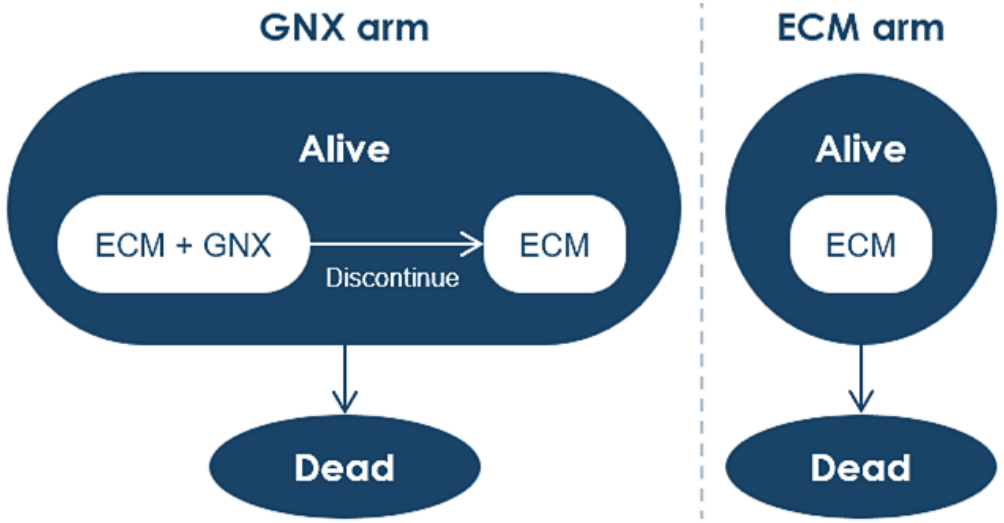
Company's model overview

Model structure:
Simple Markov state-transition model



~~**Improved length of life**~~

Improved quality of life:
- Reduce seizure frequency

→ **Increased QALYs**

Ganaxolone affects costs by:
- Increasing costs during treatment (ganaxolone plus ECM costs)
- Reduces costs associated with hospitalisation and rescue medications

Ganaxolone affects QALYs by:
- Reducing seizure frequency and improving HRQoL to generate more QALYs than ECM

Assumptions with greatest ICER effect:
- Affecting seizure frequency and ability of ganaxolone to affect it
- Utility data source and implementation
- Baseline age at ganaxolone initiation
- Relating to average length of stay for epilepsy-related hospitalisations

Abbreviations: ECM: established clinical management; GNX: ganaxolone; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Company base case key parameters

Population	1,000 people cohort with CDD
Baseline characteristics	[redacted] years (average age likely to start ganaxolone), 20.8% male
Intervention	Ganaxolone as adjunctive to ECM – up to target dose 63 mg/kg in people ≤28 kg, up to target dose 1,800 mg/kg per day in people >28 kg (as in Marigold)
Comparator	ECM: up to 4 ASMs without ganaxolone (as in Marigold). Ketogenic diet and Vagus nerve stimulation permitted if started before randomisation and stable
Efficacy data	Marigold double-blind phase HL shift estimate (27.08%); 29.31% (maintenance period) used in EAG base case
Stopping rule	At 6 months for non-responders (≥30% reduction in seizure frequency)
Cycle length	28 days with half-cycle correction
Time horizon	100 years (lifetime)
Utilities	Vignette study by Lo et al., (2022) – proxy data from people with TSC
Caregiver utilities	Lo et al., (2022); caregiver modelled as separate entity
Resource use	Proxied with healthcare resource use in people with LGS (Chin et al.)
Adverse events	No adverse effects on HRQoL – impact on costs and QoL same in both arms

Abbreviations: ASM: anti-seizure medication; CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; ECM: established clinical management; HRQoL: health-related quality of life; LGS: Lennox-Gastaut syndrome; TSC: Tuberous sclerosis complex

Model structure

TA614 cannabidiol with clobazam (Dravet syndrome)
TA808 fenfluramine (Dravet syndrome)

Background: Simple Markov 2-health state-transition model atypical for genetic epileptic syndrome appraisals (TSC, LGS, DS) – May not capture full disease or treatment impact

- Previous appraisals include discrete seizure freq.-based health states (TA614) or patient-level microsimulations (TA808)

Company:

- Small sample size of Marigold trial limit building reliable model similar other proxy conditions with larger prevalence and sample sizes
- Seizure frequency categories from proxy conditions (TSC, LGS, DS) do not correspond well with seizure type/frequency of CDD in Marigold – Markov based on seizure frequency is challenging
- Considerable proportion CDD fall in lowest or highest frequency category → improvements in QoL not captured

EAG: CDD has scarce data, but company approach is highly simplified

- Analysis may be optimistic or conservative estimate of treatment effect and outcomes if full treatment effect is not considered

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome; TSC: Tuberous sclerosis complex; QoL: quality of life

Model Trace (EAG base case)

Modelled carer QALYs (SOC, x1.8 carers)	Inc. benefit for ganaxolone (x1.8 carers)
[redacted]	[redacted]

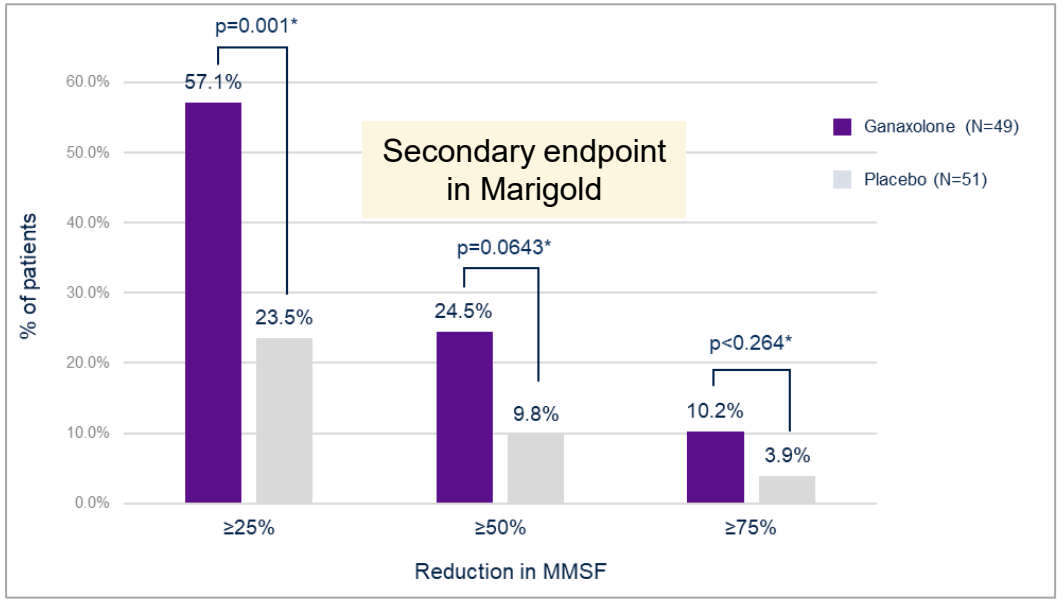
Modelled patient QALYs (SOC)	Inc. benefit for ganaxolone
[redacted]	[redacted]

Abbreviations: Gan: ganaxolone; Inc.: incremental; QALY: quality-adjusted life-year; SoC: standard of care

Stopping rule (1)

Background: Company add stopping rule (after TE) at 6 months – responders continue treatment

Company: ≥30% seizure freq. reduction from baseline at the end of double-blind phase → discontinuation rate of responders [redacted] in OLE



EAG: No clear justification on clinical decision-making for treatment continuation

- Important because people with modest benefit may have treatment stopped
- % reduction in seizure frequency does not align with secondary endpoint in Marigold
- Clinical advice: stopping at 6 months may be reasonable; Often 50% threshold in epilepsy

Clinical expert: Criteria should be failure to reach 30% reduction in disabling seizures after stable dosage for 6 months compared with baseline

≥30% stopping threshold in TAs (checked every 6 months)

- TA614 – cannabidiol + clobazam in DS (conclusive seizures)
- TA615 – cannabidiol + clobazam in LGS (drop seizures)
- TA808 – fenfluramine in DS (conclusive seizures)
- TA873 – cannabidiol in TSC

What constitutes a response in clinical practice? When would treatment discontinue? How would a stopping rule be implemented in clinical practice?

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Abbreviations: DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome; OLE: open-label extension; TE: technical engagement; TSC: Tuberous sclerosis complex

Stopping rule – implementation in model

Background: Stopping rule reduces incremental costs for ganaxolone and increases QALYs; EAG consider reasonable to include (if clinically valid) but concern with model implementation

Company: Apply [redacted]% reduction in seizure frequency to responders and associated with [redacted] increase in HRQoL for patients and [redacted] increase for caregivers (x1.8 = [redacted])

- Apply [redacted]% reduction in seizure frequency for non-responders (approx. [redacted]% population)
- Assume non-responder outcomes = full ECM arm

EAG: Response at 17-weeks in Marigold applied at 28 weeks in model – lacks face validity

- Non-responders have same seizure frequency distribution as ECM – but people in ECM arm may achieve response (if so, favours ganaxolone)
  - To find out number of responders in ECM arm and expected seizure frequency distribution
- No analysis on HL shift for non-responders (≤30% reduction) vs placebo at week 17 – favouring ganaxolone if seizure frequency increased over time, need analysis on:
  - Week-17 data (& OLE) showing non-responders have 0 shift in seizure frequency over time
  - Seizure frequency distribution shape (may affect decision to model seizure frequency using lognormal distribution

Is the company's stopping rule implemented appropriately in the model?

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Abbreviations: ECM: established clinical management; HRQoL: health-related quality of life; OLE: open-label extension; QALYs: quality-adjusted life-year

Utility values for people with CDD – company base case

Company: Lo et al., (2022) in TSC

- Differences in utility estimated by seizure frequency within a model cycle
- Seizure type in TSC expected to reflect CDD closer than DS/LGS
- Generalised seizures in Lo et al. - Seizure frequency for LGS based on drop seizures in Auvin et al., Marigold had different types of seizures
- Greater range of seizure frequency (4 categories) for caregiver utilities than Auvin et al. (80 or 110 seizures per month)

[redacted]

Lo et al., (2022) – generalised seizures		
Per day	Per 28-day cycle	Mean (SE)
0	[redacted]	0.73 (0.03)
1	[redacted]	0.18 (0.06)
2	[redacted]	0.09 (0.05)
3-4	[redacted]	-0.11 (0.06)

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome; SE: standard error; TSC: Tuberous Sclerosis Complex

Utility values – EAG critique

Seizure frequency

Seizure free days per month: Number of seizure-free days in an average month	UK						
	130	110	80	60	45	20	0
1	0.21	0.24	0.29	0.30	0.33		
3	0.26	0.28	0.32	0.30	0.33		
6	0.35	0.29	0.37	0.37	0.37		
9	0.36	0.39	0.38	0.40	0.39		
12	0.41	0.35	0.43	0.43	0.41	0.52	
15	0.43	0.44	0.48	0.49	0.49	0.54	
18	0.46	0.47	0.45	0.49	0.53	0.59	
30							0.83

EAG: Auvin et al., (2021) in DS, LGS

- Utility based on number of seizures within a month vs number of seizure free days
- Consistent with disease area in Chin et al. (resource use and mortality)
- More granular health states for seizure frequency
- Consider proportion of seizure free days

Are the utility value results from either source plausible for people with CDD?

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome

Utility values – seizure-free days

Background: Only Auvin et al., (2021) considered seizure-free days

Company:

- Auvin et al., values re-analysed after technical engagement to consider seizure-free days in weighted average utility
- Greater QALY gain (lower ICER) than original Auvin et al., values
- Alternate modelling approach: bootstrapping with individual patient data

EAG:

- Method assumed seizure-free days independent of seizure frequency – resulting in implausible or unlikely combinations of seizure frequency and seizure-free days
- Prefer different distribution for each seizure-free category
- Weighted average approach inconsistent with lognormal distribution to model seizure frequency (cannot estimate seizure-free)
- Scenarios using both utility sources may help decision-making

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Utility values for caregivers

Company: Lo et al., (2022) in TSC

- Carers modelled as separate entity to people with CDD – model assumes carer death too
- 1.8 carers until 18 years of age – because of parental care during childhood with average number of parents <2
- After 18 years of age, 1 carer – because average reduces further when reaching adulthood

EAG: Auvin et al., (2021) in DS, LGS

- Absolute utilities from Auvin et al.
- TA808 and TA614 (Dravet syndrome) committee prefer decrement only approach for carer utility in model
- High disease burden in CDD so did not consider decrements only approach to avoid negative utilities and interpretation difficulties

Lo et al., (2022) – generalised seizures			Auvin et al., (2021) (seizure/month)
Per day	Per 28-day cycle	Mean (SE)	
0	[redacted]	0.91 (0.01)	0.78 (seizure-free, 30 SFD)
1	[redacted]	0.55 (0.04)	
2	[redacted]	0.48 (0.05)	0.52 (80, 15 SFD)
3-4	[redacted]	0.319 (0.05)	0.38 (130, 3 SFD)

1.8 carer utility used in:

- TA614: Cannabidiol + clobazam in DS
- TA615: Cannabidiol + clobazam in LGS
- TA808: Fenfluramine in DS
- TA873: Cannabidiol in TSC

Which utility values are appropriate to apply to people with CDD and their caregivers?

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; DS: Dravet syndrome; LGS: Lennox-Gastaut syndrome; SE: standard error; TSC: Tuberous sclerosis complex; QoL: quality of life

Wastage in model

- Ganaxolone oral suspension, 50 mg/ml, 110 ml pack
- Recommended dose (3 equal parts): 63 mg/kg/day (≤28 kg); 1,800 mg/day (>28 kg)

Background:
Company prefer no wastage in model; EAG prefer 10% wastage (clinical expert opinion)

Company:
- No wastage or redosing evidence in trials or practice and SPC advise against redosing
- But more realistic estimate 0.47% wastage
- 0.5 ml per bottle → [redacted]% share of people missing a dose [redacted] from spitting
- In [redacted] of cases, full replacement dose would be given as extra

EAG:
- Further clinical opinion important for most suitable assumption
- Both EAG and company view on wastage not based on empirical evidence

Is there likely to be wastage during treatment with ganaxolone in clinical practice? If so, what percentage of wastage should be assumed?

Abbreviations: SPC: summary of product characteristics

Health state resource costs – hospital stays

Background: Chin et al., (2021) in company base case (data from LGS population)

- Epilepsy related hospital inpatient admissions and A&E visits differ between treatment arms*
  - Assumes reduction in seizure frequency is perfectly positively correlated with both
- But not all seizures result in hospitalisation or A&E visit – EAG suggest alternative proxy only including seizures known to be linked to hospitalisation or severe

Company: Base-case after TE use weighted average of short and long-stay hospitalisation costs

- After TE: Median length of stay in hospital is [redacted] days (international CDD registry)
- [redacted]% have length of stay >2 days (= long stay)

Admissions	Chin et al., (ECM)	Ganaxolone (27.08% reduction)
Hospital	1.5	1.09
A&E	0.85	0.62

EAG: Accept company's updated approach to hospitalisation costs

- But unclear if international CDD registry reflects UK practice
  - Suggest subgroup analysis of people in registry from UK
- NHS reference costs: uncertainty if reference costs used by company for long-stay hospitalisation are appropriate for median [redacted] days

*GP consultation, GP home visit, GP phone call, nurse consultation, nurse home visit, nurse phone call, hospital outpatient visits, hospital inpatient admissions, assumed same frequency for both arms

Would a reduction in MMSF reduce hospital stays and A&E visits by 27%?

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; ECM: established clinical management; LGS: Lennox-Gastaut syndrome; MMSF: major motor seizure frequency; TE: technical engagement

Incremental costs – company and EAG base case

Costs (£)	Company			EAG		
	ECM	GNX	Incr.	ECM	GNX	Incr.
Indirect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other direct healthcare	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (discounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

~[redacted] reduction in costs only from reduction in epilepsy related inpatient admission and A&E visits

Abbreviations: ECM; established clinical management; GNX: ganaxolone; Incr.: incremental

Severity modifier

Company: Severity modifier applied to patient and caregiver QALYs

- Caregivers impacted by the same severity of CDD – considered living with the condition
- Developmental delay and seizures have most impact on carers needing to give constant support, also impact of comorbidities (visual, respiratory, sleep, behaviour issues, scoliosis)
- Near-total dependence for people with CDD on their caregivers (24/7 task)
- No information on mortality – increased risk (as in other DEEs) adds to parental stress

NICE methods guide:

- 6.2.12: "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…"
- 6.2.16: "The committee may apply a greater weight to QALYs if technologies are indicated for conditions with a high degree of severity. The data used to estimate both absolute and proportional QALY shortfall should focus on the specific population for which the new technology will be used and be based on established clinical practice in the NHS."

- Company and EAG base cases **calculated** QALY shortfall for patients
- Company **applied** severity modifier to patient and caregiver QALYs
- EAG **applied** severity modifier to patient QALYs only
  - Scenario: modifier applied to caregivers based on caregiver QALY shortfall (1 caregiver)

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Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; DEE: Developmental epileptic encephalopathy; QALY: quality-adjusted life year

Calculating severity modifier

QALY shortfall:

	QALYs		QALY shortfall	
	CDD (ECM)	General population	Absolute	Proportional
Company	[redacted]	[redacted]	20.95	84.04
EAG	[redacted]	[redacted]	16.07	64.47

Shortfall is the same with and without stopping rule (stopping rule only affects ganaxolone arm)

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; ECM; established clinical management; GNX: ganaxolone; Incr.: incremental; QALY: quality-adjusted life year

Absolute shortfall graphs

EAG base case

Company base case

Abbreviations: Gen: general; SOC: standard of care

Applying severity modifier

Company: Apply 1.7 severity modifier for patient and caregiver QALYs

EAG: Apply 1.2 severity modifier for patient and 1 for caregiver QALYs

- Include cost-effectiveness results for:
  1. Without severity modifier for caregivers (same as EAG base case)
  2. Caregiver severity modifier calculated based on caregiver QALY shortfall for 1 caregiver, not patient QALY shortfall (caregiver as separate entity from people with CDD)

	Company			EAG		
	ECM	GNX	Incr.	ECM	GNX	Incr.
Total weighted QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Is a QALY weighting appropriate to apply? Should it be applied to people with CDD, their caregivers or both?

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; ECM: established clinical management; GNX: ganaxolone; Incr.: incremental; QALY: quality-adjusted life year

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Treatment effect	Apply full treatment effect from cycle 2 (maintenance phase)	Agree with company
Discontinuation	Short-term discontinuation from double-blind phase, long-term from OLE	With stopping rule: Per company; Without: Based on exposure time in trial and discontinuation number
Utilities	Lo et al., (2022)	Auvin et al., (2021)
Wastage	None	10%
Severity modifier	Apply 1.7 for people with CDD	Apply 1.2 for people with CDD
Caregiver severity	Caregiver QALY shortfall multiplied by 1.8; based on absolute shortfall ~21 QALYs	Separate caregiver QALY shortfall and based on 1 caregiver; based on absolute shortfall ~16 QALYs
Stopping rule	Included	Presented with and without
Hospital costs	Weighted average long/short-term hospital stay costs from Marigold	Agree with company – subject to presenting UK subgroup analysis

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Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; OLE: open-label extension; QALY: quality-adjusted life year

No impact | Medium impact | Small impact | Large impact

Company and EAG base case results

Ganaxolone + established clinical management (ECM) vs ECM	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Auvin et al. utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• 10% wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Caregiver severity modifier based on caregiver QALY shortfall not patient QALY shortfall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Caregiver QALY shortfall based on 1 caregiver not x1.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• No stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case with stopping rule & severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• **No stopping rule**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario without severity modifier for caregivers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Company base case is below the level normally considered an effective use of NHS resources
- EAG base case is above the level normally considered an effective use of NHS resources

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

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**.

Key issues

Issue	ICER impact
Marigold Open-label extension • Uncertainty in long-term treatment effect	Unknown
Model structure • Highly simplified model atypical for genetic epileptic syndrome appraisals	Unknown
Stopping rule • Clinical justification of stopping rule and likely adherence in NHS practice • Implementation in the model	Increase
Utility values for people with CDD and their caregivers • Lo et al. (2022) vs Auvin et al. (2021) proxy utility sources • Incorporating seizure-free days in the model	Increase/decrease
Wastage • If wastage is likely during treatment	Increase
Health state resource costs • Effect of reduction in seizure frequency on hospital admissions and A&E	Increase
Severity modifier • Calculating severity modifier and if it should be applied to people with CDD, their caregivers or both	Increase/decrease

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Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

NICE National Institute for Health and Care Excellence

Thank you.

Back-up

NICE National Institute for Health and Care Excellence

Recent NICE appraisals for Seizures

Technology appraisal	Condition	Recommendation
TA873 cannabidiol (2023)	Seizures caused by tuberous sclerosis complex in people aged 2 years and over	Recommended as add-on option if seizures not controlled well enough or tolerated by 2 or more antiseizure medications (alone or combination)
TA808 fenfluramine (2022)	Seizures associated with Dravet syndrome in people aged 2 years and older	Recommended as add-on to other antiseizure medicines if seizures not controlled after 2 or more antiseizure medicines
TA753 cenobamate (2021)	Focal onset seizures in epilepsy in adults	Recommended as option with or without secondary generalised seizures in drug-resistant epilepsy that has not been controlled with at least 2 antiseizure medicines
TA614 cannabidiol with clobazam (2019)	Seizures associated with Dravet syndrome in people aged 2 years and older	Recommended as an option
TA615 cannabidiol with clobazam (2019)	Seizures associated with Lennox-Gastaut syndrome in people aged 2 years and older	Recommended as an option

Marigold key secondary results – response rate (worsening)

17-week double-blind period: Cumulative response curve of worsening in 28-day MMSF vs baseline

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Abbreviations: MMSF: major motor seizure frequency

Marigold seizure frequency results (maintenance phase)

Cumulative Curves of change in 28-Day Seizure Frequency for Primary Seizure Types (13-Week Maintenance Phase, intention-to-treat population)

Company: European regulatory guidance on clinical investigations of medicinal products for epileptic disorders recommends efficacy endpoints based on seizure frequency changes in maintenance dose phase

EAG: Overall consider double-blind phase of Marigold as best quality evidence available for ganaxolone

Patient and caregiver QALY gains

		Company			EAG		
		ECM	GNX	Incr.	ECM	GNX	Incr.
Patient QALYs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregiver QALYs gained		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	Undiscounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Discounted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; ECM; established clinical management; GNX: ganaxolone; Incr.: incremental; QALY: quality-adjusted life year