Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

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

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

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. CDKL5
   b. Association of British Neurologists
   c. NHS England

4. **External Assessment Report** prepared by Peninsula Technology Assessment Group (PenTAG)

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

6. **Technical engagement response from company**
   a. Company Response
   b. Attachment 1
   c. Attachment 2
   d. Attachment 3

7. **Technical engagement responses from stakeholders:**
   - Association of British Neurologists

8. **External Assessment Group critique of company response to technical engagement** prepared by Peninsula Technology Assessment Group (PenTAG)

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

C.1 NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

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

Document B

Company evidence submission

July 2023 (confindentiaty updates only)

File name	Version	Contains confidential information	Date
ID3988_Ganaxolone_Document B_economic update of 27102022_FINAL dossier - 21122022_Fully redacted - updated conf marks 24072023	FINAL updated economic section and confidentiality marks	Yes	24th July 2023

Contents

Abbreviations

AE	Adverse event
AED	Anti-epileptic drug
ASM	Anti-seizure medications
BIM	Budget impact model
BMI	Body mass index
CDD	CDKL5 Deficiency Disorder
CDKL5	Cyclin-dependent kinase-like 5
CEM	Cost-effectiveness model
CEAC	Cost-effectiveness acceptability curve
CGI-CA	Caregiver Global impression of Change in Attention
CGI-I	Clinical Global Impression of Improvement
CGI-CSID	Caregiver Global Impression of Change in Seizure Intensity/Duration
CI	Confidence interval
CNS	Central nervous system
DEE	Developmental epileptic encephalopathy
DS	Dravet Syndrome
DSA	Deterministic sensitivity analyses
ECG	Electrocardiogram
ECM	Established clinical management
EEG	Electroencephalogram
EMA	European Medicines Agency
HAS	Haute Autorité de Santé
ICER	Incremental cost effectiveness ratio
GABA	γ-aminobutyric acid
GABAA	GABA type A (receptor)
GNX	Ganaxolone
GP	General practitioner
ICER	Incremental cost-effectiveness ratio
IWRS	Interactive web response system
LGS	Lennox-Gastaut syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
MMSF	Major motor seizure frequency
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

OR	Odds ratio
PAS	Patient Access Scheme
PBO	Placebo
PSA	Probabilistic sensitivity analysis
PSI	Parenting Stress Index
PSSRU	Personal Social Services Research Unit
PT	Preferred Term
QALY	Quality-adjusted life-year
QI-Disability	Quality of life inventory-disability
QoL	Quality of life
RCT	Randomised-controlled trial
SAE	Serious adverse event
SE	Standard error
SD	Standard deviation
SLR	Systematic literature review
SOC	System Organ Class
SoC	Standard of care
SUDEP	Sudden unexpected death in epilepsy
TEAE	Treatment-emergent adverse event
TID	Three times daily
UK	United Kingdom
US	United States
vs	Versus

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

B.1.1 *Decision problem*

The objective of this single technology appraisal is to evaluate the clinical- and cost-effectiveness of ganaxolone (GNX) as adjunctive treatment to “established clinical management” of epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in people 2 years of age and older. “Established clinical management” of CDD-related seizures includes the use of pharmacological therapies, such as anti-seizure medications (ASMs) and steroids, and non-pharmacological treatments such as the ketogenic diet and vagus nerve stimulation (see Section B.1.3.5).

The submission covers the technology’s anticipated full marketing authorisation for this indication and is in line with the scope issued by the National Institute for Health and Care Excellence (NICE) (**Error! Reference source not found.**). The indication wording for GNX proposed by Marinus Pharmaceuticals Inc. (marketing authorisation applicant) is as follows: GNX (ZTALMY®) is indicated for the adjunctive treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 deficiency disorder (CDD) in patients 2 years of age and older.

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Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People 2 years of age or older with seizures caused by CDD	As per the scope	Not applicable
Intervention	Ganaxolone (ZTALMY®)	As per the scope	Not applicable
Comparator(s)	Established clinical management without ganaxolone	As per the scope	Not applicable
Outcomes	The outcome measures to be considered include: • Seizure frequency (overall and by seizure type) • Proportion of people seizure-free (overall and by seizure type) • Seizure severity • Adverse effects of treatment • Health-related quality of life	As per the scope	Not applicable

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. **The economic modelling should include the costs associated with diagnostic testing for CDKL5 gene mutations *in people with CDD who would not otherwise have been tested*. A sensitivity analysis should be provided without the cost of the diagnostic test.**	Orion is proposing to assign no additional costs for genetic testing associated with a prescription for ganaxolone.	In the economic analysis, no additional cost has been assigned for genetic testing associated with a prescription for ganaxolone. In NHS England genomic testing is generally offered to patients with rare early onset or syndromic epilepsy (https://www.england.nhs.uk/publication/national-genomic-test-directories/). Moreover, the diagnostic testing for CDKL5 gene mutations is performed well before patients start treatment with ganaxolone, given that it is proposed as an adjunctive treatment to other ASMs (confirmed by clinical expert opinion)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	Not applicable	The population definition above is appropriate. Due to the rarity of the target condition, and thus the relatively small pivotal study, any strong conclusions regarding subgroups†may not be feasible.	Not applicable
Special considerations including issues related to equity or equality	Not applicable	No additional comments	Not applicable

Abbreviations: ASMs, anti-seizure medications; CDD: CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5; NHS, National Health Service; NICE: National Institute for Health and Care Excellence.

†Pre-defined subgroups analyses were by gender and by levels of allopregnanolone sulfate (Allo-S) (See Section B.2.7).

B.1.2 *Description of the technology being evaluated*

Table 2: Technology being evaluated

UK approved name and brand name	UK approved name: ganaxolone Brand name: ZTALMY®
Mechanism of action	Ganaxolone is a high affinity, stereoselective, positive allosteric modulator of GABAA receptors located in the central nervous system.
Marketing authorisation/CE mark status	Ganaxolone does not currently have a marketing authorisation in the UK for treating seizures caused by CDD. Regulatory submission to EMA: The application was submitted on 28th October 2021. CHMP opinion expected by [redacted], launch in UK anticipated in [redacted] Expected target date for MHRA submission: [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Anticipated indication: Ganaxolone is indicated for the adjunctive treatment of epileptic seizures associated with CDD in patients 2 years of age and older. Ganaxolone is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.
Method of administration and dosage	Ganaxolone is administered as an oral suspension. It should be titrated gradually to achieve the recommended daily dose: 63 mg/kg/day in patients weighing ≤28 kg and 1800 mg per day in those weighing >28 kg (1). A minimum dose of 33 mg/kg/day or 900 mg/day is generally required. It is recommended that total daily dosage is administered in 3 equal doses throughout the day.
Additional tests or investigations	Confirmation of the diagnosis of CDD requires genetic testing for CDKL5 mutations.
List price and average cost of a course of treatment	Indicative list price: [redacted] per 110 mL (50 mg/mL). This equates to an estimated average weekly and annual cost at list price of [redacted] respectively.
Patient access scheme (if applicable)	A patient access scheme proposal comprising of a fixed, discounted net price of [redacted] per 110 mL bottle was submitted to PASLU on 29 Sept, 2022. Confirmation that NHS England has accepted the PAS proposal received on 20th Oct, 2022. The estimated average cost per week of treatment under this PAS is [redacted], which equates to a 12-month cost of [redacted]

Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5; CHMP, Committee for Medicinal Products for Human Use; EMA, European medicines Agency; GABAA, γ-aminobutyric acid type A; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PASLU; Patient Access Scheme Liaison Unit; UK, United Kingdom

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

- **Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare, genetic developmental epileptic encephalopathy (DEE) characterised by early-onset epileptic seizures and severe global developmental impairment (2, 3)**
- **The exact epidemiology and life expectancy in CDD remain unknown due to both its rarity and recent identification (4)**
  - With an estimated incidence of **1.7–2.5 per 100,000 live births** (3, 5)[a], CDD is much rarer than other DEEs (5-8)
    - It is estimated that 11 to 16 people are born with CDD each year in England and Wales (3, 5, 9)
    - According to clinical expert opinion [redacted] the estimated number of diagnosed CDD cases in England and Wales is currently as low as 50 to 60 patients
  - No studies report on mortality in CDD (10). However, patients with epilepsy have a higher-than-expected risk of death (11, 12), with sudden unexpected death in epilepsy (SUDEP) being the major contributor to mortality (13-15)
- **CDD imposes a substantial clinical and humanistic burden on patients and their caregivers, and a considerable financial burden on healthcare systems, being characterised by early-onset refractory seizures, severe developmental delays and multiple comorbidities requiring life-long treatment (16-27)**
- **Currently, there are no therapies addressing the underlying causes of CDD and no evidence-based European guidelines for the management of this rare condition are available**
  - Recent international consensus recommendations suggest the use of vigabatrin, steroids and the combination of these as first-line therapy for CDD (28)
  - There was consensus from 100% of clinical experts that ganaxolone should be offered for CDD-associated epilepsy, if clinically indicated, dependent on local regulatory approval (28)
- **Anti-seizure medications (ASMs) are the main pharmacological therapy for CDD-associated seizures (29). However, none are specifically approved for this condition and, in most cases, their efficacy is limited and short-lved, with response rates decreasing drastically over time (29, 30)**
- **There is an unmet need for an efficacious, well tolerated treatment specific for CDD-related seizures that can improve and maintain clinical outcomes, thus, reducing the disease burden**

[a] Note that the original reported value is 1 in 40,000–60,000; however, this value has been calculated per 100,000 live births to allow comparisons with other reported incidence data (5-8)

- **Ganaxolone (GNX) is the first treatment specifically indicated for CDD-associated seizures. It is proposed as an adjunctive treatment to other ASMs for patients 2 years of age and older with CDD-associated refractory seizures. In UK clinical practice, this would place GNX as treatment option for patients requiring improved seizure control.**
- **Clinical outcomes reported in Section B.2 demonstrate that GNX as adjunctive treatment significantly reduces the frequency of major motor seizures in patients with CDD compared with placebo**

B.1.3.1 *Disease overview*

Cyclin-dependent kinase-like 5 (CDKL5) Deficiency Disorder (CDD) is an X-linked genetic disorder caused by pathogenic loss-of-function mutations in the *CDKL5* gene, which encodes a protein essential for normal brain development and function (2, 31-33). CDD is a rare, complex, debilitating developmental epileptic encephalopathy (DEE) characterised by severe early-onset treatment refractory seizures, severe developmental delays, and a wide range of comorbidities (e.g., gastrointestinal, respiratory, and sleep disorders, as well as nutritional problems (17, 29)) requiring life-long treatment and extensive care.

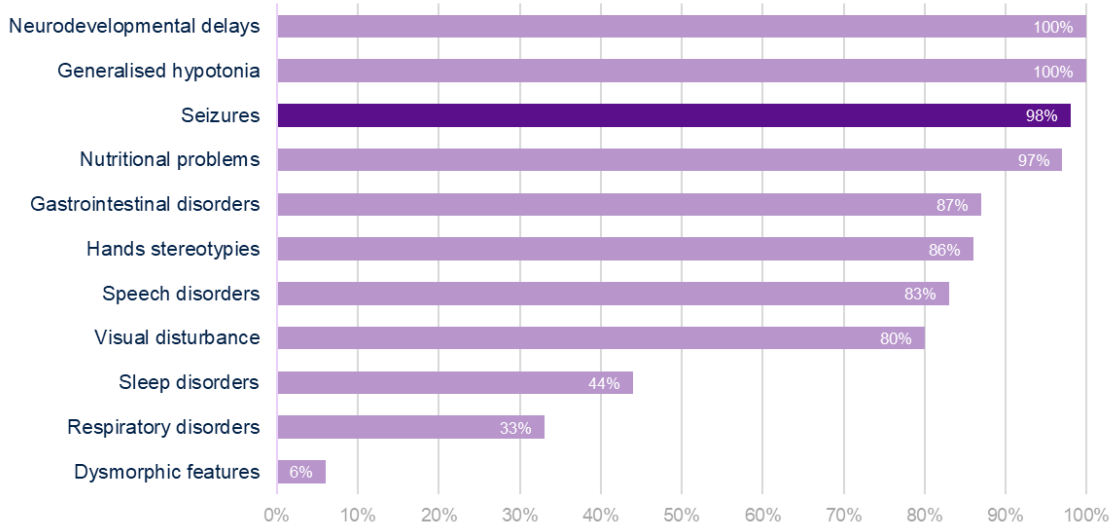
Epileptic seizures are typically the first symptom occurring in patients with CDD, presenting within the first 3 months of life in 90% of cases (3, 20, 29). Over time, seizures evolve across three stages: early epilepsy, with frequent tonic seizures and infantile spasms without hypsarrhythmia [b]; epileptic encephalopathy, with infantile spasms and hypsarrhythmia; and late resistant multifocal and myoclonic epilepsy (16, 22). On average, during their lifetime, patients with CDD experience 2.8 types of seizures (22), the most common being epileptic spasms (22, 25). In later stages, a complex seizure semiology frequently appears, with a unique pattern of hypermotor-tonic-spasm sequences (16), and 80–88.9% of patients have daily seizures (20, 23, 29). Some patients cycle through various treatment options even before they are diagnosed with CDD (18), and 84–95% ultimately develop treatment-refractory seizures (17, 26).

In patients with CDD, developmental delay is typically severe and results in physical, cognitive, communication and behavioural skill impairment. Over time, 30–75% of patients experience regression (17, 20, 25, 26). Notably, a negative association has been observed between the worsening of developmental issues over time and the seizure burden at baseline (35).

The majority of patients with CDD also suffer from several comorbidities, such as gastrointestinal, respiratory, and sleep disorders, as well as nutritional problems (17, 29) (Figure 1).

[b] Hypsarrhythmia is defined as an interictal pattern that usually changes during clinical attacks to lower-amplitude slow waves, or to a sudden flattening known as an electrodecremental period (34).

Figure 1. Common clinical characteristics of CDD affecting multiple organ systems



Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5.
Source: Jakimiec et al, 2020 (29) and Frullanti et al, 2019 (17).

B.1.3.1.1 Epidemiology

First identified in 2004 (4), CDD has been difficult to diagnose until the recent implementation of genetic testing, which has also allowed for its early diagnosis (36). Due to the rare nature of the condition, the exact epidemiology of CDD is unknown. However, its incidence has been recently estimated to be 1.7–2.5 in 100,000 live births (3, 5)[c]. Based on these reported incidence rates and on Office for National Statistics figures showing 624,828 live births in 2021, it is estimated that in England and Wales 11 to 16 people are born each year with CDD (3, 5, 9). According to clinical expert opinion [redacted] the estimated number of diagnosed CDD cases (prevalence) in England and Wales is currently as low as 50 to 60 patients. Available epidemiology data show that not only CDD is a rare condition, but it is much rarer than other DEEs, including Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) (5-8). It is also reported to affect females more than males (~4:1) (3). CDD has only been fairly recently recognised as a clinically and genetically distinct disorder (37-39); thus, the time frames for life expectancy are also unknown (4).

A recent systematic literature review (SLR) conducted by Orion has confirmed that there is a paucity of robust epidemiology studies reporting the prevalence and/or incidence of CDD (10). Of the 15 identified studies reporting epidemiology data in patients with various DEEs, such as LGS, only two studies were specific to patients with CDD (5, 40).

In a study conducted in Scotland by Symonds et al, 2019 (5), the incidence of CDD was estimated to be 2.36 per 100,000 births (95% confidence interval [CI]; 0.81, 5.59). The

[c] Note that the original reported value is 1 in 40,000–60,000 (3); however, this value has been calculated per 100,000 live births to allow comparisons with other reported incidence data (5-8).

study included 343 infants (aged <36 months) diagnosed with multiple phenotypes for child-onset genetic epilepsies from 20 regional hospitals in Scotland from 2014–2017. Of the 169,470 live births included, 62 were of children with DEEs, and four patients were identified with the CDKL5 mutation, thus providing an estimate of the incidence. The number of births in Scotland during the study period was obtained from the National Records of Scotland (2018 data). To date, this study has provided the best estimate of CDD incidence. The only other epidemiology data specific to CDD are from a small study conducted in Japan (Kobayashi et al, 2016 (40)), which reported that 27.3% (n=3/11) of patients with early-onset epileptic encephalopathies (EOEE) had mutations in CDKL5.

B.1.3.2 *Burden to patients, carers and society*

B.1.3.2.1 Clinical burden

Evidence from several studies shows that CDD is a burdensome condition with clinical hallmarks, such as early-onset epilepsy and severe developmental delay, that have a profound impact on patients and caregivers (16, 17, 20-23, 25-27).

Seizures and developmental delays

International studies, conducted mainly in Europe and US, show that **seizures associated with CDD have an early onset, can be frequent and variable in their presentation, and are transiently responsive or refractory to ASMs (17, 20, 29)**.

Seizures can occur as early as 1 day after birth (21), with a median age at onset ranging from 4 to 8 weeks (16, 20-23, 25), and within 3 months of age in 90% of cases (3, 20, 29). The vast majority of patients suffer from early-onset seizures, with reported rates of >97% in all studies except one (Cutri-French et al (25), with 88.5%). Furthermore, most patients (65.3–88.9%) experience daily seizures and typically only a minority remain seizure-free (20, 21, 23, 25); in general, spasms are the most commonly reported type of seizure (16, 22, 23, 25-27).

CDD-associated seizures are transiently responsive or refractory to ASMs and, when responsive to therapy, improvements are often short-lived (17, 23, 29). Resistance to ASM is very common in patients with CDD, with reported treatment-resistance rates between 84% and 95% (17, 26). Notably, studies in patients with CDD have found that the efficacy of ASMs in this patient population is limited as response to treatment decreases over time (29, 30). A retrospective study reviewed the response[d] to ASMs in 39 children and adults with CDD from 21 centres in Europe and US (mean number of ASMs: 9; median: 9, range: 3–21). Overall, 34 (87%) patients showed an initial response to at least 1 ASM for several weeks, but most experienced loss of efficacy over time (30), with response rate of 69% (27/39) at month 3 from beginning ASM therapy, 45% (17/38) at month 6, and only 24% (9/38) at month 12. However, it should be considered that the

[d] Response was defined as >50% reduction in seizure frequency in the last 4 weeks compared with a 4-week pre-treatment baseline period (30).

number of patients treated with each single drug was limited, varying from 3 to 34. The reported response rates over time by ASM type are presented in

Table 3. The greatest effects were initially noted in patients on felbamate, clonazepam, vigabatrin and clobazam; however, the efficacy of these agents decreased over 12 months (

Table 3).

Table 3: Response rates over time of ASMs with varying mechanisms of action

ASM	Treated patients (N)	Responder rate (>50% seizure reduction), %		
		3 months	6 months	12 months
Felbamate	3	100%	67%	33%
Clonazepam	6	33%	17%	17%
Vigabatrin	25	32%	8%	4%
Clobazam	17	24%	6%	0%
Lamotrigine	23	22%	9%	9%
Valproate	34	21%	18%	9%
Zonisamide	11	18%	9%	0%
Topiramate	31	16%	3%	3%
Levetiracetam	31	16%	13%	0%
Phenobarbital	26	8%	8%	8%
Rufinamide	13	8%	0%	0%

Abbreviations: ASM, anti-seizure medication.
Source: Muller et al, 2016(30).

Due to the decreasing efficacy of ASMs over time, many patients with CDD need treatment with multiple drug therapy which, in many cases, involves treatment with two to five ASMs (27, 29).

Fehr et al, 2016 reported that 73.1% of patients in the study were on at least 2 ASMs (23) and Amin et al, 2017 that 95.2% of patients had tried at least 2 ASMs achieving poor control, and 33.3% had tried at least 8 ASMs (27). Furthermore, a in study analysing the phenotype of patients with a *MECP2*, *CDKL5*, or *FOXG1* mutation, seizures were not controlled by therapy in 84% of *CDKL5*-mutated patients vs 21.4% of *MECP2*-mutated patients and 58.8% of *FOXG1*-mutated patients (17).

Developmental delays affect all patients with CDD; they are typically severe and impair physical, cognitive, communication and behavioural skills. Only a minority of patients

achieve milestones such as ability to stand and walk independently, climb, talk as well as functional hand use (20, 23, 25-27). Furthermore, 30% to 75% of patients experience regression where patients lose acquired language and motor skills and exhibit intellectual disability and hand stereotypies (17, 20, 25, 26). Notably, a recent study conducted in 143 children with CDD reported the association between the CDD development score at follow-up and the seizure burden at baseline. Over time, development was marginally improved in patients with lower seizure burden (<5 seizure per day) compared with those with higher seizure burden (≥5 seizure per day) at baseline (beta-coefficient: -0.49 [95%CI: -0.84, -0.13]; p<0.05), suggesting that early seizure control may positively impact on patients' development (35).

Comorbidities

CDD is associated with debilitating comorbidities that affect multiple organ systems (3, 17, 20, 21, 23, 26, 29).
The most frequent comorbidities experienced by patients with CDD include hypotonia (in up to 100% of patients with CDD) (26, 29), nutritional problems (97.4%) (17), cortical visual impairment (in 80%) (26, 29) resulting in poor eye contact and eye pointing, and hand stereotypies (85.7%) (17).

Moreover, patients experience gastrointestinal, sleep and respiratory disorders (29). In children with CDD and epilepsy, some of these problems may arise within 48 hours of birth (23). Mangatt et al reported that 86.7% of children with CDD may develop a number of gastrointestinal problems during their lifetime, including constipation, reflux, air swallowing and gastrointestinal issues requiring gastrostomy, and that only a minority (5.3%) are able to eat and drink independently (21). Children with CDD often need treatment for feeding and swallowing dysfunction including feeding therapy, thickening of liquids, and gastrostomy tubes, all of which require additional parental or carer supervision (41).

Mangatt et al also reported that 87.7% of patients had sleep problems, with night waking, diurnal problems and teeth grinding being the most common (21). Respiratory disorders were reported for 32.5% of patients: in particular, breath holding occurred in 26.4% of patients and aspiration pneumonia, a life-threatening condition, in 22.6% of patients (21). Similar comorbidities were reported by Frullanti et al, who conducted a multinational study in 32 patients with CDD (17). Finally, a small proportion (6%) (17) of patients with CDD may present dysmorphic features of the face, limbs, and hands, that may assist in differentiation from other early-onset encephalopathies (3, 20).

B.1.3.2.2 Humanistic impact

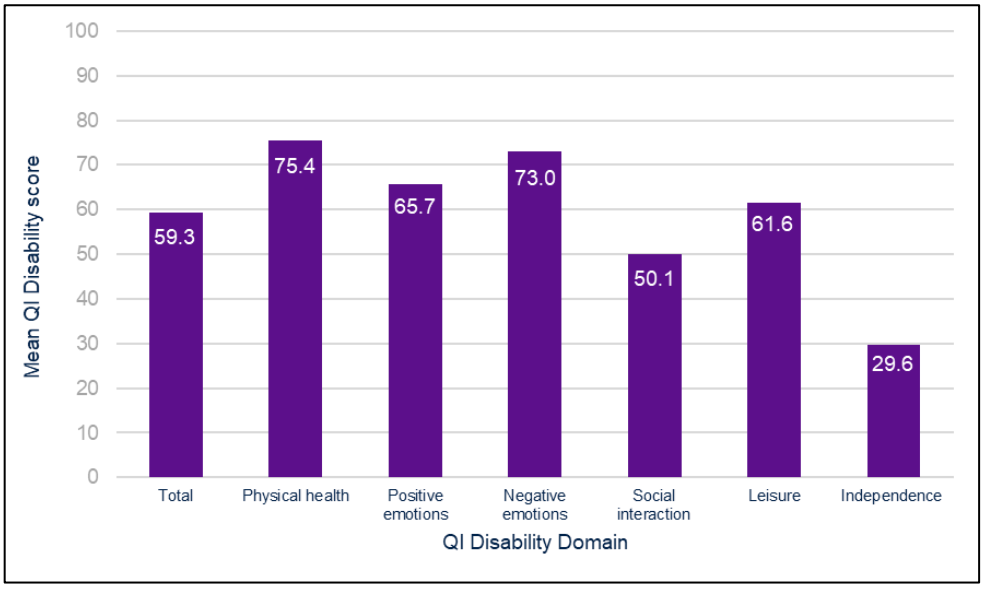
There is limited published literature on the humanistic impact of CDD on patients and caregivers (18, 19, 24, 35, 36, 42, 43). However, **evidence from available studies shows that frequent and intense seizures can affect the psychomotor and intellectual development of children with CDD, and ultimately impair the quality of life (QoL) of patients as well as the emotional and mental well-being of their caregivers (19, 24, 35).**

In the study by Leonard et al, 2021 (19), parents of 129 children with CDD (aged >3 years) in Europe, North America, Australia and New Zealand reported the QoL of their children using the quality of life inventory (QI)-Disability questionnaire, which has been specifically developed for children and adolescents with intellectual disability (19, 44, 45). There was a clear trend indicating that the higher the seizure frequency was, the lower was the QoL rated. While overall, functional impairment including lack of ability to sit, use hands, and communicate had the greatest adverse impact on children's QoL (19). Parents reported that their children had severely impaired functional abilities, and physical and mental health:

- **Functional abilities:** Children with CDD had severely impaired functional abilities, with only 24% being able to walk unaided, and 25% requiring some form of enteral feeding. Less than 20% were able to sign or use spoken language
- **Physical health:** At least 5 seizures per day were experienced by 31% of patients and 44.2% of patients were taking three or more ASMs; 52.7% of patients had moderate to severe sleep difficulties, and 37.2% experienced respiratory problems
- **Mental health:** High scores on the Anxiety, Depression, and Mood Scales social avoidance, depressed mood and hyperactive behaviour scales were common

Overall, the mean total health-related QoL score, as measured by the QI disability scale was 59.3 (Figure 2). The physical health domain had the highest score (75.4), while social interaction and independence had the lowest scores (50.1 and 29.6 respectively), suggesting that children with CDD are likely to be quite isolated and reliant on caregivers.

Figure 2: Summary of mean QI-Disability domain scores for children with CDD



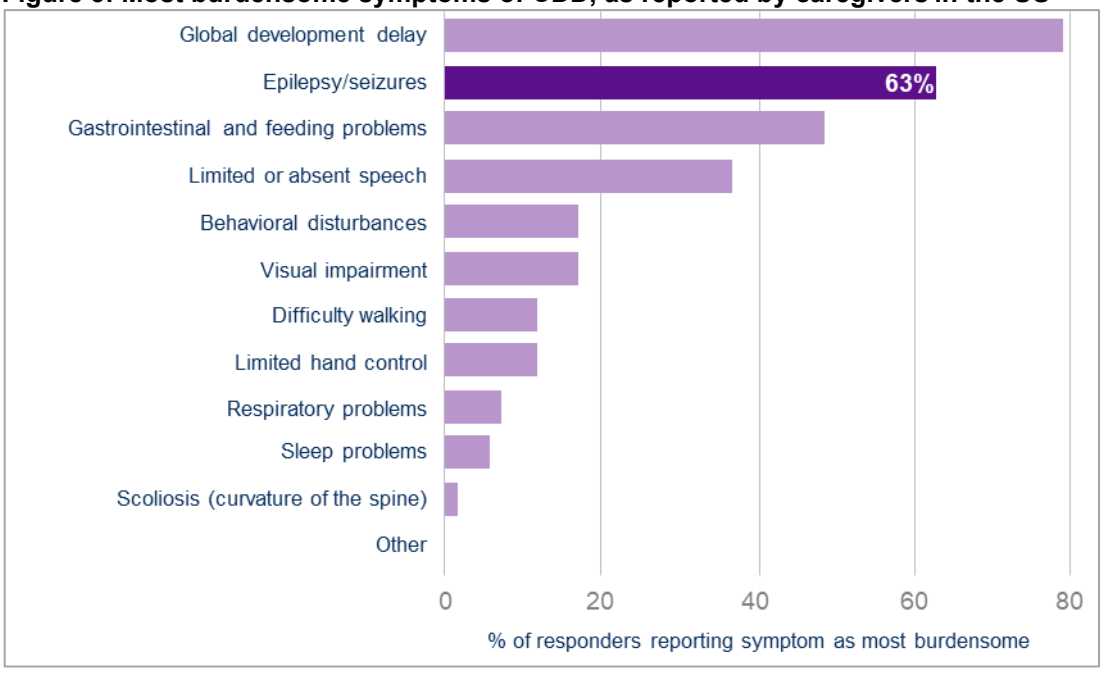
Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5; QI, quality of life inventory.
The 32 items of QI-Disability are worded positively to measure well-being, except for the items related to

"negative emotions", which are reverse coded. Each QI-Disability item is rated on a Likert scale of never, rarely, sometimes, often, and very often. After reverse coding of the “negative emotions” items, the scores are transformed to a range of 0–100, where never is scored as 0, rarely as 25, sometimes as 50, often as 75 and very often as 100 (19, 45). Finally, the converted scores are averaged over the items within the domains and over all the items (3). Therefore, scores closer to 0 indicate worsening QoL.
Source: Leonard et al, 2021 (19).

In a subsequent study conducted in 143 children with CDD, Leonard et al, 2022 demonstrated that patients with higher vs lower seizure burden (i.e., ≥5 vs <5 seizure per day, respectively) at baseline had a slightly worse development over time (as measured by the CDD development score; $p<0.05$) and that those with deteriorated development had poorer QoL (as measured by the QI-Disability Score) compared with those with stable or improved development (average total score: 8.5 [95%CI: 3.1–13.8] points lower) (35).

In line with the study by Leonard et al, a survey among 52 caregivers of children with CDD in the US, revealed that seizures are one of the most burdensome symptoms affecting patients, second only to global development delay. Caregivers in the survey also reported that the profound multisystem complications of CDD had a devastating impact on their family life (Figure 3) (18).

Figure 3: Most burdensome symptoms of CDD, as reported by caregivers in the US



Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5; US, United States.
Source: Loulou Foundation, 2020 (18).

Sleep disturbances are among the most burdensome and frequent symptoms in children with CDD. Downs et al, 2022 (42) explored the effects of insomnia and sleepiness on QoL in patients with CDD, using the QI-Disability questionnaire, the Disorders of Maintaining Sleep (DIMS) and the Disorders of Excessive Somnolence (DOES) items of

the Sleep Disturbance Scale for Children. Items from the DIMS and DOES questionnaires were rated on a 5-point Likert scale with higher scores representing more frequent sleep problems. Caregivers of 129 children with CDD completed the questionnaires. Results from the study showed that a unit increase in DOES score was associated with reduced QoL total (coefficient −3.06, 95% CI;1.35,7.80), physical health (coefficient −7.20; 95% CI −10.64, −3.76) and negative emotions (coefficient −3.90, 95% CI; −7.38, −0.42) scores; a unit increase in DIMS score was associated with reduced negative emotions (coefficient −6.02, 95% CI; −10.18, −2.86).

Impact of CDD on caregivers

The impact of CDD on caregivers was assessed by a study by Mori et al, 2017 (24). The well-being of 192 primary caregivers of patients with CDD was measured using the Short Form 12 Health Survey Version 2. Overall, caregivers had considerably impaired emotional wellbeing. This was associated with increased severity of child sleep problems and family financial difficulties. Notably, sleep problems for both patients and families may worsen in patients with high seizure frequency, as they increase the risk of nocturnal seizures. Family QoL was generally rated lowest in those using respite care extensively, suggesting that these families may be more burdened by daily caregiving. Furthermore, caregivers whose children were dependent on enteral nutrition had considerably poorer physical health (mean physical component summary score 49.6) compared with those whose child fed orally (mean physical component summary score 54.3; coefficient, −4.72; p=0.013). The same trend was also observed in caregivers who worked part-time (mean PCS score 50.4) compared with full-time homemakers (mean physical component summary score 55.1; coefficient, −4.69; p=0.006).

The caregivers' mental component summary scores were also greatly impacted. The severity of the child sleep disturbances was negatively associated with mental component summary, with a mean of 38.2 in the highest quartile (i.e., the greatest difficulty dealing with sleep disturbances) to 45.2 for the lowest quartile (i.e., the least difficulty dealing with sleep disturbances) (p=0.010). Mothers of children who were totally dependent on enteral nutrition had the highest mental component summary with a mean score of 47.4, significantly higher than those whose children were totally orally fed (p=0.013). Experiencing financial hardship also adversely affected mental health (coefficient, 4.89; p=0.011).

Another study described the experiences of 37 parents receiving their child's CDD diagnosis using semi-structured qualitative interviews (36). The main theme expressed by parents was grief. Parents' experience was different depending on their prognostic awareness at the time of diagnosis.

B.1.3.2.3 Economic impact

While published evidence on the economic burden of CDD is limited, two studies suggest that CDD imposes a considerable financial burden on both the healthcare systems and families (21, 24). The refractory nature of CDD-associated seizures and the debilitating comorbidities were shown to increase the likelihood of hospital admission

(21) while families reported experiencing financial difficulties to meet their child extensive healthcare needs (21, 24).

Mangatt and colleagues analysed data from International databases collected over 15 years and found a total of 531 hospitalisations due to seizures, respiratory infections, and other acute illnesses for 167 patients with CDD (98.0% having experienced 1 or more episodes of seizures) (21). Overall, seizures accounted for nearly two-thirds (63.5%) of hospitalisations in patients with CDD, with an incidence of 47.4 admissions/100 person-year and an average length of stay in hospital of 27.4 days. Moreover, 29.1% of patients had at least one hospitalisation related to respiratory problems over their lifetime, and these accounted for 11.7% of all hospitalisations, with an incidence of 8.2 admissions/100 person-year (21).

An International CDKL5 Disorder Database registry-based study investigating the impact of CDD on maternal health and family QoL reported that nearly 50% of families of a child with CDD in North America, Western Europe, Australia and New Zealand had faced financial difficulty to meet their child's extensive healthcare needs (24).

B.1.3.3 *Clinical pathway of care*

Currently, there are no therapies that can address the underlying causes of CDD (29). The therapeutic approach in patients with CDD is aimed at controlling symptoms and the most problematic complaints that increase patients' disability. Anti-seizure medications (ASMs) are the main pharmacological therapy for the management of seizures associated with CDD. However, none of the currently available ASMs are specifically approved for CDD, and they have limited and short-lived efficacy, with response rates decreasing drastically over time in most treated patients (29, 30).

Besides ASMs, non-pharmacologic methods, including a special, low-carbohydrate diet known as ketogenic diet, and vagus nerve stimulation or other surgical interventions may be offered to patients with CDD who have a suboptimal response to anti-seizure therapies (29).

While guidance on the assessment and management of CDD has been recently issued by an international panel of expert clinicians (28) and by the Haute Autorité de Santé (HAS) in France (46), there are no evidence-based European guidelines specific for CDD (see Section B.1.3.6).

The lack of specific clinical guidelines for CDD and the suboptimal efficacy of ASMs (29, 30) (Section B.1.3.2.1) have contributed to increase the complexity of the clinical pathway of care and patient journey which often involves multiple rounds of treatment switches/add-ons and multidisciplinary care, with neurologists acting as the ultimate decision makers (

Figure 4: The CDD patient journey in Europe) (47). Therefore, there is an unmet need for an efficacious, well tolerated treatment specific for CDD-related seizures that can improve and maintain clinical outcomes, thus reducing the disease burden.

Figure 4: The CDD patient journey in Europe

Abbreviations: AE, adverse event; ASM, anti-seizure medication; CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5; EEG, electroencephalogram; MRI, magnetic resonance imaging; VNS, Vagus nerve stimulation.
Source: Orion Pharma, 2022. Data on File (47).

B.1.3.3.1 Ganaxolone place in therapy

In the setting of CDD, GNX has demonstrated to be efficacious and well tolerated for the adjunctive treatment of CDD-associated epileptic seizures in a Phase III double-blind randomised, placebo-controlled trial (48) (Section B.2.6). Therefore, in England, it is anticipated that GNX will be offered as an add-on therapy for patients with CDD 2 years of age and older who are in need of improved seizure control despite treatment with current ASMs.

B.1.3.4 *Life expectancy*

Since CDD was first identified in 2004, the exact time frames for life expectancy are unknown (4). The SLR conducted by Orion to identify evidence on the burden of CDD in Europe (10) confirmed that there are no studies reporting mortality data in patients with CDD.

In contrast, a number of studies reported mortality data in patients with other DEEs (11, 12, 49-55), such as LGS and DS, which share some key features with CDD. A retrospective analysis of data from 256 patients with confirmed (43%) or probable (57%) LGS reported a crude mortality rate of 6.17 and 4.17 deaths per 1,000 person-years, respectively (11), which is higher than that reported for the general population in England (0.6 per 1,000 person-years) (56).

In a UK study conducted in 54 patients with confirmed or probable DS, less than 5 deaths were reported, suggesting a mortality rate lower than 9.25%[e] (53). Similarly, a Swedish study conducted in 53 patients with DS reported a mortality rate of 13% (49). Another study of 64 patients with probable DS in Germany reported a mortality rate of 11.9%, which was significantly higher compared with the rate observed in matched controls (1.2%, $p<0.001$) (12).

Furthermore, patients with epilepsy have a higher-than-expected risk of death throughout life, especially during the first 2 years following diagnosis, with persistent seizures being strongly related to excess mortality compared with no seizures (standardised mortality rate: 3.3 vs 1.4) (15). In this population, the major contributor to mortality is sudden unexpected death in epilepsy (SUDEP), which accounts for 35–50% of all epilepsy-related deaths (13, 14) and has an estimated incidence of approximately 1 per

[e] Note: The authors did not disclose the exact number to protect against potential reidentification (53).

1,000 patient-years both in children and adults (13). Notably, in patients with LGS; another DEE that shared with CDD early-onset epilepsy (typically within the first year of life) and the associated developmental delay (64), the mortality rate was estimated to be higher in those experiencing SUDEP and in those with a higher seizure burden (57), further supporting the concept that improved seizure management may be the best strategy to reduce the mortality risk. In the above-mentioned Swedish study, 3/7 deaths were attributed to definite of possible SUDEP (49).

B.1.3.5 *Relevant NICE guidance, pathways or commissioning guides*

B.1.3.5.1 Related NICE recommendations and NICE Pathways

Related Technology Appraisals

None

Related Guidelines

'Epilepsies in children, young people and adults' (2022). NICE guidelines NG217 (58)

Related Interventional Procedures

- 'Deep brain stimulation for refractory epilepsy in adults' (2020). NICE interventional procedures guidance IPG678 (59)
- 'MRI-guided laser interstitial thermal therapy for drug-resistant epilepsy' (2020). NICE interventional procedures guidance IPG671 (60)
- 'Vagus nerve stimulation for refractory epilepsy in children' (2004). NICE interventional procedures guidance IPG50 (61)

Related Quality Standards

- 'Epilepsy in adults' (2013). NICE quality standard QS26 (62)
- 'Epilepsy in children and young people' (2013). NICE quality standard QS27 (63)

B.1.3.5.2 Related National Policy

- 'Department of Health & Social Care (2021) The UK Rare Diseases Framework (64)
- 'NHS England (2020) Implementation Plan for the UK Strategy for Rare Diseases – progress report (65)
- 'The NHS Long Term Plan, 2019. NHS Long Term Plan (66)
- 'NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapters 11,78,119 (67)
- 'Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 2 and 4 (68)

B.1.3.6 *Clinical guidelines*

Currently, there are no evidence-based European guidelines for the management of CDD.

In June 2022, an international multidisciplinary panel of expert clinicians and researchers have issued guidance on the assessment and management of patients with CDD (28). While there was no consensus for any of the first-line suggested therapies, the standard

treatments of vigabatrin, steroids and the combination of these featured most strongly as first-line therapy among the surveyed experts (Table 4).

Table 4: First-line therapies for the management of CDD – International consensus recommendation for the assessment and management of CDD

Options suggested	Surveyed (n, %) experts favouring suggested therapy as first-line
Combination therapy with steroids and vigabatrin	15 (37.5%)
Steroids monotherapy	14 (35%)
Vigabatrin monotherapy	11 (27.5%)
Ketogenic diet	0 (0%)

Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5.
Source: Amin et al, 2022 (28)

Similarly, there was no consensus among second- or further-line therapy options; however, among a choice of steroids, vigabatrin, combination of these or the ketogenic diet, the ketogenic diet was selected by nearly a quarter of experts as a second-line therapeutic option.
Of note, there was 100% consensus among the experts that ganaxolone should be offered for epilepsy associated with CDD, if clinically indicated, dependent on local regulatory approval (28). Similary, offering cannabidiol (Epidyolex) was supported by 92.6% of the experts. However, it should be noted that, currently, Epidyolex is not authorised by the European Medicines Agency (EMA) or the UK Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of CDD, but only for some of the more prevalent DEEs, such as DS and LGS (69). Ganaxolone is the only treatment with efficacy demonstrated in a pivotal program specifically for CDD (Section B.2.6), and with an ongoing EMA approval process for CDD (Section B.1.2).

Specific guidance for the pharmacological treatment of patients with CDD has also been issued by the HAS in France, in collaboration with the Reference Center Intellectual Disabilities of Rare Causes and Rare Epilepsies, with recommendations that are broadly in line with those from the international consensus panel (46).

In addition, clinical guidelines for the management of epilepsies in children, young people and adults are available for the NICE in the UK (58). Although these guidelines do not specifically mention CDD, they cover other DEEs (e.g., DS and LGS). Key recommendations for the pharmacological treatment of epilepsies in children and adults are summarised in Appendix M.

B.1.3.7 *Issues relating to current clinical practice*

CDD imposes a substantial clinical and humanistic burden on patients and their caregivers, being characterised by severe and debilitating early onset seizures and multiple comorbidities. Therefore, patients require life-long treatment and extensive care and support (3, 16-23, 25-27).

Currently, in Europe there are no treatments specifically approved for CDD, nor the seizures associated with the condition. The therapeutic approach is primarily aimed at controlling symptoms and the most problematic complaints that increase patients' disability (29). Anti-seizure medications are the main pharmacological therapy for CDD-associated seizures. However, currently available ASMs have limited and short-lived efficacy in CDD, with response rates decreasing drastically over time in most treated patients (29, 30).

Therefore, there is an unmet need for an efficacious, well tolerated treatment specific for CDD-related seizures that can improve and maintain clinical outcomes, thus reducing the disease burden on patients and their caregivers.

B.1.4 *Equality considerations*

No equality issues have been identified.

B.2. Clinical effectiveness

Clinical evidence shows that ganaxolone (GNX), as adjunctive treatment to other ASMs, significantly reduces the frequency of major motor seizures in patients with CDD compared with placebo (PBO), and that the effect is sustained over time

- **Marigold**, a Phase III, global, double-blind, randomised, placebo-controlled trial, provides **pivotal clinical evidence** for GNX as an adjunctive treatment for major motor seizures in patients (2–19 years) with CDD. The ongoing **open-label extension (OLE) phase of Marigold** (interim results; cut-off date [redacted]) provides **long-term efficacy and safety** evidence for GNX in the same patient population
- **In the Marigold study, the primary efficacy endpoint (i.e., percentage change from baseline in 28-day major motor seizure frequency [MMSF] during the 17-week study period) was met**
  - Patients treated with GNX experienced a **statistically significant**, **4.5-fold reduction** from baseline in median 28-day MMSF vs patients receiving PBO (30.7% vs 6.9%, p=0.0036; difference: 27.1% [95% confidence interval [CI]; 47.9, 9.6])
- **Adjunctive treatment with GNX resulted in considerably higher response rates compared with PBO**
  - During the entire double-blind phase, **response rate** (i.e., the percentage of patients with a ≥50% reduction from baseline in MMSF) was **2.5-fold greater** in the GNX group compared with the PBO group, approaching statistical significance (24.5% vs 9.8%; difference 14.7%; p=0.064)
  - During the maintenance period (i.e., weeks 5–17, when patients have reached their individually optimised target dose after titration) the **proportion of ≥50% responders** was **significantly higher** with GNX than with PBO (difference: [redacted]); this difference was also greater than that observed during the entire DB period, where in the first 4 weeks patients were on suboptimal dosing.
- **Clinical global impression ratings suggested overall patient improvements with GNX compared with PBO**
  - **Caregivers** rated 62.5% of GNX-treated patients as improved, compared with 43.8% in the PBO group (odds ratio [OR], 1.9; 95% CI: 0.9, 3.9)
  - **Clinicians** rated 54.2% of GNX-treated patients as improved, compared with 41.7% in the PBO group (OR, 1.4; 95% CI: 0.7, 2.9)
- **Patients in the GNX group experienced a directional increase in the percentage of major motor seizure-free days compared with PBO (median change from baseline: 4.91% vs 0.17%)**

- **Caregiver reporting suggested improvements with GNX in seizure intensity and duration compared with PBO**
    - A **substantially higher** proportion of patients in the GNX group experienced **improvements** in **seizure intensity and duration** compared with PBO (62% vs 36%), as reported by the caregivers on the CGI-CSID
- **Trends of QoL improvement were observed in patients treated with GNX compared with PBO**
    - GNX-treated patients had a greater improvement from baseline to week 17 in [redacted] domains in the quality of life-inventory (QI) disability scale, with an overall mean change from baseline of 4.28 in the GNX group and 1.84 in the PBO group
- **During the OLE phase of Marigold, GNX showed sustained efficacy in reducing the frequency of major motor seizures in treated patients**
    - In patients who switched from PBO to GNX treatment, reductions in MMFS observed over the first 4 weeks continued up to Months 19 to 20. In patients who continued treatment with GNX, reductions in MMSF were maintained up to Months 19 to 20 (Section B.2.6.2.1 and Figure 12)
    - Patients who switched from PBO to GNX reached similar response rates ([redacted]) within one month as the original GNX group ([redacted]) (Section B.2.6.2.2)
    - At week 17 of the OLE, patients were reported as improved by 68.0% and 73.6% of clinicians and caregivers, respectively, following the same trend as the double-blind phase of the trial

In the Marigold study, GNX displayed a favourable tolerability profile, which was maintained over time during the open-label extension phase

- GNX was generally well tolerated with the majority of treatment-emergent adverse events (TEAEs) being categorised as mild or moderate in severity (B.2.10.1.1)
- During the open-label extension of Marigold[f], GNX maintained a predictable tolerability profile in patients treated for ≥12 months, with no new safety signals identified (Section B.2.10.1.2)

B.2.1 *Identification and selection of relevant studies*

B.2.1.1 *Search strategy*

A systematic literature review (SLR) was conducted in November 2021, and updated in August 2022, to identify all available clinical and burden of illness evidence in patients with CDD. Given that evidence specific for this rare disorder was expected to be limited,

[f] Data cut-off point of [redacted]

the scope of the SLR was extended to include evidence relating to other forms of developmental and epileptic encephalopathies (DEE), including early-onset epileptic encephalopathies (EOEE), Lennox-Gastaut syndrome (LGS), Dravet Syndrome (DS) and Rett syndrome.

The data sources used to identify the relevant studies included electronic databases and hand-searching of grey literature including reference lists of included studies and other supplementary sources.

Full details of the methodology used for the SLR including the search strategy, databases searched, and selection criteria is presented in Appendix D.

B.2.1.2 *Study selection*

A summary of the inclusion and exclusion criteria is shown in Table 5.

Table 5: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population[†]	**Clinical SLR:** Patients with a diagnosis of CDKL5 deficiency disorder (CDD) **BOI SLR:** Patients with a diagnosis of CDD, Rett syndrome, DS, epileptic encephalopathy (LGS) or TSC[‡]	Other non-relevant populations
Intervention	Not restricted at present	-
Comparators	Not restricted at present	-
Outcomes	**Clinical SLR** • Frequency of motor seizures – both individually and grouped were reported • % reduction in seizures • Seizure free days • Seizure reported as response rate (i.e. (% with 50% and 30% reduction in seizures vs baseline) • Change in CGI of attention, change in target behaviour, improvement in seizure intensity and duration. • Physician CGI-I, overall score • Caregiver CGI-I, overall score • Frequency of concomitant medication use • Adverse events **BOI SLR** • **Epidemiological burden** o Incidence o Prevalence o Mortality o Risk factors • **Economic evaluation** o Incremental cost effectiveness ratios (ICERs) o Summary health outcomes (e.g., quality adjusted life years [QALYs], life years gained [LYG]) o Model summary (including perspective, time horizon and discounting) and structure	• Pharmacokinetic outcomes • Pre-clinical/in-vitro outcomes

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	○ Assumptions underpinning model structures ○ Sources of clinical, cost and quality of life inputs • **Cost/resource use** ○ Direct medical costs ○ Direct non-medical costs ○ Transportation ○ Childcare costs ○ Additional caregiver costs ○ Caregiver burden ○ Indirect/societal costs ○ Productivity losses ○ Absenteeism ○ Presenteeism ○ Withdrawal from labour force ○ Estimates of healthcare resource use ○ Length of stay ○ Vagus nerve stimulation ○ Surgery ○ Cost drivers including hospitalisation and length of stay ○ Assumptions underpinning resource use ○ Methods of valuation • **Humanistic burden** ○ Patient voice – descriptive information from families about the impact of the conditions on the child and family. ○ Utilities derived using generic preference-based instruments (e.g. EQ-5D, SF-6D, HUI2, HUI3, AQoL) for relevant health states ○ Direct utility estimates (e.g. standard gamble, time trade off) ○ Mapping studies, from disease-specific to generic preference-based measures or between different generic preference-based measures ○ Disease-specific or generic non-preference based QoL questionnaires	

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	○ Descriptive summary of health states, and/or change in health status/QoL results	
Study design	**Clinical SLR** • RCTs • Non-RCTs • Observational studies • SLR, MA, NMA (for reference checking only) **BOI SLR** • Any studies reporting original epidemiology, HRQoL/HSUV or cost and/or resource use data • Economic evaluations including: ○ Cost-effectiveness analysis ○ Cost-utility analysis ○ Cost-minimisation analysis ○ Cost-consequence analysis ○ Cost-benefit analysis ○ Cost offset analysis	• Animal / in-vitro studies • Editorials • Case reports • Narrative reviews
Language restrictions	English language publications (English language abstracts of foreign language publications will be considered for inclusion.)	Non-English language publications without an English abstract.

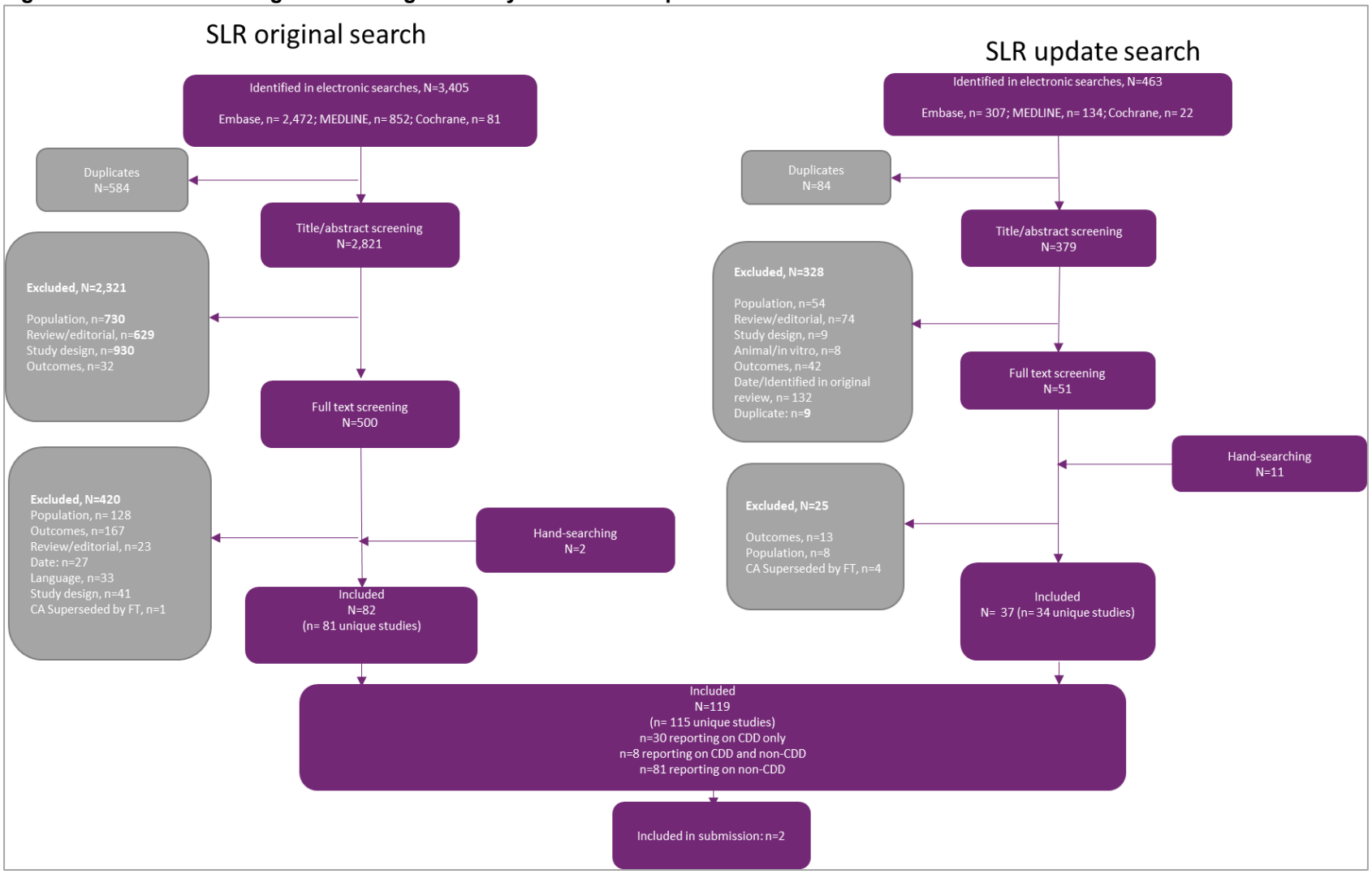
Abbreviations: BOI, burden or illness; CDD, CDKL5 deficiency disorder; CDKL5, cyclin dependent kinase like 5; CGI, Caregiver Global Impression; DS, Dravet syndrome; ICER, incremental cost effectiveness ratio, LGS, Lennox-Gastaut syndrome; SLR, systematic literature review; HSUV, health state utility value; HRQoL, health related quality of life; LYG, life year gained; MA, meta-analysis; NMA, network meta-analysis; QALY, quality adjusted life year; TSC, Tuberous Sclerosis Complex
† While the primary population of interest is patients with CDD, initial scoping searches revealed very little BOI evidence in this population. Therefore, the listed conditions, which are considered similar to CDD in certain respects, were included in the searches. These data could be used to populate the model should the CDKL5 literature be insufficient. ‡ Patients with TSC will be a population of interest only if reported as an economic evaluation.

The PRISMA flow diagram of the numbers of records included and excluded at each stage of both the original and updated searches is shown in Figure 5.

Overall, the electronic database search identified 3,868 citations (3,405 during the original search and 463 during the updated search), of which 668 were identified as duplicates and excluded (584 and 84, respectively). The remaining 3,200 citations were screened on the basis of title and abstract (2,821 during the original search and 379 during the updated search), and 2,649 were then excluded (2,321 and 328, respectively), leaving 551 citations to be screened on the basis of the full publications (500 and 51, respectively). During full text screening, 445 publications were subsequently excluded (420 during the original search and 25 during the updated search) resulting in 106 publications from the electronic database searches to be included in the SLR (80 and 26, respectively). Hand searching identified a further 13 citations that met the eligibility criteria (2 during the original search and 11 during the updated search), resulting in a total of 119 final included publications (82 and 37, respectively) relating to 115 unique studies (81 and 34, respectively). Of these, 30 reported data on CDD only, 8 on both CDD and non-CDD conditions, and 81 on non-CDD conditions only. A total of 2 clinical studies (on CDD only) were identified as relevant to this submission.

A complete list of included studies along with the full list of excluded studies with the rationale for exclusion is provided in Appendix D.

Figure 5: PRISMA flow diagram showing the study identification process



Abbreviations: CA, congress abstract; CDD, cyclin-dependent kinase-like 5 deficiency disorder; FT, full text; SLR, systematic literature review

B.2.2 *List of relevant clinical effectiveness evidence*

The systematic review of clinical evidence identified a single Phase III, randomised controlled trial (RCT) of ganaxolone (GNX) in the population of interest to this submission – the Marigold study (Table 6). The ongoing open-label extension (OLE) phase of the Marigold study was also identified in the systematic review. Interim results from this study (data from latest available cut-off point: [redacted]) are of relevance to this submission as they provide evidence of the long-term efficacy and safety and of GNX in the same patient population and informed the economic model for GNX. The study is anticipated to be completed by the end of December 2022.

The systematic review also identified a Phase IIa, open-label proof of concept trial (Study 1042-0900) evaluating GNX as adjunctive therapy for uncontrolled seizures in patients with different DEEs, including CDD (70). However, Study 1042-0900 only enrolled a small number of patients with CDD (n=7) and did not inform the economic model for GNX; therefore, evidence from this trial is considered supportive for this submission and is presented in Appendix D.

In addition, the systematic review identified an open-label prospective trial conducted in the US assessing the efficacy and safety of cannabidiol (given as part of state access programs for compassionate use) for the treatment of patients with severe childhood-onset epilepsy, including patients with CDD (n=20/55; 36%) (71). Nevertheless, this study is not deemed relevant for this submission as cannabidiol is not currently approved for use in CDD by the EMA or the UK MHRA.

A more detailed overview of the relevant trials (i.e., the Marigold study and its open-label extension) is presented in Table 7.

Table 6: List of relevant clinical evidence

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Refs identified but not used further	Is study excluded from further discussion? If yes state rationale
1042-CDD-3001 (Marigold)	Patients aged 2–21 years† with a pathogenic or probably pathogenic CDKL5 variant and at least 16 major motor seizures (defined as bilateral tonic, generalised tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic) per 28 days in each 4-week period of an 8-week historical period (N=101)	GNX + other ASMs	PBO + other ASMs	• Pestana-Knight et al, 2022 (48) • CSR (72)	Not applicable	No
Open-label extension phase of 1042-CDD-3001	All eligible patients from double-blind phase (N=88)	GNX + other ASMs	Not applicable	• Olson et al, 2022 (Abstract) (73) • Supporting information from (74)	Not applicable	No

Abbreviations: ASMs, anti-seizure medications; CDKL5, cyclin-dependent kinase like 5; CSR, clinical study report; GNX, ganaxolone; PBO, placebo
†Patients up to 21 years of age were eligible for the study; however, only patients aged 2 to 19 years were recruited in the trial.

Table 7: Clinical effectiveness evidence

Study	1042-CDD-3001 (Marigold)	Open-label extension phase of 1042-CDD-3001 (Marigold)
Study design	Phase III, double-blind, randomised, placebo-controlled	Phase III, open-label
Population	Patients aged 2-21 years with a pathogenic or probably pathogenic CDKL5 variant and at least 16 major motor seizures (defined as bilateral tonic, generalised tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic) per 28 days in each 4-week period of an 8-week historical period (N=101)	All eligible patients from double-blind phase (N=88)
Intervention(s)	GNX (oral suspension 50 mg/mL, TID) + other ASMs (n=50)	GNX (oral suspension 50 mg/mL, TID) + other ASMs (n=88)
Comparator(s)	PBO + other ASMs (n=51)	None (open-label GNX in all)
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	Not applicable	Not applicable
Reported outcomes specified in the decision problem	• **Seizure frequency (overall and by seizure type)†** • Proportion of people seizure-free (overall and by seizure type) • Seizure severity • **Adverse effects of treatment** • **Health-related quality of life**	
All other reported outcomes	*Efficacy endpoints* • Number (%) of patients with a ≥50% reduction from baseline in MMFS • Change from baseline in the percentage of seizure-free days during the 17-week double blind treatment phase • QoL measured by the QI-disability and PSI scales • CGI-I at the last scheduled visit in the 17-week double-blind treatment phase • CGI-C in parent/caregiver identified behavioural target (potential domains include sociability, communication, irritability, and hyperactivity) • CGI-CA score • CGI-CSID score *Safety endpoints*	

Study	1042-CDD-3001 (Marigold)	Open-label extension phase of 1042-CDD-3001 (Marigold)
	• Clinical laboratory tests • Vital signs including temperature, blood pressure, pulse rate, respiration rate • Physical, neurological, and developmental examinations • ECG	

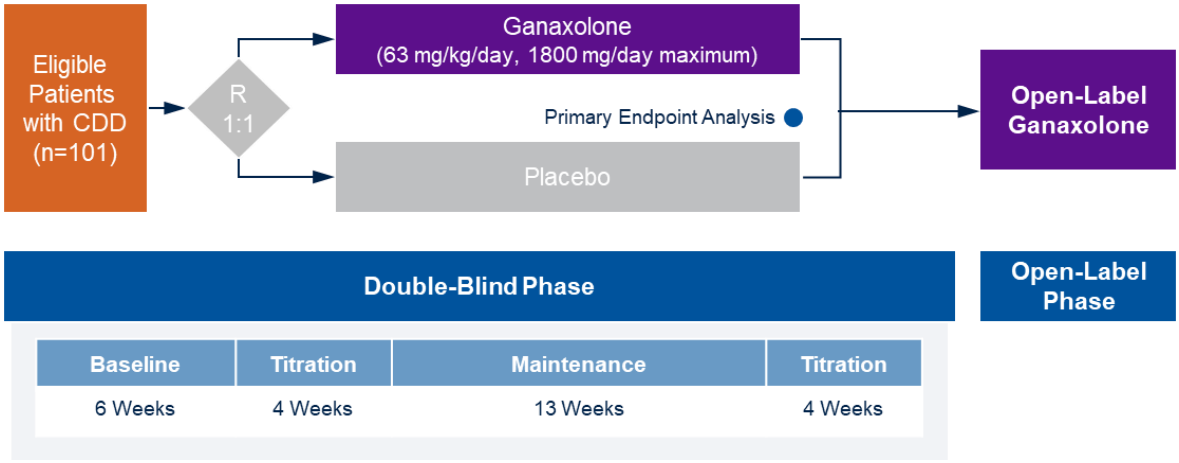
Note: the outcomes incorporated into the economic model are marked in bold.
Abbreviations: ASM, anti-seizure medication; CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5 deficiency disorder; CGI-C, caregiver global impression of change; CGI-CA, caregiver global impression of change in attention; CGI CSID, caregiver global impression of change in seizure intensity/duration; CGI-I, clinical global impression improvement; CGI-CA, caregiver global impression of change in attention; ECG, electrocardiogram; GNX, Ganaxolone; MMFS, major motor seizure frequency; PBO, placebo; PSI, Parenting Stress Index; QI, Quality of life Inventory; TID, three times daily
†This outcome includes the percentage change from baseline in 28-day MMSF during the 17-week double-blind treatment and, based on the major motor seizure types.

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

B.2.3.1 *Comparative summary of RCT methodology*

The Marigold study (1042-CDD-3001) was a Phase III, global, double-blind, randomised, placebo-controlled trial conducted to evaluate the efficacy, safety, and tolerability of GNX as adjunctive treatment for major motor seizures in patients (2–21 years) with CDD. This trial consisted of a 6-week prospective baseline period to collect seizure data, followed by a 17-week double-blind treatment phase, which was then followed by an ongoing open-label phase to evaluate long-term seizure changes in eligible patients receiving GNX. The design and methodology of Marigold and of its open-label extension phase are summarised in Figure 6 and Table 8, respectively.

Figure 6: Marigold study design overview



Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5 deficiency disorder; R, randomisation.

Table 8: Comparative summary of trial methodology

Trial number (acronym)	1042-CDD-3001 (Marigold)	OLE phase of 1042-CDD-3001 (Marigold)
Trial design	Phase III, DB, randomised, placebo-controlled trial	Phase III, OL
Duration	23 weeks in total: 6-week prospective baseline period and a 17-week DB treatment phase	Currently ongoing; estimated duration: 2–3 years
Settings and locations where the data were collected	39 outpatient clinics in 8 countries (Australia, France, Israel, Italy, Poland, Russian Federation, United Kingdom, and the US)	
Eligibility criteria for participants (extended information on eligibility criteria is provided in Table 9)	Patients aged 2–21 years with a pathogenic or probably pathogenic CDKL5 variant and at least 16 major motor seizures (defined as bilateral tonic, generalised tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic) per 28 days in each 4-week period of an 8-week historical period	All eligible patients from DB phase
Method of randomisation	Patients were randomised in a 1:1 ratio to receive either GNX or PBO, in addition to their ASM treatment, during the 17-week DB phase of the study. An IWRS centrally randomised patients	Not applicable (OL study)
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	**Experimental arm (n=50)**: • GNX, oral suspension (50 mg/mL) taken three times daily, and titrated for 4 weeks as follows: o *Patients weighing ≤28 kg*†: starting dose of 6 mg/kg TID (i.e., 18 mg/kg/day) on day 1–7 and weekly increments of 15 mg/kg/day up to a maximum target dose of 63 mg/kg/day o *Patients weighing >28 kg*†*:* starting dose of 150 mg TID (i.e., 450 mg/day) on day 1–7 and weekly increments of 450 mg/day up to a maximum dose of 1,800 mg/day • Established clinical management	**Experimental arm (N=88)**‡ • GNX, oral suspension (50 mg/mL) taken three times daily: o *Patients treated with GNX during the DB phase*: continued on the same dose o *Patients treated with PBO during the DB phase*: started GNX at 6 mg/kg TID or 150 mg/TID based on body weight and then increased the dose, following the titration scheme used in the DB phase, up to the maximum target dose • Established clinical management

Trial number (acronym)	1042-CDD-3001 (Marigold)	OLE phase of 1042-CDD-3001 (Marigold)
	Comparator arm (n=51) • PBO, oral suspension, taken three times daily and titrated for 4 weeks following the same titration scheme used for GNX • Established clinical management	**No comparator**, all patients on GNX
Permitted and disallowed concomitant medication	• Participants were on a stable regimen of zero to 4 anti-seizure medications (including moderate or strong inducer or inhibitor anti-seizure medications e.g. carbamazepine, phenytoin, etc.) for ≥ 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of the double-blind phase • The use of felbamate was allowed provided that the subject had been maintained on a stable dose of felbamate for > 6 months and had stable liver function (AST and ALT) and haematology during the course of treatment, and was expected to remain constant throughout the double-blind phase • Concomitant Epidiolex (CBD) use was allowed in the double-blind phase provided the subject had been on a stable dose for at least 1 month prior to screening and was expected to remain on a stable dose • Concomitant PRN topical or intranasal steroids for dermatologic reactions and allergic rhinitis were allowed • Concurrent use of ACTH, prednisone or other glucocorticoid was not permitted, nor use of moderate or strong inducers or inhibitors of CYP3A4/5/7	
Primary outcomes (including scoring methods and timings of assessments)	Percentage change from baseline in 28-day major motor seizure frequency (MMSF) during the 17-week DB treatment phase. Post-baseline 28-day seizure frequency was calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with seizure data in the phase, multiplied by 28. Similar calculation was applied for the pre-baseline period of 6 weeks¶	

Other outcomes used in the economic model/specified in the scope	**Efficacy endpoints**
	• Key secondary endpoints:
	  ○ Number (%) of patients with a ≥50% reduction from baseline in MMSF
	• Pre-specified secondary endpoints included
	  ○ Change from baseline in the percentage of seizure-free days during the 17-week DB treatment phase, based on the major motor seizure types§
		The same efficacy, exploratory, quality of life, and safety endpoints for the DB phase will also be used for the OLE phase, except for the changes in seizure frequency during the titration and the maintenance phase.

Trial number (acronym)	1042-CDD-3001 (Marigold)	OLE phase of 1042-CDD-3001 (Marigold)
	○ Change in seizure intensity/duration/severity (by CGI CSID score)§ ○ CGI-C in parent/caregiver identified behavioural target (potential domains include sociability, communication, irritability, and hyperactivity) ○ CGI-CA score • Exploratory endpoints ○ QoL measured by the QI-disability and PSI scales§ **Safety endpoints** • AEs§ • Clinical laboratory tests • Vital signs including temperature, blood pressure, pulse rate, respiration rate • Physical, neurological, and developmental examinations • ECG	
Pre-planned subgroups	Patients stratified by gender and Allo-S levels	Not applicable

Abbreviations: ACTH, Adrenocorticotropic hormone; AE, adverse event; ALT, alanine transaminase; ASM, antiseizure medication; AST, aspartate aminotransferase; CBD, cannabidiol; CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5; CGI-C, caregiver global impression of change; CGI-CA, caregiver global impression of change in attention; CGI CSID, caregiver global impression of change in seizure intensity/duration; CGI-I, clinical global impression improvement; DB, double-blind; ECG, electrocardiogram; GNX, ganaxolone; IWRS, Interactive web response system; MMSF, major motor seizure frequency; OL open-label; OLE, open-label extension; PBO, placebo; PRN, pro re nata (i.e., as needed); PSI, Parenting Stress Index; QI, Inventory disability; QoL, quality of life; TID, three times daily; US, United States
†Patients weighing ≤28 kg were dosed on a mg/kg basis, and patients weighing >28 received the maximal dose. The dosing regimens during the initial 28-day taper for patients weighing ≤28 kg and patients weighing >28 kg are described in (1). ‡Forty-three patients were from the experimental arm of the DB phase and 45 from the comparator arm. They are referred to as GNX/GNX and PBO/GNX, respectively. §Phenytoin and carbamazepine were permitted as background AEDs although they are moderate CYP 3A4 inducers. ¶Outcomes used to inform the economic model and/or specified in the scope.
….

Table 9: Extended eligibility criteria for Marigold

Trial number (acronym)	1042-CDD-3001 (Marigold)
Inclusion criteria	• Molecular confirmation of a pathogenic or likely pathogenic CDKL5 variant, early onset, difficult to control seizures, and neurodevelopmental impairment were required • Male or female patients aged 2 through 21 years‡ inclusive • Failure to control seizures despite appropriate trial of ≥2 ASMs at therapeutic doses • Had ≥16 seizures of major motor seizure† types: bilateral tonic (sustained motor activity ≥ 3 seconds), generalised tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic per 28 days in each 1-month period in the 2-month period prior to screening • Participants were on a stable regimen of zero to 4 ASMs for ≥ 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of the double-blind phase. VNS, ketogenic diet, and modified Atkins diet did not count towards this limit but must have been unchanged for 3 months prior to screening • The PI must have reviewed the results of the genetic analysis and confirmed that gene mutation was likely to be the cause of the epilepsy syndrome. If the patient had a de novo variant of unknown significance in the kinase domain of the CDKL5, parental testing was negative and met all other inclusion criteria, then the patient was included. • Genetic mutations were confirmed by the sponsor's chosen central laboratory. In France, genetic mutations may have been confirmed by an approved French organization, in compliance with French legislation prior to Screening Visit 1. • Patients must have had seizure onset by 1 year of age and lack of independent ambulation by 2 years of age. • Patient/parent or LAR was willing to give written informed consent/assent, after being properly informed of the nature and risks of the study and prior to engaging in any study-related procedures. • Patient was approved to participate by sponsor and/or designee (i.e., Epilepsy Consortium) after review of medical history, genetic testing, seizure classification, and historical seizure calendars. • Patients with surgically implanted VNS could enter the study if all the following conditions were met: • The VNS had been in place for ≥1 year prior to the screening visit. • The settings remained constant for 3 months prior to the screening visit and remained constant throughout the double-blind phase. • The battery was expected to last for the duration of the double-blind phase. • Felbamate: The use of felbamate was allowed provided that the patient had been maintained on a stable dose of felbamate for >6 months and had stable liver function (AST and ALT) and haematology during the course of treatment and was expected to remain constant throughout the double-blind phase.

Trial number (acronym)	1042-CDD-3001 (Marigold)
	• Parent/caregiver was able and willing to maintain an accurate and complete daily electronic seizure calendar for the duration of the study. • Was able and willing to take investigational product with food TID. GNX must have been administered with food. • Sexually active female of childbearing potential must have used a medically acceptable method of birth control and had a negative quantitative serum β-hCG test collected at the initial screening visit. Childbearing potential was defined as a female who was biologically capable of becoming pregnant. A medically acceptable method of birth control included intrauterine devices in place for at least 3 months prior to screening, surgical sterilization, or adequate barrier methods (e.g., diaphragm and foam). An oral contraceptive alone was not considered adequate for the purpose of this study. Hormonal oral contraceptives must also have been used when a condom was used. In patients who were not sexually active, abstinence was an acceptable form.
Exclusion criteria	• Previous exposure to GNX • West Syndrome with hypsarrhythmia pattern on EEG or seizures predominantly of IS type; if EEG pattern/seizure type was uncertain, study inclusion was reviewed and determined by the sponsor/sponsor delegate • Concurrent use of ACTH, prednisone or other glucocorticoid was not permitted, nor use of moderate or strong inducers or inhibitors of CYP3A4/5/7. Moderate or strong inducer or inhibitor AEDs were allowed (e.g., carbamazepine, phenytoin, etc.) • Patients on ACTH, prednisone, or other systemically (non-inhaled) administered steroids should have been off the product >28 days prior to screening. Concomitant PRN topical or intranasal steroids for dermatologic reactions and allergic rhinitis were allowed and did not warrant exclusion from the study§ • Changes in AEDs within the last month prior to screening. All AEDs must have been stable in dose for at least 1 month prior to screening unless otherwise noted • Had an active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive as evaluated by brain imaging (MRI) • Pregnant or breastfeeding • Patients with a positive result on THC or CBD test (via urine or plasma drug screen) at the screening visit, and a positive result on THC or CBD test (via plasma) at the baseline visit without prescription for Epidiolex (may go by another name in countries outside the United States) in epilepsy were excluded from the study. Concomitant Epidiolex (CBD) use was allowed in the double-blind phase provided the patient had been on a stable dose for at least 1 month prior to screening and was expected to remain on a stable dose without a foreseeable change for the duration of the double-blind phase. THC and/or CBD were allowed in the open-label phase

Trial number (acronym)	1042-CDD-3001 (Marigold)
	• Use of dietary supplements or herbal preparations were not permitted if patient had been using them consistently for less than 3 months prior to screening or did not plan on remaining on stable doses for the duration of the double-blind phase. Use of St. John's Wort was not permitted • Had any disease or condition (medical or surgical; other than CDKL5) at screening that might have compromised the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, or hepatic systems; or other conditions that might have interfered with the absorption, distribution, metabolism, or excretion of the IP, or would have placed the patient at increased risk • An AST (SGOT) or ALT (SGPT) >3 x ULN at study entry. If AST or ALT increased >3 x ULN during the study, patient was followed with weekly laboratory repeat testing and continued in study if levels were trending down. Patient was discontinued if levels did not decline to <3 x ULN • Total bilirubin levels greater than ULN at study entry. In cases of documented, stable medical condition (i.e., Gilbert's Syndrome) resulting in levels of total bilirubin greater than ULN, the medical monitor determined if a protocol exception could be made. If total bilirubin increased to 1.5 x ULN or more during study, the patient was discontinued • Patients with significant renal insufficiency, eGFR <30 mL/min (calculated using the Cockcroft-Gault formula, Paediatric GFR calculator or Bedside Schwartz), were excluded from study entry or were discontinued if the criteria were met post-baseline • Had been exposed to any other investigational drug within 30 days or less than 5 half-lives prior to screening • Were unwilling to withhold grapefruit, Seville oranges, or star fruit from diet during the entire clinical trial • Were unwilling to withhold alcohol throughout the entire clinical trial. • Had active suicidal plan/intent or had active suicidal thoughts in the past 6 months or a suicide attempt in the past 3 years • Had a known sensitivity or allergy to any component in the IP, progesterone, or other related steroid compounds • Had plasma Allo-S levels ≥6.0 ng/mL at the screening visit¶

Abbreviations: ACTH, adrenocorticotropic hormone; AED, anti-epileptic drug; Allo-S, Allopregnanolone Sulfate; ALT, alanine aminotransferase; ASM, anti-seizure medication; AST, aspartate aminotransferase; β-hCG CBD, cannabidiol; CDKL5, cyclin-dependent kinase-like 5; CNS, central nervous system; EEG, electroencephalogram; eGFR, estimated glomerular filtration rate; GNX, ganaxolone; IP, Investigational product; IS, infantile spasms; LAR, legally authorised representative; MRI, magnetic resonance imaging; PI, principal investigator; PRN, pro re nata; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; THC, ∆9-tetrahydrocannabinol; TID, three times daily; ULN, upper limit of normal; VNS, vagus nerve stimulator

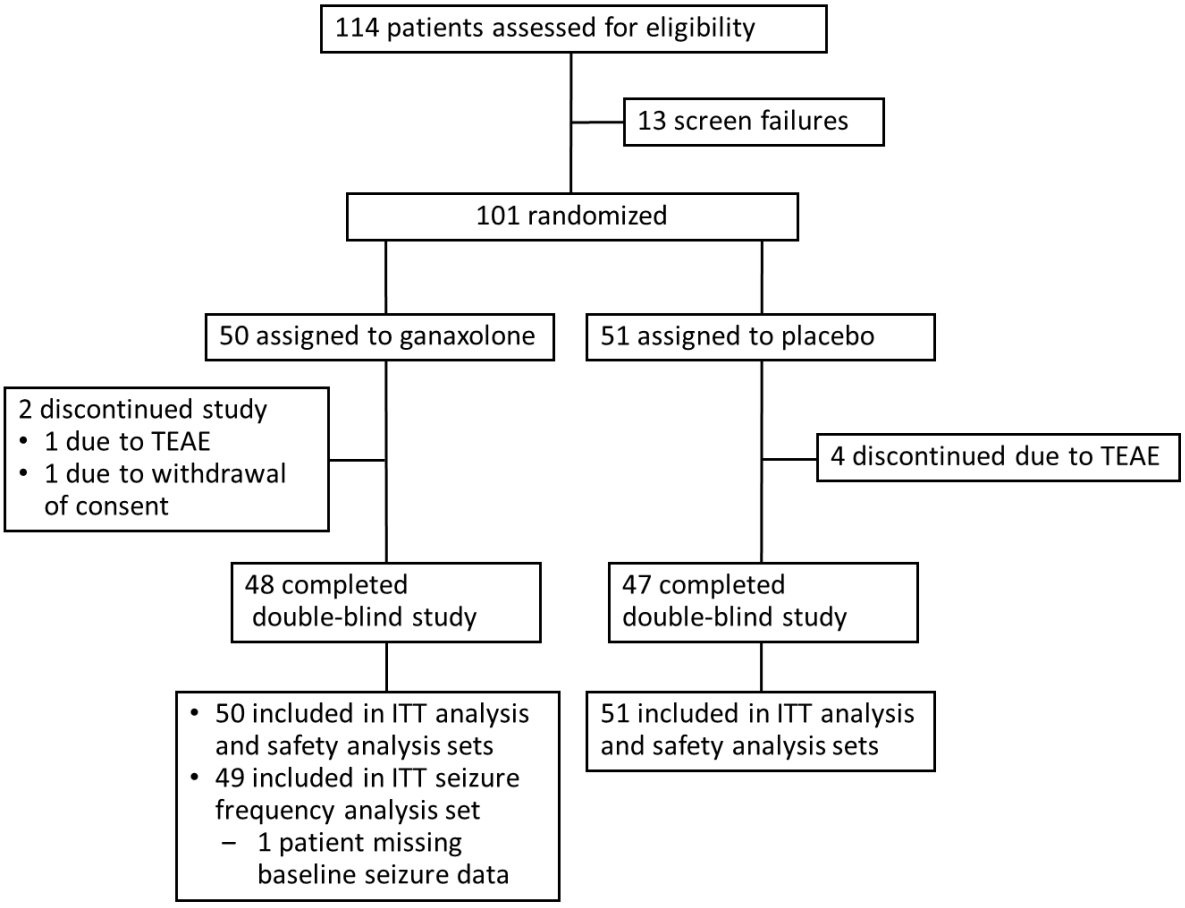
†The term "primary seizures" was used in the Study 1042-CDD-3001 protocol to refer to the seizure types evaluated for the primary endpoint; the more commonly accepted clinical term "major motor seizures" is used for those seizure types in this document. Major motor seizures include bilateral tonic (sustained motor activity ≥3 seconds), generalised tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic seizures. ‡Patients up to 21 years of age were eligible for the study; however, only patients aged 2 to 19 years were recruited in the trial. §Patients could take rescue medication for seizure control as required. Use of rescue medications (ASMs) were recorded in the patient's e-diary. ¶Note that this criterion was removed in an amendment made approximately 6 months after study enrolment start.

B.2.3.2 *Patient disposition*

B.2.3.2.1 Double-blind phase of study 1042-CDD-3001 (Marigold)

Of the 101 patients randomised, 95 (94.1%) completed the 17-week double-blind phase and 6 (5.9%) patients discontinued from the study. Discontinuations from study were due to adverse events (AEs) (1 [2.0%], GNX group; 4 [7.8%], placebo [PBO] group) and withdrawal by patient or parent/legally authorised representative (LAR) (1 [2.0%], GNX group). The patient in the GNX group who discontinued the study drug due to an AE continued in the study until the end of the double-blind phase. Patient disposition is presented in Figure 7 and reasons for study discontinuation are summarised in Table 10.

Figure 7: Patient disposition (all patients)



Note: 50 patients were randomised to GNX and received the study drug thus comprising the ITT population. One patient randomised to GNX experienced seizures during the 6-week baseline period, but the frequency of those seizures was not recorded in their electronic seizure diary (e-diary). Thus, all seizure-related efficacy endpoints, including the primary endpoint, were based on data from 100 patients (GNX, n=49; PBO, n=51). All demographics and safety analyses do include this patient and are therefore evaluated in a population of 101 patients (GNX, n=50; PBO, n=51)
Abbreviations: ITT, intent-to-treat; TEAE, treatment-emergent adverse events

Table 10: Patient disposition and reason for study discontinuation (17-week double-blind phase)

Category	Ganaxolone n (%)	Placebo n (%)	Total n (%)
Patients randomised†	50	51	101 (100)
Safety/ITT Population‡§	50 (100)	51 (100)	101 (100)
PP Population‡⁋	48 (96.0)	48 (94.1)	96 (95.0)
Patients who completed 17-week DB Phase††	48 (96.0)	47 (92.2)	95 (94.1)
Patients who completed 17-week DB Phase but stopped taking Study Drug Before the End††	3 (6.0)	0 (0)	3 (3.0)
Reason for Discontinuation††			
Adverse event	1 (2.0)	4 (7.8)	5 (5.0)
Withdrawal by patient or parent/LAR	1 (2.0)	0 (0)	1 (1.0)

†Percentages are based on screened patients. ‡Percentages are based on randomised patients. §The safety and ITT populations include all randomised patients who received at least 1 dose of study drug. ⁋ The PP population includes ITT patients who received study drug for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and had no major protocol violations. ††Percentages are based on safety population.
Abbreviations: DB, double-blind; ITT, intent-to-treat; LAR, legally authorised representative; PP, per protocol.

B.2.3.2.2 Open-label phase of study 1042-CDD-3001 (Marigold)

Overall, 88/101 (87.1%) patients randomised to the double-blind phase continued to the open-label extension (OLE). Of these, 43 patients were initially randomised to GNX (GNX/GNX group) and 45 to PBO (PBO/GNX group). As of data cut-off point of [redacted], 57 (64.8%) patients are ongoing in the open-label treatment phase (30 [69.8%], GNX/GNX group; 27 [60.0%], PBO/GNX group). Most trial discontinuations were due to lack of efficacy (7 [16.3%], GNX/GNX group; 5 [11.1%], PBO/GNX group); AEs (1 [2.3%], GNX/GNX group; 8 [17.8%], PBO/GNX group); or withdrawal by patient or parent/LAR (4 [9.3%], GNX/GNX group; 4 [8.9%], PBO/GNX group). Patient disposition and reason for study discontinuation are summarised in Table 11.

Table 11. Patient disposition and reason for study discontinuation (open-label extension phase, safety population)

Category	GNX n (%)	PBO n (%)	Total n (%)
Patients from the DB phase who continued into the OLE phase†	43 (86.0)	45 (88.2)	88 (87.1)

Category	GNX n (%)	PBO n (%)	Total n (%)
Treatment groups during OL phase	**GNX/GNX n (%)**	**PBO/GNX n (%)**	**Total**
Patients who are ongoing in the OLE phase‡ (at time of data cut off)§	30 (69.8)	27 (60.0)	57 (64.8)
Patients who completed OLE phase‡	0 (0)	0 (0)	0 (0)
Patients who discontinued in the OLE phase‡ (at time of data cut off)§	13 (30.2)	18 (40.0)	31 (35.2)
Reason for discontinuation‡			
AE	1 (2.3)	8 (17.8)	9 (10.2)
Lost to follow-up	0 (0)	0 (0)	0 (0)
Lack of efficacy	7 (16.3)	5 (11.1)	12 (13.6)
Physician decision	0 (0)	1 (2.2)	1 (1.1)
Withdrawal by patient or parent/LAR	4 (9.3)	4 (8.9)	8 (9.1)
Protocolviolation/protocol deviation	0 (0)	0 (0)	0 (0)
Death	1 (2.3)	0 (0)	1 (1.1)
Sponsor decision	0 (0)	0 (0)	0 (0)

Abbreviations: AE, adverse event; DB, double blind; GNX, ganaxolone; LAR, legally authorised representative; OLE, open label extension; PBO, placebo.
Patients are grouped by the treatment received in the DB phase. †Percentages are based on safety population in the double-blind phase. ‡Percentages are based on the number of patients who continued into open-label extension phase. §Data cut-off: [redacted]

B.2.3.3 *Patient demographics and baseline characteristics*

Overall, patient demographics and baseline characteristics in the GNX and PBO groups were comparable (Table 12). The majority of patients were white (n=93, 92.1%), female (n=80, 79.2%) of not Hispanic or Latino (n=87, 86.1%) ethnicity. The mean age was 7.26 (standard deviation [SD]: 4.5) years and mean body mass index (BMI) was 15.53 (6.3) kg/m^2. Enrolled patients had experienced treatment failure on a median of 7 previous ASMs, were taking an average of 2.4 concomitant ASMs at baseline (most commonly valproate, levetiracetam, clobazam, and vigabatrin) and continuing to have frequent seizures (Table 13).

Table 12: Patient demographics and baseline characteristics – double-blind phase

Category	Ganaxolone n (%)	Placebo n (%)	Total n (%)
Demographics			
Age (years)			
n	50	51	101
Mean (SD)	6.78 (4.7)	7.73 (4.4)	7.26 (4.5)
Sex, n (%)			
Male	11 (22.0)	10 (19.6)	21 (20.8)
Female	39 (78.0)	41 (80.4)	80 (79.2)
Ethnicity, n (%)			
Hispanic or Latino	4 (8.0)	6 (11.8)	10 (9.9)
Not Hispanic or Latino	44 (88.0)	43 (84.3)	87 (86.1)
Unknown	1 (2.0)	1 (2.0)	2 (2.0)
Not reported	1 (2.0)	1 (2.0)	2 (2.0)
Race, n (%)			
White	46 (92.0)	47 (92.2)	93 (92.1)
Black or African American	0 (0)	0 (0)	0 (0)
Asian	2 (4.0)	3 (5.9)	5 (5.0)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
Other	2 (4.0)	1 (2.0)	3 (3.0)
Baseline physical characteristics			
Weight, kg			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Category	Ganaxolone n (%)	Placebo n (%)	Total n (%)
Height (cm), mean (SD)	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; IQR, interquartile range; Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation.

With regard to prior and concomitant treatments, generally, the proportion of patients using ASMs, non ASM, and non-pharmacological therapies prior or during the study were similar for both the GNX and PBO cohorts (Table 13).

Table 13: Summary of prior and concomitant medications used

Medications used		Ganaxolone	Placebo	Total
Patients to have taken an ASM, n (%)	Prior to first dose	48 (96.0)	50 (98.0)	98 (97.0)
	During study	49 (98.0)	48 (94.1)	97 (96.0)
Patients to have taken a non-ASM, n (%)	Prior to first dose	7 (14.0)	14 (27.5)	21 (20.8)
	During study	42 (84.0)	47 (92.2)	89 (88.1)
Patients to have taken a non-pharmacological therapy, n (%)	Prior to first dose	9 (18.0)	8 (15.7)	17 (16.8)
	During study	29 (58.0)	26 (51.0)	55 (54.5)
Prior and concomitant ASMs				
Median number of prior ASMs used, n (range)		7 (2–16)	7 (1–14)	7 (1–16)
Mean number of concomitant ASMs, n (SD)		2.6 (1.39)	2.2 (1.14)	2.4 (1.28)
Valproate semisodium, n (%)		18 (36.0)	16 (31.4)	34 (34.0)
Levetiracetam, n (%)		13 (26.0)	13 (25.5)	26 (26.0)
Clobazam, n (%)		12 (24.0)	13 (25.5)	25 (2.05)
Vigabatrin, n (%)		10 (20.0)	12 (23.5)	22 (22.0)

Abbreviations: ASM, anti-seizure medication; SD, standard deviation.

Overall, 97.0% of patients (GNX group, 96.0%; PBO group, 98.0%) used any prior ASM medication, with a median number of 7 (range: 1–16) ASMs taken and stopped prior to treatment for all patients (GNX group, 7 [range: 2–16]; PBO group, 7 [range: 1–14]).

Concomitant ASMs were used by 96.0% of patients (GNX group, 98.0%; PBO group, 94.1%). Patients enrolled in the study could be on a stable regimen of up to 4 concomitant ASMs (see inclusion criteria, Table 9). The mean (SD) number of concomitant ASMs used by patients was 2.4 (1.28) (GNX group, 2.6 [1.39]; PBO group, 2.2 [1.14]). The most frequently used concomitant ASMs (used by ≥10 patients in either treatment group) were valproate semisodium, levetiracetam, clobazam, and vigabatrin (Table 13).

In both groups, use of non-AMS increased during the study. Prior to the study, 21% of patients (GNX group, 14.0%; PBO group, 27.5%) used any non-ASM, whereas during the study, concomitant non-ASM were used by 88.1% of patients (GNX group, 84.0%; PBO group, 92.2%). The most frequently used concomitant non-ASMs were paracetamol (GNX group, 30.0%; PBO group, 29.4%) and Macrogol 3350 (GNX group, 10.0%; PBO group, 21.6%]).

Ketogenic diet was the most frequently used prior non-pharmacological therapy and was administered to 5.9% of patients (GNX group, 6.0%; PBO group, 5.9%); all other prior therapies were administered to ≤2 patients in either treatment group. During the double-blind phase, concomitant ketogenic diet was reported for 10.9% of patients (GNX group, 8.0%; PBO group, 13.7%). Concomitant therapies were administered to 54.5% of patients (GNX group, 58.0%, PBO group, 51.0%), the most frequent being physiotherapy, speech rehabilitation, and occupational therapy.

Patients who continued to the OLE phase represented 87.1% of those originally randomised in the double-blind phase with a fairly even split of 86% from the double-blind GNX arm and 88.4% from the PBO arm, respectively. Therefore, patient baseline characteristics during the two phases of the study are considered similarly distributed, except for seizure frequency, which was already improved to the level of week 17 in patients treated with GNX but not in those treated with PBO.

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

A CONSORT diagram provides details of the numbers of eligible participants, and on the number of participants randomised and allocated to each treatment arm in the Marigold trial (Figure 7).

B.2.4.1 *Populations analysed*

B.2.4.1.1 Study 1042-CDD-3001 (Marigold)

Definitions of the populations analysed in Marigold are listed below:

- **Safety and intent-to-treat (ITT) population:** This population comprises all randomised subjects who received ≥1 dose of study drug. In addition to being the population for the safety analyses, it is the primary population for the efficacy analyses.
- **Per-protocol (PP) population:** The PP population includes ITT patients who received study drug for ≥6 weeks, provided ≥5 weeks of post-baseline seizure data, and had no major protocol violations

In the double-blind phase, all efficacy analyses were conducted in the ITT population. A supportive analysis of the primary and secondary efficacy endpoints also was conducted in the PP population.

B.2.4.1.2 Open-label phase of study 1042-CDD-3001 (Marigold)

For the open-label phase, no PP analysis was performed.

B.2.4.2 *Statistical analysis*

B.2.4.2.1 Study 1042-CDD-3001 (Marigold)

A summary of the statistical methods used in Marigold is presented in Table 14. Due to the highly rare occurrence and severity of this condition limiting study participation, the study sample size was small and powered only for the statistical analysis of primary end point.

Table 14: Summary of statistical analyses in the Marigold trial

Trial no. (acronym)	**1042-CDD-3001 (Marigold)**
Hypothesis objective	To demonstrate the benefit on the percent change in 28-day major motor seizure frequency on GNX minus that on placebo in patients (2–19 years) with CDD
Statistical analysis of primary efficacy endpoint	The difference between the treatment groups in the percent changes from baseline was tested for statistical significance. Since the percent differences were

	anticipated to display skewness and/or outliers, the tests were performed using the Wilcoxon Rank-Sum statistic. Formal hypothesis testing was performed for the single primary efficacy endpoint. Because of the planned interim analyses (planned to be conducted when 50 and 75 subjects were at least 17 weeks post randomisation)† using an O'Brien-Fleming boundary, at least 0.0250 - 0.0013 = 0.0237 of the (one-sided) false positive error remained for the final analysis. Hence, the two-sided p-value of statistical significance at the final analysis was approximately 0.048. The null hypothesis was rejected for the primary efficacy endpoint at the two-sided α-level allocated to the final analysis of the primary endpoint (p = 0.0036). Statistical hypothesis testing was then performed on the two key secondary endpoints sequentially.
Statistical analysis of secondary efficacy endpoints	Comparison for statistical significance of endpoints ended when the first non-significant result was encountered (analysis of the 50% responder rate endpoint [p=0.0643]). All secondary efficacy endpoints compared GNX and PBO at the end of the 17-week DB treatment phase relative to the 6-week prospective baseline phase. If any endpoint value at baseline was zero, then any percentage changes from baseline for that endpoint would be missing. Results were summarised using descriptive statistics. All secondary analyses were conducted primarily in the ITT population and secondarily in the PP population, while all exploratory analyses were performed in the ITT population
Statistical analysis of safety endpoints	All safety analyses were performed in the Safety population.
Sample size, power calculation	Based on data from the 7 patients in Study 1042-0900 evaluating GNX in CDKL5 patients (75) the standard deviation for the percent change in 28-day seizure frequency for seizure types tonic (sustained motor activity ≥ 3 seconds), tonic-clonic, atonic/drop, epileptic spasms, or clonic (generalised or unilateral) was estimated to be 44.5. Therefore, it was estimated that with a percent change in 28-day seizure frequency on GNX minus that on PBO truly of 30%, a trial with 100 subjects randomized in a 1:1 manner would have 92% power to detect this effect when using an ANOVA that preserves a (one-sided) 2.5% false positive error rate. If the true difference in the percent changes was 35%, then the study would have 97.5% power. The threshold for achieving statistical significance at the final analysis when 100 subjects have completed their 17-week DB treatment phase would be an estimate of the difference that is approximately 17.5% (the actual analysis has used a Wilcoxon rank-sum test, which has approximately the same power as the ANOVA.)

Data management, patient withdrawals	The primary analysis used all available data. While careful educating and monitoring of the study sites attempted to limit the amount of missing data to nearly zero, some missing data still arose. To address this, a sensitivity analysis on the primary efficacy endpoint was performed in which any missing data was replaced When an item from an endpoint was missing, any subscales or totals that included it were also considered as missing. Patients who prematurely discontinued from the study were asked to complete the non-seizure assessments at the Taper Visit. For analysis purposes, their data from the Taper Visit was reassigned to the first visit at which the assessment was originally scheduled

Abbreviations: ANOVA, analysis of variance; CDKL5, cyclin-dependent kinase-like 5; CDD, CDKL5 deficiency disorder; DB, double blind; GNX, Ganaxolone; ITT, intent-to-treat; PBO, placebo; PP, per protocol.
† According to the Data Monitoring Committee (DMC) charter, O'Brien-Fleming boundaries were to be applied for these two interim analyses (IAs). Specifically, to claim superiority, for IA-50, the (one-sided) nominal p-value corresponding to the Z-value of 3.73 was 0.0001; and for IA-75, the (one-sided) nominal p-value corresponding to the Z-value of 3.03 was 0.0012. IA-50 was performed for both safety and efficacy analyses. The p-value for the primary endpoint was 0.003, which did not cross the superiority boundary The DMC recommended that the study could continue without modification. The IA-75 was not performed as, due to accelerated enrolment, it would have been performed when only 10 subjects remained on study, all of whom were to complete the study prior to the DMC meeting to review data from the IA-75.
Source: Marinus Pharmaceuticals.Clinical study 1042-3001. Statistical analysis plan, 2021 (44)

B.2.4.2.2 Open-label phase of study 1042-CDD-3001 (Marigold)

All the analyses for the double-blind phase were repeated for the open-label phase, with the following differences:

- Results were presented overall and by the treatment received by patients during the double-blind phase
- The post-baseline seizure endpoints were derived starting from the first dosing day of the open-label treatment
- The seizure frequencies during the titration and maintenance phases were not analysed separately
- The time points for the efficacy, exploratory, and QoL endpoints were at Weeks 21, 34, 52, and every 16 weeks thereafter of open-label treatment relative to the 6-week prospective baseline phase. For the seizure endpoints, this corresponds to the first 4, 17, 35, 51, etc. weeks from the start of the open-label extension phase
- The differences between the DB treatment groups were not tested for statistical significance
- No PP analyses were performed

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

The quality assessment for the Marigold study (and its open-label extension), which is the only identified clinical study of relevance to this submission, is presented in Table 15.

Table 15: Quality assessment results for Marigold and open-label extension phase

	Marigold study	Open-label extension
Was randomisation carried out appropriately?	**Yes**: randomisation was carried out in a 1:1 ratio using IWRS.	**Not applicable**: After completing the double-blind phase, all eligible patients were treated with GNX in the open-label phase of the study. GNX patients continued treatment with GNX (GNX/GNX group) and PBO patients were titrated onto GNX treatment (PBO/GNX group).
Was the concealment of treatment allocation adequate?	**Yes**: a centralised interactive response system was used to allocate patients.	
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes**: all demographic and baseline characteristics known to influence clinical outcomes were well-balanced between study arms, including median 28-day MMSF, and prior and concomitant treatments (see Table 12 and Table 13).	Patient demographic and baseline characteristics in the open-label phase are considered similar to those in the double-blind phase, as 86% and 88.4% of GNX and PBO groups, respectively, continued to the OLE phase.
Were the care providers, participants and outcome assessors blind to treatment allocation?	**Yes**: all providers, assessors and patients were blind to treatment allocation. An interactive web response system was used to randomise patients, dispense drug, track treatment, and maintain the blind throughout the duration of the study.	**No**: Open-label To maintain the blind from the double-blind phase, patients initially randomised to GNX underwent a false titration (increasing PBO doses) for 4 weeks, while PBO patients underwent a 4-week dose titration up to 63 mg/kg/day GNX (1,800 mg/day max) during the same time.
Were there any unexpected imbalances in drop-outs between groups?	**No**: discontinuations rates were comparable between the two treatment arms (see Table 10).	**No**: discontinuations rates were comparable between the two treatment arms (see Table 11).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No**: the primary, key secondary, pre-specified and exploratory outcomes listed in the methodology section are consistent with those reported in the results section.	
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes**: in the double-blind phase, all efficacy analyses were conducted in the ITT population. A supportive analysis of the primary and secondary efficacy	**Yes**: All the analyses for the double-blind phase will be repeated for the open-label phase, with the following differences:

	Marigold study	Open-label extension
	endpoints was also conducted in the PP population. The ITT and PP populations were defined as follows: • The safety and ITT populations included all randomised patients who received ≥1 dose of study drug • The PP population included ITT patients who received study drug for ≥6 weeks, provided ≥5 weeks of post-baseline seizure data, and had no major protocol violations To account for any missing data, a sensitivity analysis on the primary efficacy endpoint was performed. When an item from an endpoint was missing, any subscales or totals that included it were also considered as missing. Patients who prematurely discontinued from the study were asked to complete the non-seizure assessments at the Taper Visit. For analysis purposes, their data from the Taper Visit was reassigned to the first visit at which the assessment was originally scheduled	• The seizure frequencies during the titration and maintenance phases were not analysed separately • The differences between the double-blind treatment groups were not tested for statistical significance • No PP analyses were performed

Abbreviations: AE, adverse event; BMI, body mass index; GNX, ganaxolone; ITT, intent-to-treat; IWRS, Interactive Web Response Systems; MMSF, major motor seizure frequency; OLE, open label extension; PBO, placebo; PP, per protocol.

B.2.6 *Clinical effectiveness results of the relevant studies*

B.2.6.1 *Study 1042-CDD-3001 (Marigold)*

B.2.6.1.1 Primary efficacy outcome

The primary efficacy endpoint was defined as the percentage change from baseline in 28-day major motor seizure frequency (MMFS) during the 17-week double-blind treatment phase[g].

The primary efficacy endpoint in this study was met. At the end of the 17-week double-blind phase, there was a statistically significant difference in the median percent change from baseline in seizure frequency for patient in the GNX group compared with those in the PBO group (−30.7%, GNX group[,h] −6.9%, PBO group; Wilcoxon Test p=0.0036). The Hodges-Lehmann estimate of location shift was −27.1% (95% CI; −47.9, −9.6), indicating a significant improvement in the GNX group compared with the PBO group (see Table 16 and Figure 8). These results are notable given that patients had a high seizure burden at baseline, with an average of 3.7/4.1 daily major motor seizures (104 and 115 per 28 days in the PBO and GNX groups, respectively), and having received a median of seven prior ASMs (see Table 13).

Table 16: Summary of 28-day seizure frequency for major motor seizure types (17-week double-blind phase, ITT population)

Interval	Ganaxolone (N=50)	Placebo (N=51)
Number of major motor seizures per 28days		
Baseline period		
Patients, n	49	51
Mean (SD)	115.4 (138.4)	103.9 (173.0)
Median (95% distribution-free CI)	54.0 (38.2, 106.7)	49.2 (32.2, 60.7)
Hodges-Lehmann estimate of location shift (95% CI)[†]	12.0 (−8.4, 32.7)	
Wilcoxon test p-value	0.2384	
17-week post-baseline phase		
Patients, n	50	51
Mean (SD)	93.7 (133.9)	151.0 (469.5)

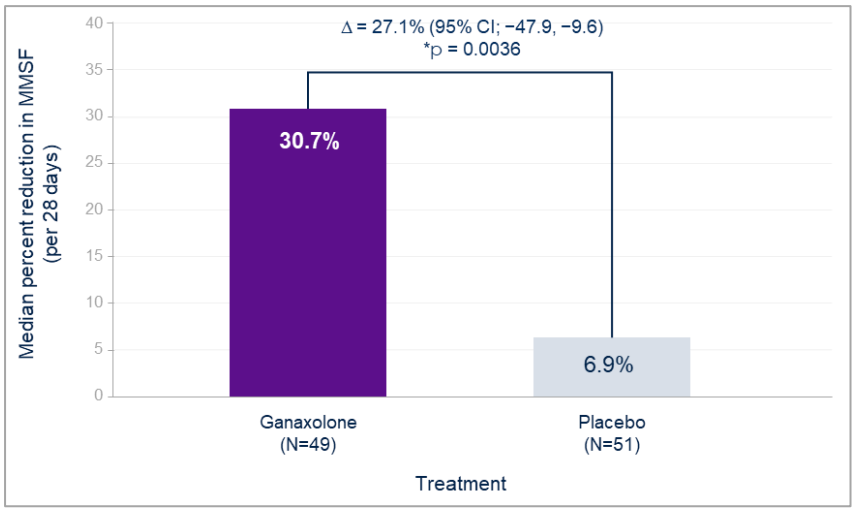
[g] Post-baseline 28-day seizure frequency was calculated as the total number of seizures in the 17-week double-blind treatment phase (including dose titration period) divided by the number of days with seizure data in the phase, multiplied by 28. Similar calculation was applied for the pre-baseline period of 6 weeks.

[h] For all seizure-related outcomes that require a baseline period, the sample size for GNX-treated patients is n=49.

Interval	Ganaxolone (N=50)	Placebo (N=51)
Median (95% distribution-free CI)	45.0 (31.8, 76.0)	55.5 (35.8, 80.1)
Hodges-Lehmann estimate of location shift (95% CI)†	−4.2 (−24.6, 14.3)	
Percent change from baseline		
Patients, n	49	51
Mean (SD)	−14.0 (64.5)	64.6 (272.5)
Median (95% distribution-free CI)	−30.7 (−36.0, −12.0)	−6.9 (−16.5, 15.3)
Hodges-Lehmann estimate of location shift (95% CI)†	−27.1 (−47.9, −9.6)	
Wilcoxon test p-value	0.0036	
Wilcoxon test Z-value‡	−2.9098	

Abbreviations: CI, confidence interval; ITT, intent-to-treat; SD, standard deviation.
Notes: Summaries are based on the sum of the individual seizures, the countable seizures, and the clusters with uncountable seizures (each cluster with uncountable seizures counts as 1 seizure). Within the baseline and post-baseline intervals, 28-day seizure frequency was calculated as the total number of seizures in the interval divided by the number of days with available seizure data in the interval, multiplied by 28.
The major motor seizure types include bilateral tonic (sustained motor activity = 3 seconds), generalised tonic-clonic, atonic/drop, bilateral clonic, and focal to bilateral tonic-clonic.
The baseline interval consists of the 6 weeks prior to the first dose.
The 17-week Post-Baseline interval consists of the first day after the first dose up to the day before Visit 5 (Week 17), if available; otherwise up to the last day with seizure data. However, if a patient successfully completes the double-blind phase without a Visit 5, with a Taper Visit, and does not enter the open-label extension, then the interval ends the day before the Taper Visit.
Duplicate seizure diary entries were excluded from this analysis.
†An estimate of how far the responses in the GNX group are shifted from the PBO group. ‡A Z-value lesser than or equal to −1.9603 is required for statistical significance at the 0.025 1-sided level.

Figure 8: Percent change from baseline in 28-day seizure frequency for major motor seizure types (17-week double-blind phase, ITT population)



Abbreviations: ITT, intent-to-treat; MMSF, major motor seizure frequency
*p-value is based on Wilcoxon test.
Δ = Hodges-Lehman estimate of location shift

B.2.6.1.2 Sensitivity analysis of primary outcome

Results for the sensitivity analyses of the primary endpoint (percent change from baseline in 28-day MMSF) were in line with those for the primary analysis of the primary endpoint. Key results from the sensitivity analyses are as follows:

- **Sensitivity Analysis 1** (imputation of median PBO group counts): there was a statistically significant difference in the median percent change from baseline in seizure frequency [redacted] GNX group, [redacted] PBO group; [redacted]) with a median shift from the PBO group to the GNX group of [redacted] indicating improvement in the GNX group compared with the PBO group
- **Sensitivity Analysis 2** (imputation of median of 5 highest PBO group counts): there was a statistically significant difference in the median percent change from baseline in seizure frequency ([redacted] GNX group, [redacted] PBO group; p=0.0086) with a median shift from the PBO group to the GNX group of [redacted], indicating improvement in the GNX group compared with the PBO group
- **Sensitivity Analysis 3** (subjects with low baseline Allo-S levels): there was no statistically significant difference in the median percent change from baseline in seizure frequency (−25.37% GNX group, −9.53% PBO group; p=0.0706) with a median shift from the PBO group to the GNX group of −20.99%, indicating improvement in the GNX group compared with the PBO group

B.2.6.1.3 Key secondary efficacy outcomes

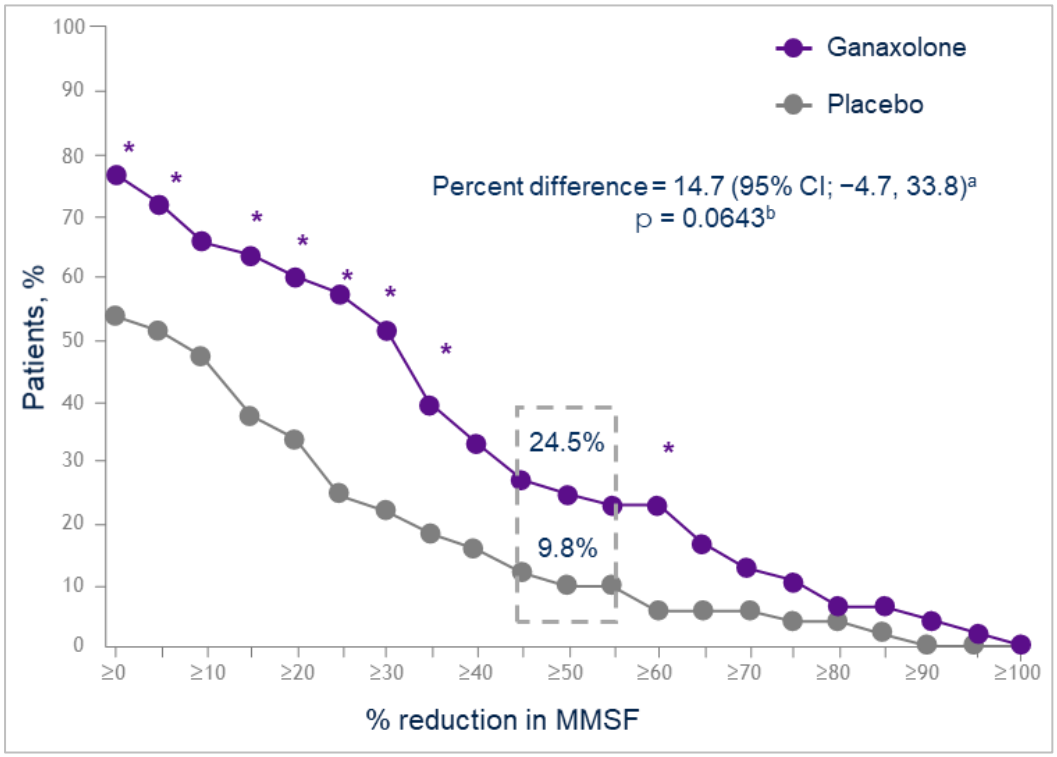
Since the primary endpoint was met, formal statistical analysis was permitted for the first of three secondary endpoints, the number [%] of patients with a ≥50% reduction from baseline in MMSF (response rate). The other two key secondary efficacy endpoints were CGI-I parent/caregiver scores at the last scheduled visit in the 17-week double-blind phase, and CGI-I clinician scores at the same time point. Overall, results for these endpoints were in favour of GNX (Figure 9 and Table 17), in line with the primary efficacy endpoint.

Response rate

The percentage of patients with a ≥50% reduction from baseline in MMSF (response rate) was in numerical favour for the GNX group (12 [24.5%], GNX group; 5 [9.8%], PBO group), approaching statistical significance (p=0.0643, Figure 9). Of note, the small sample size was the main limitation to reaching statistical significance for this endpoint; one GNX-treated patient experienced a 49.5% reduction in MMSF, which prevented from reaching a potential p-value of 0.02.

Overall, response rates in the GNX group were greater than those in the PBO group, with rates up to 95% (Figure 9). Notably, at any response level between ≥0 to ≥95% the rate of responders numerically favoured GNX compared with PBO. The difference in the response rates was statistically significant up to a response of ≥35% (p<0.05).

Figure 9: Proportion of ≥50% responders depicted against the cumulative response curve (week 17, ITT population)



Abbreviations: ITT, intent-to-treat; MMSF, major motor seizure frequency.
"Responder" in this main responder analysis was defined as a patient with at least 50% reduction from baseline in 28-day MMSF. *p-value was based on Fisher's Exact test.

An additional responder analysis, similar to the one performed for the entire double-blind period, was conducted for the maintenance period only (i.e., excluding the first 4 weeks of dose titration, when GNX dose is still suboptimal). This analysis indicated that, during the maintenance period, the difference in the ≥50% response rate between GNX and PBO was statistically significant [difference [redacted] (Fisher's exact test)], and slightly greater than that observed during in the entire double-blind period (see Section B.2.6.1.5, Figure 11).

CGI-I parent/caregiver and clinician score at the last scheduled visit in the 17-week double-blind treatment phase

During the double-blind phase of the trial, an overall improvement was observed in patients treated with GNX compared with those receiving PBO, as measured by the CGI-I parent/caregivers and clinician scales (Table 17).

The **CGI-I parent/ caregiver**-administered scale rated 62.5% of patients in the GNX group as improved compared with 43.8% of patients in the PBO group (OR, 1.9; 95% CI: 0.9, 3.9). A lower proportion of parents/caregivers of patients in the GNX group rated the response to treatment as "worsened or no change" compared with parents/caregivers of patients in the PBO group.

The **CGI-I clinician**-administered scale rated 54.2% of patients in the GNX group as improved compared with 41.7% of patients in the PBO group (OR, 1.4; 95% CI: 0.7, 2.9). A lower proportion of clinicians of patients in the GNX group rated the response to treatment as “worsened or no change” compared with clinicians of patients in the PBO group.

Table 17: CGI-I scores at end of 17-week double-blind treatment phase (ITT population)

Variable	Ganaxolone (N=50)	Placebo (N=51)
CGI-I (parent/caregiver), N	48	48
Improved n, (%)	30 (62.5)	21 (43.8)
Worsened or no change, n (%)	18 (37.5)	27 (56.2)
Odds ratio (95% CI)	1.9 (0.9, 3.9)	
Logistic regression p-value‡	0.971	
CGI-I (clinician), N	48	48
Improved, n (%)	26 (54.2)	20 (41.7)
Worsened or no change, n (%)	22 (45.8)	28 (58.3)
Odds ratio (95% CI)	1.4 (0.7, 2.9)	
Logistic regression p-value‡	0.3518	

Abbreviations: CGI-I, clinical global impression of improvement; CI, confidence interval, ITT, intent-to-treat. The baseline interval consisted of the 6 weeks prior to the first dose.
‡CGI-I analysis was based on ordinal logistic regression model adjusted for treatment group as a fixed factor. The analysis is based on the CGI-I values reported at the last scheduled visit in the 17-weeks double-blind treatment phase.

B.2.6.1.4 Pre-specified seizure control and behavioural/neuropsychiatric secondary endpoints

Pre-specified secondary efficacy endpoints measured in the study included seizure control- and behavioural/neuropsychiatric- endpoints:

- **Seizure control**
  - Change from baseline to week 17 in percentage of seizure-free days

- Caregiver Global Impression of Change in Seizure Intensity/Duration/Severity (CGI-CSID) score

- **Behavioural/neuropsychiatric**
  - Caregiver Global Impression of Change (CGI-C – target behaviour) score in parent/caregiver-identified behavioural target
  - Caregiver Global Impression of Change in Attention (CGI-CA) score

Patients in the GNX group experienced a directional increase in the percentage of major motor seizure-free days compared with PBO, with a median change from baseline of 4.91% and 0.17% for patients in the GNX and PBO groups, respectively. The median shift from the GNX group to the PBO group was 1.72%, indicating improvement in the GNX group compared with the PBO group (Table 18).

Caregiver reporting also indicated improvements with GNX in seizure intensity and duration. A substantially higher proportion of patients treated with GNX had CGI-CSID scores of "very much improved," "much improved," or "minimally improved" at their last visit compared with patients in the PBO group (62% vs 36%) (Table 18).

Additionally, treatment with GNX, compared with PBO, was associated with a trend towards improvement in attention and several aspects of caregiver-assessed behaviour (i.e., sociability, communication, irritability, and hyperactivity) (Table 18). These findings demonstrate the benefit of GNX on seizure intensity and duration, which may lead to improvements in attention and behavioural aspects in CCD patients with high refractory epilepsy.

Table 18: Summary of the pre-specified secondary outcomes from the double-blind phase

	Ganaxolone (N=50)	**Placebo (N=51)**
Secondary seizure control endpoints		
Change from baseline to week 17 in percentage of seizure-free days, based on major motor seizure types, n	49	50
Median, % (IQR)	4.9 (0.0 to 15.6)	0.2 (–3.0 to 15.2)
GNX–PBO (95% CI)	1.7 (–2.7, 7.8)	
Caregiver Global Impression of Change in Seizure Intensity/Duration/Severity score at week 17, n	45	47
Improved, n (%)	28 (62)	17 (36)
Odds ratio (95% CI)	2.56 (1.20, 5.45)	
Secondary behavioural/neuropsychiatric endpoints		
Caregiver Global Impression of Change in Attention score at week 17, n	45	47
Improved, n (%)	24 (53)	22 (47)

	Ganaxolone (N=50)	Placebo (N=51)
Odds ratio (95% CI)	0.97 (0.45, 2.09)	
Caregiver Global Impression of Change in parent or caregiver identified behavioural target score at week 17 (potential domains include sociability, communication, irritability, and hyperactivity), n	45	46
Improved, n (%)	24 (53)	20 (43)
Odds ratio (95% CI)	0.94 (0.44, 2.01)	

Abbreviations: CI, confidence interval; IQR, interquartile range; GNX, ganaxolone; PBO, placebo.

B.2.6.1.5 Exploratory secondary endpoints

A number of exploratory endpoints were included in the study to assess changes from baseline in parameters related to all seizure types including:

- Responder analysis (major motor and all seizure types)
- Changes from baseline to other types of seizures (non-major motor)

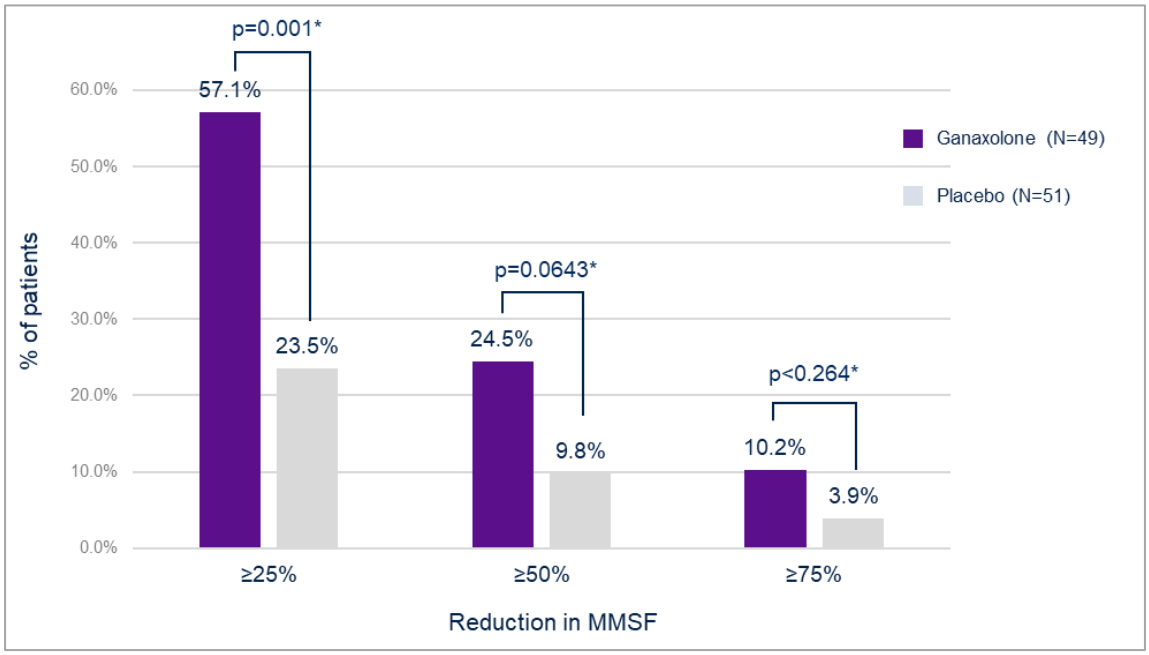
Responder analysis (major motor and all seizure types)

To complement the key secondary end point analysis of response rate (≥50% reduction in MMSF), an additional responder analysis was conducted. For this responder analysis, treatment responders were defined as patients with a ≥25% and ≥75% reduction from baseline in seizure frequency. In general, greater proportions of patients in the GNX group were 25% and 75% responders for both major motor and all seizure types compared with patients in the PBO group.

Notably, a significantly higher proportion of patients in the GNX group experienced a ≥25% reduction in MMSF from baseline compared with those in the PBO group (57.1% vs 23.5%; p=0.001). In addition, a numerically higher proportion of patients in the GNX group were 75% responders compared with those in the PBO group (10.2% vs 3.9%; p=0.264) (Figure 10).

For all seizure types, [redacted] of patients in the GNX and PBO groups, respectively were 25% responders; while [redacted] of patients in the GNX and PBO groups, respectively, were 75% responders.

Figure 10: Responder analysis – Major motor seizures (17-week double-blind phase, ITT population)



Abbreviations: ITT, intent-to-treat; MMSF, major motor seizure frequency
*p-value based on Fisher exact test

Changes from baseline in all seizure types (including non-major motor)

Generally, results for other types of seizures were similar to those for major motor seizure types.

- The median percent change from baseline in seizure frequency for all seizure types was greater in the in the GNX group (−19.09%) compared with the PBO group (−8.91%), with a median shift from the PBO group to the GNX group of −17.38%
- The number (%) of patients with a ≥50% reduction from baseline in the frequency of all seizure types was greater in the GNX group than in the PBO group [redacted]
- For patients in both the GNX and PBO groups, there was no difference from baseline in the percentage of seizure-free days (considering all seizure types) at the end of the 17-week double-blind phase (median change from baseline: [redacted]

Percent change from baseline in 28-day seizure frequency within each of the titration and maintenance portions of the double-blind phase (major motor and all seizure types)

Overall, GNX-treated patients experienced greater improvements from baseline in 28-day seizure frequency of both major motor and all seizure types during each of the titration and maintenance portions of the double-blind phase, compared with the PBO.

During the titration period of the double-blind phase (weeks 1–4), median shifts in 28-day seizure frequency from the the PBO groupto the GNX group of −18.7% and −11.8% (for major motor seizure types and all seizure types, respectively) were observed, indicating improvement in the GNX group compared with the PBO group.

During the maintenance period (weeks 5–17) of double-blind phase, a median shift in the 28-day seizure frequency from the PBO group to the GNX group of −29.31% was observed, indicating improvement in patients treated with GNX group compared with those treated with PBO (Table 19). Similar results were seen for all seizure types for which a median shift from the PBO group to the GNX group of [redacted] indicated improvement in favour of GNX compared PBO (Table 19).

Table 19: Summary of 28-day seizure frequency for primary (major motor) seizures and all seizure types during the maintenance period of the double-blind phase (week 5–17) – ITT population

	Primary (major motor) seizure types		All seizure types	
Percent change from baseline in 28-day seizure frequency	Ganaxolone (n=49)	Placebo (n=50)	Ganaxolone (n=49)	Placebo (n=50)
Median (95% distribution-free CI)	−29.39 (−42.12, −10.46)	−6.49 (−11.46, 20.60)	[redacted]	[redacted]
Mean (SD)	−12.39 (78.340)	70.19 (312.441)	[redacted]	[redacted]
Hodges-Lehmann Estimate of Location Shift (95% CI)	−29.31 (−51.45, −8.90)		[redacted]	

Abbreviations: CI, confidence interval; SD, standard deviation

Notes: Summaries are based on the sum of the individual seizures, the countable seizures, and the clusters with uncountable seizures (each cluster with uncountable seizures counts as 1 seizure). The primary seizure types include bilateral tonic (sustained motor activity ≥3seconds), generalised tonic clonic, atonic/drop, bilateral clonic, and focal to bilateral tonic-clonic. Within the baseline and postbaseline intervals, 28-day seizure frequency was calculated as the total number of seizures in the interval divided by the number of days with available seizure data in the interval, multiplied by 28. The baseline interval consists of the 6 weeks prior to the first dose. The maintenance portion interval consists of the 13 weeks following the 4-week titration portion of the double-blind post baseline phase. [1] An estimate of how far the responses in the ganaxolone group are shifted from the placebo group. Duplicate seizure diary entries are not used in the

analysis.
Source: Marigold study Clinical Study Report. Appendix Tables 14.2.5.5.1 and 14.2.5.5.2 (72).

Response rate during the maintenance portion of the double-blind phase

An additional responder analysis, similar to the one performed for the entire double-blind period (Section B.2.6.1.3), was conducted for the maintenance period only (i.e., excluding the first 4 weeks of dose titration, when GNX dose is still suboptimal). The difference in in the ≥50% response rate between GNX and PBO during the maintenance period was statistically significant [difference [redacted] (Fisher's exact test)], and slightly greater than in the full double-blind period. Additionally, the overall cumulative distribution of response, both for the entire double-blind phase and for the maintenance period of the double-blind phase, supports the finding for the primary endpoint, with [redacted] at multiple levels of response [redacted] (Figure 11).

Figure 11. Cumulative responder curve of 28-day seizure frequency for primary (major motor) seizure types – 13-week maintenance phase, ITT population (Marigold study)

*p-value is based on Fisher's exact test.
Source: Marinus Pharmaceuticals, 2022. Data on file (76).

B.2.6.1.6 Quality-of-life (QoL)

Response to QoL inventory – disability (QI-disability) scale

Responses to the QI-disability scale were recorded at Visit 3, Visit 4, Visit 5, and the taper visit (for patients who did not continue into the open-label phase or who discontinued early) and compared with responses recorded at baseline.

Overall, after the 17-week double-blind period, the mean change from baseline was 4.28 in the GNX group and 1.84 in the PBO group. The mean change from baseline in each

domain of the QI disability scale for both treatment groups is provided in Table 20 (77). Compared with patients in the PBO group, patients in the GNX group had a greater improvement from baseline at the end of the 17-week double-blind period in [redacted] domains. For the other [redacted] QI-disability domains [redacted] patients in both treatment groups showed similar improvement from baseline.

Table 20: Summary of responses to the QI-disability scale† (17-week double blind phase)

QI-disability scale, mean change in score from baseline	Ganaxolone	Placebo
Positive emotions	[redacted]	[redacted]
Social interaction	[redacted]	[redacted]
Leisure and the outdoors	[redacted]	[redacted]
Independence	[redacted]	[redacted]
Physical health	[redacted]	[redacted]
Negative emotions	[redacted]	[redacted]

Abbreviations: QI, quality of life inventory.
† The QI-Disability is a parent/caregiver reported quality of life scale specifically developed for children and adolescents with intellectual disability. The measure consists of 32 items that are rated on a five-point Likert scale (1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, or 5 = Very often). The items are grouped into six domains: physical health, positive emotions, negative emotions, social interaction, leisure, and the outdoors (leisure) and independence. The items are worded positively to measure well-being, except for the items related to the Negative Emotions domain, which are reverse scored before all items are transformed to a 100-point scale (19, 45). Specifically, domains are scored as follows: firstly, each of the Negative emotion raw scores are reversed (6 – raw score). Then each item's raw score (after reversing for Negative Emotions) is transformed as 25 x (raw score – 1), with never being scored as 0, rarely as 25, sometimes as 50, often as 75 and very often as 100. Finally, the converted scores are averaged over the items within the domains and over all the items (44).

Response to Parenting Stress Index

Responses to the PSI were recorded at Visit 3, Visit 4, Visit 5, and the taper visit (for patients who did not continue into the open-label phase or who discontinued early) and compared with responses recorded at baseline. Overall, parents of patients in the GNX group had a greater improvement on the PSI at the end of the 17-week double-blind period compared with parents of patients in the PBO group; the mean change from baseline was [redacted] for parents of patients in the GNX and PBO groups, respectively.

B.2.6.1.7 Conclusion

Marigold is the first, relatively large Phase III pivotal trial to evaluate a treatment specifically for CDD-related seizures. It provides key clinical evidence of the efficacy of GNX, as adjunctive treatment to other ASMs, in significantly reducing the frequency of major motor seizures in patients with CDD compared with PBO. These results are notable considering the high seizure burden reported for patients at baseline, when the average number of major motor seizures per day was approximately 4, and the median nearly 2, despite a history of heavy treatment with ASMs. Indeed, although these

children had already tried a median of 7 ASMs before the study (range: 1–16) and were on 2.4 concomitant ASMs at baseline (Table 13), they still had refractory seizures.

Adjunctive treatment with GNX, compared with PBO, resulted in considerably higher response rates. The difference in the proportion of ≥50% responders between GNX and PBO approached statistical significance in the entire double-blind phase (i.e., including the 4-weeks dose titration phase), and approximately 10% of the patients treated with GNX achieved a remarkable 75% or greater response. During the maintenance period, the difference in the 50% response rate was statistically significantly higher with GNX vs PBO. Additionally, in both the entire double-blind phase and the maintenace period, the overall cumulative distribution of response supports the finding for the primary endpoint.

A slight increase in the median percentage of major motor seizure-free days was also seen, with a change of 4.9% with GNX and 0.2% with PBO, compared with baseline, respectively.

Adjunctive treatment with GNX also resulted in numerically higher proportions of patients with overall patient improvements as well as improvements in seizure intensity and duration, in attention and in several aspects of behaviour, compared with PBO. Moreover, treatment with GNX has a potential for QoL improvements in both patients and caregivers.

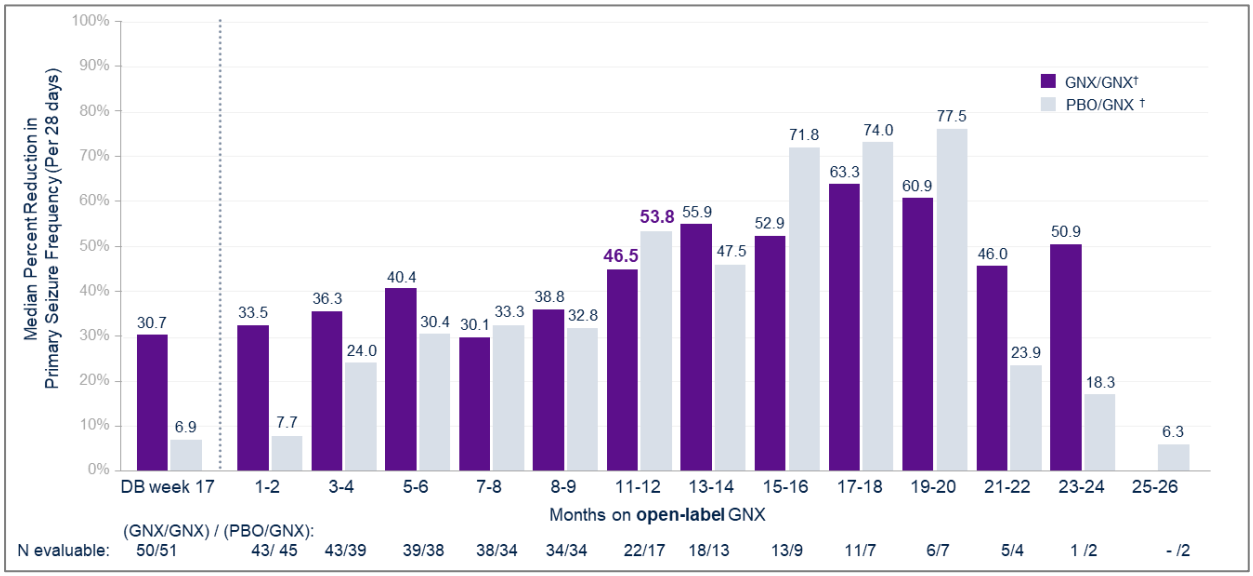
B.2.6.2 *Open-label phase of study 1042-CDD-3001*

B.2.6.2.1 Percent reduction in major motor seizure frequency (MMFS) (primary efficacy outcome)

Overall, results indicate that in the open-label extension phase GNX reduced the frequency of major motor seizures in patients who switched from PBO to GNX (PBO/GNX group), and its efficacy was maintained in patients who continued treatment with GNX (GNX/GNX group).

Data were collected from the end of the double-blind treatment phase with subsequent 2-month intervals. In the first four weeks of the open-label extension phase, the percentage reduction from baseline in MMFS was 32.0% for patients in the GNX/GNX group and 22.0% for those in the PBO/GNX groups. In comparison, the median percent reduction from baseline in MMFS at the end of the double-blind phase was 30.7% and 6.90% for patients in the GNX group and PBO group, respectively. More importantly, the improvement in the PBO/GNX group observed over the first 4 weeks continued through Months 19 to 20, while the reduction in MMFS was maintained in the GNX/GNX group. Figure 12 presents the results recorded every two months, from the end of the double phase to month 26.

Figure 12: Percent reduction in MMFS at the end of the double-blind phase and at 2-month intervals in the open-label extension (ITT population)†



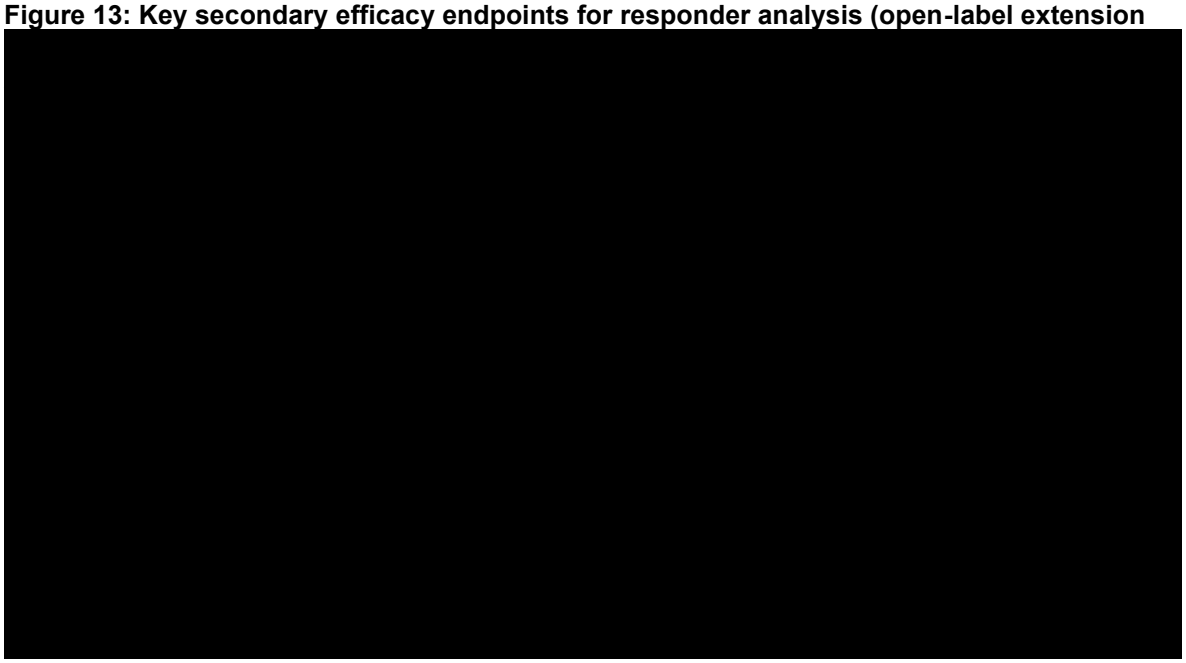
Abbreviations: GNX, ganaxolone, ITT, intent-to-treat; MMFS, major motor seizure frequency (i.e. primary seizure frequency).
Only patients who completed a 2-month interval were included at that time point. Sample size varies due to patient discontinuations and due to patients still ongoing in the open-label extension. Patients are grouped by their treatment assignment during the double-blind phase. All patients received open-label GNX in the open-label extension independent of their double-blind treatment assignment.
†Note: the prospective 6-week baseline of the double-blind phase was the baseline period used in calculating percent change in MMSF for both groups in the open-label phase.

B.2.6.2.2 Responder analysis

Patient response assessed in the responder analysis is shown in

Figure 13. In the first 4 weeks, the number (%) of patients with ≥50% reduction in MMFS (response) was higher in the GNX/GNX group ([redacted] compared with the PBO/GNX group [redacted] Comparatively, at the end of the double-blind phase of the study, the response rate from baseline was [redacted] for the GNX group and [redacted] for the PBO group, indicating that the efficacy of GNX was maintained in the long-term. In addition, a greater proportion of patients in the GNX/GNX group experienced a ≥25% reduction in MMFS compared with the PBO/GNX group ([redacted]) Approximatively [redacted] of patients in each group experienced a reduction ≥75% in MMSF.

Figure 13: Key secondary efficacy endpoints for responder analysis (open-label extension



Abbreviations: ITT, intent-to treat.
Note: The term “primary seizures” was used in the Study 1042-CDD-3001 protocol to refer to the seizure types evaluated for the primary endpoint; the more commonly accepted clinical term “major motor seizures” is used for those seizure types in this document. Major motor seizures include bilateral tonic (sustained motor activity ≥3 seconds), generalised tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic seizures. The terms “primary seizures” and “major motor seizures” are synonymous.

B.2.6.2.3 Seizure-free days

In the first 4 weeks of the open-label extension phase, the percentage of seizure-free days was higher for patients in the PBO/GNX group compared with those in the GNX/GNX group ( ). These results were consistent thereafter for both PBO/GNX and GNX/GNX groups. In the same study period, a greater proportion of patients in the PBO/GNX group experienced improvements in the longest seizure-free interval compared with those in the GNX/GNX group.

B.2.6.2.4 Behavioural/Neuropsychiatric

Most patients experienced behavioural improvements, irrespective of treatment subgroup they were in. Improvements on CGI-I assessments ("minimally improved or better) were similar between GNX-GNX and PBO-GNX groups, ranging from 66.6% to 82.1% for the caregiver, and from 68.9% to 76.9% for the clinician observations at approximately 8 months (73).

For the CGI-CA, most parents/caregivers of patients in both groups rated the response to treatment as “much improved”, “minimally improved”, or “no change”. The responses to treatment were similar across the GNX/GNX and PBO/GNX groups. Most parents/caregivers of patients in both groups reported improvement (“much improved”, “minimally improved”, or “no change”) in attention and in the chosen target behaviour (sociability, communication, irritability, or hyperactivity).

B.2.6.2.5 Conclusion

The ongoing open-label extension study is evaluating the long-term efficacy of GNX in the treatment of refractory seizures associated with CDD. At the cut-off date of [redacted], results showed that the efficacy of GNX in reducing seizure frequency was sustained in patients who received long-term treatment. Notably, patients who switched from PBO to GNX reached similar response rates within one month as the original GNX group. Moreover, the overall patient improvements observed during the double-blind phase were sustained during the open-label extension phase.

B.2.7 *Subgroup analysis*

Two pre-specified subgroup analyses were performed for the primary efficacy endpoint with comparisons based on gender and plasma allopregnanolone sulphate (Allo-S) level at baseline (low, middle, or high). Allo-S, the endogenous analogue of GNX, has a similar receptor efficacy to GNX, at both synaptic and extrasynaptic receptors (78, 79), but with a significantly shorter anti-seizure response (80). Allo-S level subgroups were considered based on the results from Study 1042-0900 which suggested that the benefit of GNX, compared with PBO, may be greater in patients with lower Allo-S levels. However, this exploratory analysis was mainly based on data from patients with an epileptic syndrome other than CDD, since all seven CDD patients in that study had low Allo-S at baseline.

Overall, patients in all subgroups treated with GNX as adjunctive treatment showed greater reduction in MMSF from baseline compared with those treated with PBO (Table 21). In the gender subgroup analysis, improvements from baseline in MMSF reduction were similar with GNX for both male and females (27.5% and 32.0%, respectively), and were consistent with those for all patients. In the Allo-S subgroup analysis, the largest difference in median 28-day MMSF between the GNX and PBO groups was observed in patients with medium and high Allo-S levels though results by Allo-S level were consistent with those for all patients, and the sample size in the higher Allo-S subgroups was very small (Table 21). Thus, on basis of the Marigold subgroup analyses, Allo-S levels can not be used as a predictive biomarker for efficacy in CDD.

Table 21: Pre-specified subgroup analyses of percentage change from baseline in median 28-day MMSF (primary endpoint) by gender and Allo-S levels

Subgroup	Ganaxolone	Placebo	Ganaxolone – Placebo (95%CI)‡
Gender†			
Female	−27.5% (n=38)	−10.2% (n=41)	−22.2§ (−48.4, −1.4)
Male	−32.0% (n=11)	7.5% (n=10)	−42.1§ (−95.2.4, −8.4)
Allo-S levels†			
Patients with **low** baseline levels (≤2.5 ng/mL)	−25.4% (n=39)	−9.5% (n=37)	−21.0†† (−47.3, 2.2)
Patients with **medium** baseline levels (>2.5 ng/mL and <6.0 ng/mL)	−40.9% (n=5)	−3.5% (n=12)	−48.0†† (−149.4, −16.8)
Patients with **high** baseline levels (≥6.0 ng/mL)	−39.0% (n=4)	8.9% (n=2)	−47. 9†† (−83.1, 6.2)

Abbreviations: Allo-S, allopregnanolone sulphate; CI, confidence interval; MMSF, major motor seizure frequency
†Median percentage change from baseline in 28-day major motor seizure frequency over 17 weeks.
‡Hodges-Lehmann estimate of median difference (95% confidence interval).§After enrolment started, the protocol was amended to exclude patients with allopregnanolone sulfate levels ≥6.0 ng/mL at screening.
††Favours ganaxolone group.
Sources: Marigold study Clinical Study Report (72); Pestana-Knight et al, 2022 (Supplementary Appendix) (48)

B.2.8 *Meta-analysis*

Only one relevant RCT evaluating GNX as adjunctive treatment for seizures caused by CDD was identified in the SLR; therefore, no meta-analysis was performed.

B.2.9 *Indirect and mixed treatment comparisons*

Indirect or mixed treatment comparisons were not conducted, as there are no available clinical data in the CDD setting which could be used for this purpose. Furthermore, the study comparator arm in Marigold reflects the established clinical management for patients with CDD in the UK as it consisted of placebo with up to 4 concomitant ASMs (average: 2.4 ASMs, following several other previously discontinued ASMs), while also ketogenic diet and vagus nerve stimulation were allowed, if stable at baseline.

B.2.10 *Adverse reactions*

B.2.10.1 *Studies reported in section 2.2*

Safety evidence for GNX in the population of interest for this submission is provided by the Marigold study and the open-label extension phase (interim results cut-off date: [redacted]). Key safety outcomes for both studies are presented in the Section B.2.10.1.1 and B.2.10.1.2, respectively.

B.2.10.1.1 Study 1042-CDD-3001 (Marigold)

The safety endpoints measured in the Marigold study included: treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital signs, physical examinations, electrocardiogram (ECG), and neurological and developmental examinations. The extent of exposure to GNX treatment is also summarised in the section below.

Extent of exposure

Exposure to study drug is summarised in Table 22. The duration of exposure to study drug in both treatment groups reflected the treatment duration, with mean (SD) number of days dosed of [redacted] days and [redacted] days in the GNX and PBO groups, respectively. At the end of the 4-week titration phase, [redacted] patients in the GNX group and [redacted] patients in the PBO group achieved the optimal dose level of 1800 mg/day (patients weighing >28 kg), and [redacted] patients in the GNX group and [redacted] patients in the PBO group achieved the optimal dose level of 63 mg/kg/day (patients weighing ≤ 28 kg). Overall, [redacted] patients in the GNX group and [redacted] patients in the PBO group needed a dose reduction after reaching the optimal dose (1800 mg/day for patients weighing >28 kg, 63 mg/kg/day for patients weighing ≤28 kg) during titration.

Table 22: Summary of extent of exposure (17-week double-blind phase, safety population)

	Ganaxolone (N=50)	**Placebo (N=51)**
Number of Days Dosed		
n	50	51
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Percentage of Days Dosed		
n	50	51
Mean (SD)	[redacted]	[redacted]

	Ganaxolone (N=50)	Placebo (N=51)
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
At Least 90% of Days Dosed (N/% of patients)	[redacted]	[redacted]
Total Dosage (mg)†		
n	50	51
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation.
†Patients who were dosed with a mg/kg regimen had their dosage converted to mg using the most recent weight prior to the dose.

Overview of treatment-emergent adverse events

The TEAEs reported by patients in the GNX and PBO groups during the 17-week double-blind phase are summarised in Table 23. Overall, the proportion of patients in the GNX and PBO groups reporting TEAEs (86.0% vs 88.2%), serious TEAEs (12.0% vs 9.8%), and TEAEs leading to study drug discontinuation (4.0% vs 7.8%) were similar between treatment groups. Compared with the PBO group, higher proportions of patients in the GNX group reported treatment-related TEAEs (70.0% vs 43.1%), TEAEs leading to dose reduction or temporary study drug discontinuation (22.0% vs 15.7%), and TEAEs of special interest (8.0% vs 5.9%). No TEAEs resulting in death were reported in either treatment group.

Table 23: Summary of TEAEs – Marigold study

Adverse event	Ganaxolone (N=50)		Placebo (N=51)	
	Patients n (%)	Events n	Patients n (%)	Events n
TEAEs†	43 (86.0)	153	45 (88.2)	175
TEAEs by severity‡				
Mild	16 (32.0)	102	27 (52.9)	134
Moderate	26 (52.0)	50	15 (29.4)	37
Severe	1 (2.0)	1	3 (5.9)	4
Serious TEAEs	6 (12.0)	6	5 (9.8)	10
Treatment related TEAEs	35 (70.0)	79	22 (43.1)	60
TEAE leading to study drug discontinuation	2 (4.0)	4	4 (7.8)	8
TEAE leading to dose reduction or temporary study drug discontinuation	11 (22.0)	17	8 (15.7)	11
TEAE of special interest§	4 (8.0)	4	3 (5.9)	3
TEAE resulting in death	0 (0)	0	0 (0)	0

Abbreviations: TEAE, treatment-emergent adverse event.
Note: If a patient experienced more than 1 adverse event in a category, the patient was counted only once in that category.
†TEAE, defined as an AE that occurred or worsened on the day of or after the first dose of study drug and, for patients who entered the open-label extension phase, before the first dosing day of that phase. ‡Highest severity for patients. §Includes Rash and TEAEs in the reproductive system and breast disorders system organ class.

TEAEs by primary System Organ Class (SOC) and preferred term (PT)

TEAEs reported in ≥3% of patients in either treatment group are presented by System Organ Class (SOC) and Preferred Term (PT) in Table 24. The most frequent (reported in ≥10 patients in either treatment group) TEAEs by SOC were nervous system disorders, infections and infestations, gastrointestinal disorders, general disorders and administration site conditions, and respiratory, thoracic, and mediastinal disorders.

The most frequent (reported in ≥10 patients in either treatment group) TEAEs by PT were somnolence and vomiting. TEAEs by PT were reported by similar proportions of patients in each treatment group except for somnolence (36.0% vs 15.7%) and pyrexia (18.0% vs 7.8%) which were reported by higher proportions of patients in the GNX group, and vomiting (10.0% vs 19.6%), which was reported by a higher proportion of patients in the PBO group.

Table 24: TEAEs (≥3% in either treatment group) by SOC and PT (17-week double-blind phase, safety population)

Adverse event	Ganaxolone (N=50)		Placebo (N=51)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Any TEAE†	43 (86.0)	153	45 (88.2)	175
Nervous system disorders	27 (54.0)	41	20 (39.2)	35
Somnolence	18 (36.0)	20	8 (15.7)	8
Seizure	7 (14.0)	8	9 (17.6)	12
Sedation	3 (6.0)	3	2 (3.9)	2
Hypersomnia	2 (4.0)	2	0 (0)	0
Lethargy	2 (4.0)	2	2 (3.9)	2
Hyperaesthesia	0 (0)	0	2 (3.9)	2
Infections and infestations	22 (44.0)	31	26 (51.0)	38
Upper respiratory tract infection	5 (10.0)	6	3 (5.9)	3
Bronchitis	2 (4.0)	2	0 (0)	0
Ear infection	2 (4.0)	2	3 (5.9)	3
Influenza	2 (4.0)	2	1 (2.0)	1
Rhinitis	2 (4.0)	4	4 (7.8)	5
Respiratory tract infection viral	1 (2.0)	1	3 (5.9)	3
Urinary tract infection	1 (2.0)	2	3 (5.9)	3
Nasopharyngitis	0 (0)	0	5 (9.8)	5
Sinusitis	0 (0)	0	2 (3.9)	2
Varicella	0 (0)	0	2 (3.9)	3
Gastrointestinal disorders	14 (28.0)	16	22 (43.1)	33
Vomiting	5 (10.0)	6	10 (19.6)	12

Adverse event	Ganaxolone (N=50)		Placebo (N=51)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Constipation	3 (6.0)	3	3 (5.9)	3
Salivary hypersecretion	3 (6.0)	3	1 (2.0)	1
Diarrhoea	1 (2.0)	1	4 (7.8)	5
Abdominal pain	0 (0)	0	2 (3.9)	2
Gastroesophageal reflux disease	0 (0)	0	3 (5.9)	3
General disorders and administration site conditions	13 (26.0)	15	8 (15.7)	18
Pyrexia	9 (18.0)	10	4 (7.8)	5
Gait disturbance	2 (4.0)	2	1 (2.0)	1
Respiratory, thoracic, and mediastinal disorders	10 (20.0)	13	10 (19.6)	13
Nasal congestion	2 (4.0)	2	1 (2.0)	1
Rhinorrhoea	1 (2.0)	1	2 (3.9)	2
Cough	0 (0)	0	3 (5.9)	3
Psychiatric disorders	8 (16.0)	9	9 (17.6)	12
Insomnia	2 (4.0)	2	2 (3.9)	3
Irritability	2 (4.0)	2	2 (3.9)	2
Metabolism and nutrition disorders	5 (10.0)	5	2 (3.9)	4
Investigations	4 (8.0)	6	4 (7.8)	5
Body temperature increased	0 (0)	0	2 (3.9)	3
Skin and subcutaneous tissue disorders	3 (6.0)	3	7 (13.7)	8
Rash	3 (6.0)	3	4 (7.8)	4
Alopecia	0 (0)	0	2 (3.9)	2

Adverse event	Ganaxolone (N=50)		Placebo (N=51)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Eye disorders	2 (4.0)	2	0 (0)	0
Immune system disorders	3 (6.0)	3	0 (0)	0
Seasonal allergy	3 (6.0)	3	0 (0)	0
Injury, poisoning and procedural complications	2 (4.0)	5	3 (5.9)	4
Renal and urinary disorders	1 (2.0)	1	2 (3.9)	2

Abbreviations: PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.
Note: If a patient experienced more than 1 adverse event in a category, the patient was counted only once in that category.
†TEAE, defined as an AE that occurred or worsened on the day of or after the first dose of study drug and, for patients who entered the open-label extension phase, before the first dosing day of that phase.

Study drug related TEAEs

Study drug related TEAEs reported in ≥3% of patients in either treatment group are presented by SOC and PT in Table 25. The most frequent (reported in ≥10 patients in either treatment group) study drug related TEAE by SOC was nervous system disorders, and the most frequent study drug related TEAE by PT was somnolence. In general, study drug related TEAEs by PT were reported by similar numbers of patients in each treatment group apart from somnolence, which was reported by higher proportions of patients in the GNX group (34.0% vs 5.9%). However, in most cases (11 out of 18, see Table 24) somnolence severity was graded as “mild”, with no cases being graded as “severe”.

Table 25: Study drug related TEAEs reported in ≥3% of patients in either treatment group by SOC and PT – 17-week double-blind phase (safety population)

System organ class Preferred term	Ganaxolone (N=50)		Placebo (N=51)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any study drug related TEAE†	35 (70.0)	79	22 (43.1)	60
Nervous system disorders	24 (48.0)	35	13 (25.5)	23
Somnolence	17 (34.0)	19	3 (5.9)	3
Seizure	5 (10.0)	5	4 (7.8)	7
Sedation	3 (6.0)	3	2 (3.9)	2

System organ class Preferred term	Ganaxolone (N=50)		Placebo (N=51)	
	Patients n (%)	Events n	Patients n (%)	Events n
Hypersomnia	2 (4.0)	2	0 (0)	0
Lethargy	2 (4.0)	2	2 (3.9)	2
Hyperaesthesia	0 (0)	0	2 (3.9)	2
Gastrointestinal disorders	9 (18.0)	10	9 (17.6)	11
Constipation	3 (6.0)	3	0 (0)	0
Salivary hypersecretion	3 (6.0)	3	1 (2.0)	1
Vomiting	2 (4.0)	2	2 (3.9)	3
Abdominal pain	0 (0)	0	2 (3.9)	2
Diarrhoea	0 (0)	0	2 (3.9)	2
Gastroesophageal reflux disease	0 (0)	0	2 (3.9)	2
Psychiatric disorders	7 (14.0)	8	7 (13.7)	10
Insomnia	2 (4.0)	2	2 (3.9)	3
Irritability	2 (4.0)	2	2 (3.9)	2
General disorders and administration site conditions	4 (8.0)	4	3 (5.9)	3
Gait disturbance	2 (4.0)	2	1 (2.0)	1
Investigations	3 (6.0)	4	0 (0)	0
Metabolism and nutrition disorders	3 (6.0)	3	0 (0)	0
Respiratory, thoracic, and mediastinal disorders	3 (6.0)	4	5 (9.8)	7
Eye disorders	2 (4.0)	2	0 (0)	0
Injury, poisoning and procedural complications	2 (4.0)	5	1 (2.0	2
Skin and subcutaneous tissue disorders	2 (4.0)	2	1 (2.0)	1

System organ class Preferred term	Ganaxolone (N=50)		Placebo (N=51)	
	Patients n (%)	Events n	Patients n (%)	Events n
Renal and urinary disorders	0 (0)	0	2 (3.9)	2

Abbreviations: PT, Preferred Term; SOC, System Organ Class; TEAE, treatment emergent adverse events.
Note: If a patient experienced more than 1 adverse event in a category, the patient was counted only once in that category.
†TEAE, defined as an AE that occurred or worsened on the day of or after the first dose of study drug and, for patients who entered the open-label extension phase, before the first dosing day of that phase.
Adverse events of special interest are summarised in Appendix (Section **Error! Reference source not found.**).

Serious adverse events

Overall, 6 (12.0%) patients in the GNX group and 5 (9.8%) patients in the PBO group reported a treatment-emergent SAE (Table 23). Three patients in the GNX group and 2 patients in the PBO group had treatment-emergent SAEs that led to dose reduction or withdrawal of study drug. Causes of discontinuation from the GNX were as follows (1 patient for each event):

- Urinary Tract Infection (unrelated to study drug), temporary discontinuation
- Bronchitis (unrelated to study drug), temporary discontinuation
- Oxygen Saturation Decreased (related to study drug), dose reduction

Causes of discontinuation from the PBO were as follows (1 patient for each event):

- Hypoxia (related to study drug), permanent withdrawal
- Unresponsive to stimuli (related to study drug), permanent drug withdrawal and withdrawn from the study

Clinical laboratory evaluations, vital signs and neurological/developmental examinations

No significant findings related to clinical laboratory evaluations of haematology, chemistry, and urinalysis, and no significant findings related to vital signs, physical examination, ECG, neurological and developmental examinations were observed for patients in the study. Detailed results for these safety endpoints are presented in Appendix F.1.

B.2.10.1.2 Open-label phase of study 1042-CDD-3001 (Marigold)

Overall, during the open-label phase of the trial (data cut-off point of [redacted] the tolerability profile of GNX was consistent with that observed during the double-blind phase.

In total, 73 (83.0%) patients reported TEAEs[i] during the open-label phase of the Marigold trial (Table 26). Fewer TEAEs were reported in patients who continued treatment with GNX (GNX/GNX group) compared with patients who switched from PBO to GNX (PBO/GNX), with rates of 76.7% and 88.9%, respectively. Fewer treatment-related TEAEs were also reported in the GNX/GNX group compared with the PBO/GNX group (34.9% vs 53.3%). Patients in the GNX/GNX group were also less likely to discontinue treatment due to TEAEs (2.3% vs 22.2%) and reported fewer severe TEAEs (16.3% vs 24.4%), compared with the PBO/GNX group. There was one death considered as unlikely related to study drug by the investigator and serious TEAEs were reported by similar percentages of patients from the GNX/GNX and PBO/GNX groups (25.6% vs 24.4%). Taken together, these observations are consistent with events occurring early in treatment (i.e., during the double-blind phase) or reducing with long-term treatment.

[i] TEAEs in the open-label phase were defined as an AE that occurred or worsened during the open-label phase.

Table 26: Overview of TEAEs – (Marigold Study – Open-label phase, safety population)

Category	GNX/GNX (n=43)		PBO/GNX (n=45)		Total, (N=88)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
TEAEs†	**33 (76.7)**	**155**	**40 (88.9)**	**236**	**73 (83.0)**	**391**
TEAE by severity‡						
Mild	12 (27.9)	87	13 (28.9)	121	25 (28.4)	208
Moderate	14 (32.6)	54	16 (35.6)	99	30 (34.1)	153
Severe	7 (16.3)	14	11 (24.4)	16	18 (20.5)	30
Serious TEAEs	11 (25.6)	29	11 (24.4)	23	22 (25.0)	52
Treatment related TEAE	15 (34.9)	37	24 (53.3)	49	39 (44.3)	86
TEAE leading to study drug discontinuation	1 (2.3)	3	10 (22.2)	12	11 (12.5)	15
TEAE leading to dose reduction or temporary study drug discontinuation	7 (16.3)	15	7 (15.6)	11	14 (15.9)	26
TEAE of special interest§	0 (0)	0	7 (15.6)	9	7 (8.0)	9
TEAE resulting in death	1 (2.3)	1	0 (0)	0	1 (1.1)	1

Abbreviations: GNX, ganaxolone; PBO, placebo; TEAE, treatment-emergent adverse event.
Note: If a patient experiences more than 1 adverse event in a category, the patient is counted only once in that category.
Patients are grouped by the treatment received in DB phase.
†TEAE defined as an AE that occurred or worsened during the open-label extension phase. ‡Highest severity for patients. §Includes Rash and TEAEs in the reproductive system and breast disorders system organ class.

Severe TEAEs and SAEs in the open-label phase for both the GNX/GNX group and the PBO/GNX group were more frequent than observed during the double-blind phase (Table 23 and Table 26). The increases observed in the open-label phase are likely due to the greater duration of treatment exposure (mean [SD] GNX exposure; 113.0 [23.32] days double-blind phase; 299.8 [155.98] days open-label phase). TEAEs leading to discontinuation were more frequent in the PBO/GNX group compared with GNX group during the double-blind phase (Table 23), while the discontinuations in the GNX group were consistent between study phases (Table 26). Newly experienced study drug-related effects and random factors may have contributed to the higher incidence of

discontinuations in the PBO/GNX group. No other trends or patterns were observed, and no new or worsening trends were identified with long term use of GNX.

Common treatment-emergent adverse events

A summary of TEAEs reported in ≥3% of patients in either the PBO/GNX or GNX/GNX treatment group is presented by SOC and PT in Table 27. Overall, TEAEs were similar to the double-blind phase with seizure (19.3%), somnolence (18.2%), pyrexia (13.6%), and vomiting (12.5%) being the most frequently observed. Somnolence was reported by a lower proportion of patients in the GNX/GNX group compared with the PBO/GNX group (14.0% vs 22.2%) which is consistent with these events occurring early in treatment or reducing with long-term treatment. Rash was also reported by a higher proportion of patients in the PBO/GNX group (8.9% vs 0%) which is consistent with these events occurring early in treatment. Moreover, lower proportions of patients in the GNX/GNX group compared with those in the PBO/GNX group reported TEAEs of seizure (16.3% vs 22.2%) during the open-label phase. However, seizures were numerically similar between the GNX and PBO groups during the double-blind and open-label phases (Table 24). No new or worsening TEAEs associated with long term use were identified during the open-label phase to date.

Table 27: TEAEs (≥3% in either treatment group) by SOC and PT (Marigold study – open-label phase, safety population)

System organ class Preferred term	GNX/GNX (n=43)		PBO/GNX (n=45)		Total (N=88)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAE[†]	33 (76.7)	155	40 (88.9)	236	73 (83.0)	391
Nervous system disorders	16 (37.2)	27	23 (51.1)	40	39 (44.3)	67
Seizure	7 (16.3)	10	10 (22.2)	14	17 (19.3)	24
Somnolence	6 (14.0)	8	10 (22.2)	13	16 (18.2)	21
Lethargy	1 (2.3)	1	3 (6.7)	3	4 (4.5)	4
Drooling	0 (0)	0	2 (4.4)	2	2 (2.3)	2
Infections and infestations	18 (41.9)	43	20 (44.4)	43	38 (43.2)	86
Nasopharyngitis	4 (9.3)	4	5 (11.1)	6	9 (10.2)	10
Upper respiratory tract infections	2 (4.7)	2	7 (15.6)	8	9 (10.2)	10
Urinary tract infection	3 (7.0)	3	4 (8.9)	4	7 (8.0)	7

System organ class Preferred term	GNX/GNX (n=43)		PBO/GNX (n=45)		Total (N=88)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Ear infection	1 (2.3)	1	4 (8.9)	5	5 (5.7)	6
Rhinitis	3 (7.0)	4	2 (4.4)	2	5 (5.7)	6
Bronchitis	1 (2.3)	1	2 (4.4)	2	3 (3.4)	3
Covid-19	2 (4.7)	2	1 (2.2)	1	3 (3.4)	3
Pneumonia	3 (7.0)	3	0 (0)	0	3 (3.4)	3
Gastroenteritis	0 (0)	0	2 (4.4)	2	2 (2.3)	2
Gastrointestinal viral infection	0 (0)	0	2 (4.4)	2	2 (2.3)	2
Pharyngitis streptococcal	2 (4.7)	3	0 (0)	0	2 (2.3)	3
Pneumonia viral	2 (4.7)	2	0 (0)	0	2 (2.3)	2
Sinusitis	0 (0)	0	2 (4.4)	2	2 (2.3)	2
Viral infection	2 (4.7)	2	1 (2.2)	1	3 (3.4)	3
Gastrointestinal disorders	8 (18.6)	12	13 (28.9)	37	21 (23.9)	49
Vomiting	5 (11.6)	6	6 (13.3)	9	11 (12.5)	15
Diarrhoea	2 (4.7)	2	6 (13.3)	7	8 (9.1)	9
Salivary hypersecretion	0 (0)	0	2 (4.4)	2	2 (2.3)	2
Toothache	0 (0)	0	2 (4.4)	14	2 (2.3)	14
General disorders and administration site conditions	12 (27.9)	21	8 (17.8)	33	20 (22.7)	54
Pyrexia	7 (16.3)	12	5 (11.1)	5	12 (13.6)	17
Gait disturbance	3 (7.0)	3	1 (2.2)	1	4 (4.5)	4
Respiratory, thoracic, and mediastinal disorders	10 (23.3)	15	7 (15.6)	9	17 (19.3)	24
Cough	5 (11.6)	5	1 (2.2)	1	6 (6.8)	6

System organ class Preferred term	GNX/GNX (n=43)		PBO/GNX (n=45)		Total (N=88)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Pneumonia aspiration	2 (4.7)	3	1 (2.2)	1	3 (3.4)	4
Acute respiratory failure	2 (4.7)	2	0 (0)	0	2 (2.3)	2
Productive cough	0 (0)	0	2 (4.4)	2	2 (2.3)	2
Respiratory disorder	0 (0)	0	2 (4.4)	2	2 (2.3)	2
Investigations	6 (14.0)	7	5 (11.1)	7	11 (12.5)	14
Weight decreased	3 (7.0)	3	1 (2.2)	1	4 (4.5)	4
Metabolism and nutrition disorders	7 (16.3)	8	4 (8.9)	7	11 (12.5)	15
Decreased appetite	4 (9.3)	4	2 (4.4)	2	6 (6.8)	6
Dehydration	1 (2.3)	1	2 (4.4)	2	3 (3.4)	3
Psychiatric disorders	5 (11.6)	8	7 (15.6)	24	12 (13.6)	32
Attention-seeking behaviour	1 (2.3)	1	2 (4.4)	2	3 (3.4)	3
Agitation	2 (4.7)	3	0 (0)	0	2 (2.3)	3
Insomnia	0 (0)	0	2 (4.4)	18	2 (2.3)	18
Skin and subcutaneous tissue disorders	3 (7.0)	3	7 (15.6)	8	10 (11.4)	11
Rash	0 (0)	0	4 (8.9)	5	4 (4.5)	5
Reproductive system and breast disorders	1 (2.3)	1	6 (13.3)	8	7 (8.0)	9
Menorrhagia	0 (0)	0	2 (4.4)	2	2 (2.3)	2
Polymenorrhoea	0 (0)	0	2 (4.4)	2	2 (2.3)	2

Abbreviation: AE, adverse event; Covid-19, coronavirus 19 disease; GNX, ganaxolone; PBO, placebo; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Note: If a patient experiences more than 1 AE in a category, the patient is counted only once in that category. Patients are grouped by the treatment received in DB phase.
†TEAE, defined as an AE that occurred or worsened during the open-label extension phase

Clinical laboratory evaluations and vital signs

Overall, there were no clinically meaningful shifts in haematology, chemistry and urinalysis laboratory values, or vital sign values in the open-label phase (see Appendix F.2 for further details).

B.2.10.2 *Additional studies*

The clinical systematic review, detailed in Section B.2.1, also included adverse events, and did not identify any additional studies.

B.2.10.3 *Safety overview*

Adjunctive GNX was generally well tolerated, with the majority of TEAEs categorised as mild or moderate in severity. During the double-blind phase, TEAEs generally occurred at a similar frequency in both the GNX and PBO groups, except for somnolence, pyrexia, and upper respiratory tract infection, salivary hypersecretion, and sedation, which were more common among patients treated with GNX. The proportion of patients who had dose reductions or temporarily discontinued the study drug due to TEAEs was similar between the GNX and PBO groups, and less than 5% of patients in the GNX group discontinued treatment due to a TEAE. There were no deaths during the double-blind phase. In patients treated for ≥12 months during the open-label extension phase of Marigold (interim results with cut-off date: [redacted]), GNX maintained a predictable tolerability profile, with no new safety concerns.

B.2.11 *Ongoing studies*

The following clinical studies of GNX in patients with CDD are currently ongoing:

- Open-label extension phase of the Marigold study (interim results reported from latest available data cut-off point: [redacted]) (see Section B.2.2)
- Double-blind, randomised, placebo-controlled trial of GNX in patients with 6 months to <2 years old (NCT05249556)
    - This is a global, Phase III trial of adjunctive GNX treatment in participants with genetically confirmed CDD. Twenty patients will be included. Primary endpoint will be the percent change from baseline in 28-day frequency of countable seizures through the end of the 12-week, double-blind treatment phase relative to the 4-week prospective baseline phase.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

B.2.12.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

B.2.12.1.1 Summary of efficacy evidence

In the Marigold study, adjunctive treatment with GNX resulted in a statistically significant 4.5-fold reduction from baseline in 28-day major motor seizures seizure frequency (MMSF) compared with placebo (PBO) (30.7% vs 6.9%; p=0.0036). When considering the entire 17-week double-blind period, including the 4 weeks of dose titration, treatment with GNX resulted in a 2.5-fold greater response rate (defined as the percentage of patients with a ≥50% reduction from baseline in MMSF) compared with PBO (24.5% vs 9.8%), with the difference approaching statistical significance (p=0.064). Of the GNX-treated patients, 10.2% achieved a remarkable 75% or greater reduction in the MMSF. Notably, when considering the maintenance period (weeks 5–17) only, the proportion of 50% responders was significantly higher with GNX than with PBO (difference: [redacted].

The study was designed primarily to detect a clinically significant difference in the primary endpoint only (i.e., change from baseline in MMSF) in the overall study population. For the detection of statistically significant differences in any of the further efficacy endpoints, as well as in, or between the subgroups, the size of the study was likely underpowered. Nevertheless, numerical improvements over PBO in MMSF reduction were observed in all subgroups analysed, including patients stratified by gender, or by low, medium or high Allo-S level at baseline (see Section B.2.7).

In addition, all secondary and exploratory efficacy endpoints, whether reported by clinicians or caregivers, were directionally in favour of GNX. Based on caregiver reporting, a higher proportion of GNX-treated patients showed improvements in seizure intensity and duration compared with PBO (62% vs 36%). Overall patient improvements were observed with GNX over PBO, as suggested by clinical global impression ratings from caregivers and clinicians (Section B.2.6.1.3). Favourable changes with GNX were also observed in several aspects of behaviour (i.e., sociability, communication, irritability, and hyperactivity) compared with PBO. Furthermore, patients treated with GNX experienced a directional increase in the percentage of major motor seizure-free days compared with PBO (median change from baseline: 4.91% vs 0.17%. Importantly, GNX also demonstrated the potential to improve the QoL of both patients and caregivers, as measured by the QI-disability and the Parenting Stress Index scales, respectively (see Section B.2.6.1.6).

Thus, all results from the Marigold study appear to consistently indicate that GNX offers unprecendented and clinically meaningful benefits for patients with CDD who need improved seizure control despite treatment with current ASMs.

Open-label extension phase

During the open-label extension phase of the Marigold study (interim results cut-off date [redacted] GNX showed sustained efficacy in reducing seizure frequency in patients who received long-term treatment. Patients treated with GNX for ≥12 months experienced a sustained reduction in 28-day MMSF, suggesting a maintained effect. In patients who switched from PBO to GNX treatment, reductions in MMFS observed over the first 4 weeks continued up to Months 19 to 20, while in the patients originally randomised to GNX and continuing treatment in the open-label period, the reductions in MMSF from week 17 were maintained up to Months 19 to 20 (see Figure 12). Additionally, response rates (defined as at least 50% improvement in MMSF) were maintained in patients who continued treatment with GNX (28.5%), and for those who switched from PBO to GNX a similar response rate (20%) was reached within 1 month (see

Figure 13). Interim results of the open-label extension also indicate that the overall patient improvements observed during the double-blind phase, as measured by the clinicians and caregivers CGI-I scales, are sustained during the open-label extension phase (see Section B.2.6.2).

B.2.12.1.2 Summary of safety evidence

During the double-blind phase the Marigold study, GNX was generally well tolerated in patients with CDD, with the majority of TEAEs categorised as mild or moderate in severity (see Section B.2.10.1.1). Adjunctive GNX did not increase the overall rate of TEAEs, with the reported rates for patients receiving GNX or PBO being similar (86.0% vs 88.0%). The most commonly reported events in GNX-treated patients were CNS-related AEs of mild to moderate intensity. Consistent with a GABAergic mechanism of action (81), mild or moderate somnolence was the most common AE reported by GNX-treated patients (36.0% vs 16% for PBO). Of note, fewer patients on GNX than PBO experienced vomiting (10% vs 20%). Overall, less than 5% of patients who received GNX discontinued from the study, with TEAEs leading to study drug discontinuation being comparable between treatment groups (GNX, 4.0%; PBO, 7.8%).

Open-label extension phase

During the open-label extension phase, GNX maintained a predictable tolerability profile in patients treated for 12 months or longer, with no new safety signals identified (see Section B.2.10.1.2). Overall, TEAEs were similar to those in the double-blind phase with seizure, somnolence, pyrexia, and vomiting being the most frequently observed. Somnolence seemed, however, to settle over time to a rate similar to that reported in the PBO group during the double-blind study period (14–22% vs 16%). The incidence of vomiting in both groups was similar, and lower than that observed in the PBO group during the double-blind study period.

B.2.12.1.3 Conclusions

There is a substantial unmet need for treatments that can improve clinical outcomes and reduce the seizure burden associated with CDD, a rare and complex disorder, with the vast majority of patients being refractory to established clinical management options. The Marigold study, the first Phase III trial of pivotal quality conducted specifically in CDD, and its open-label extension show that treatment with GNX results in unprecedented clinical benefits for patients in managing treatment-refractory seizures, a finding that is of clinical relevance for this patient population affected by a severely disabling, life-long condition, and for their families.

B.2.12.2 *Strengths and limitations of the clinical evidence base for the technology*

B.2.12.2.1 Strengths of the evidence base

Marigold is the first, relatively large Phase III clinical trial in CDD and provides pivotal evidence in patients suffering from this rare and complex disorder. Indeed, the rarity of CDD and the severe intellectual disability affecting children with this condition represent

a major challenge when running a trial in this setting. Nonetheless, the Marigold trial recruited 101 eligible patients. This represents a key strength of the trial, considering that in clinical studies investigating rare conditions the median number of participants enrolled is 61, with nearly 75% of completed trials enrolling fewer than 100 patients (82).

Marigold is a robustly designed global, double-blind, randomised, placebo-controlled trial which includes a population that closely reflects the real-world patient population eligible for treatment with GNX, in line with the proposed indication.

- Marigold is a trial with well-balanced treatment arms and is therefore robustly designed to assess the efficacy and safety of GNX in patients with CDD.
- Importantly, the study population in Marigold reflects the real-world CDD population; enrolled patients experienced treatment failure on a median of 7 previous ASMs before study entry took an average of 2.4 concomitant ASMs at baseline and continued to have frequent seizures.
- Results from the Marigold study are based on a relatively large patient population with CDD, supported by sensitivity and subgroup analyses which consistently point to directionally similar results. Furthermore, efficacy and safety results are deemed to be generalisable to UK population as the trial was conducted in patients from several centres in Europe, including the UK.
- In addition, interim results from the ongoing open-label extension of Marigold show the long-term efficacy and safety of GNX in the treatment of seizures caused by CDD.

The Marigold study addresses the decision problem:

- The patient population included in the trial matches that of the final NICE scope, i.e., patients who are two years of age or older with seizures caused by CDD.
- The key outcomes outlined in the NICE scope have been evaluated in the Marigold study including change in seizure frequency, percentage of seizure-free days, seizure severity, AEs of treatment, and HRQoL.
- In the Marigold trial, GNX is directly compared with PBO (plus a wide range of concomitant ASMs [mostly as combinations]) and, occasionally, ketogenic diet or VNS). This is in line with established clinical practice in the UK where there are currently no treatments specifically approved for CDD and ASMs are the main pharmacological therapy for the management of seizures caused by CDD.

Furthermore, the key clinical outcomes assessed in the Marigold study (and its open-label extension) are of high relevance to the clinical benefits that patients could experience in practice. Currently used ASMs have a suboptimal efficacy in CDD, with response rates decreasing over time (23, 29, 30). According to a key UK clinical expert, not uncommonly these patients may have cycled through 6 or more ASMs by the time they reach the age of 4. Thus, there is a substantial unmet need for efficacious

treatments specifically developed for CDD-related seizures that can improve and maintain clinical outcomes, thus reducing the seizure burden on patients. The primary endpoint in the Marigold study (i.e., change from baseline in 28-day MMSF) and other key outcomes assessed in this trial are of high relevance to address the unmet need in CDD. Indeed, in real-world practice these outcomes would translate into important clinical benefits to patients including significant reduction in seizure frequency, improvements in seizure intensity and duration, a potential small increase in seizure-free days in some patients, as well as sustained efficacy and tolerability in the long-term (see Section B.2.12.1 for further details).

B.2.12.2.1 Potential limitations

As with other randomised, placebo-controlled clinical trials of ASMs, the Marigold study has some limitations, such as the potentially confounding use of different concomitant ASMs and the relatively short treatment duration of the double-blind period of the study. However, the proportion of patients using ASMs, non ASM, and non-pharmacological therapies prior or during the study were similar for both the GNX and PBO cohorts (see Table 13). Indeed, the maintenance period of 13 weeks is similar to the 12-week maintenance period most often used in trials of ASMs (83). Due to the rare occurrence and severity of this condition limiting study participation, the study sample size was powered only for the statistical analysis of primary efficacy endpoint. Although other relevant endpoints were not tested for statistical significance, they all consistenty showed a trend in favour of GNX vs PBO. Similarly, the subgroup analyses performed pointed to the same direction, although the size of the subgroups was too small to derive definite conclusions.

While evidence on the long-term efficacy and safety of GNX is available from the ongoing open-label extension phase of Marigold, the robustness of these results may be potentially limited by the small size of the trial population. Thirteen percent of the patients who participated in the double-blind phase of the trial did not enter the open-label phase, and as the study is still ongoing, the final results are not yet available. However, it should be noted that small size populations are not uncommon in trials enrolling patients with rare conditions, such as CDD. Despite this potential limitation, interim results from the open-label extension (cut-off date [redacted]) indicate that the efficacy and favourable tolerability profile of GNX are maintained in patients who receive long-term treatment (see Section B.2.12.1.2).

B.2.12.3 *End-of-life criteria*

Ganaxolone, as an adjunctive treatment for seizures caused by CDD, is not eligible as an end-of-life therapy. The genetic cause of CDD was first identified in 2004; thus, data on the long-term prognosis and life-expectancy are not currently available (3, 4). Accordingly, life expectancy in patients with CDD was not among the measured outcomes in the Marigold trial.

B.3. Cost effectiveness

A de novo model structure was developed to address the decision problem (Section B.1.1) and assess the cost-effectiveness of ganaxolone (GNX) as adjunctive treatment to established clinical management (ECM), compared with ECM alone, in patients with cyclin-dependent kinase-like 5 (CDKL5) Deficiency Disorder (CDD)

- **In the absence of other treatments specifically developed and approved for CDD, ECM is the only relevant comparator in this patient population**
- **The key source of clinical effectiveness data used to inform the model is the Marigold study, a global, double-blind, randomised placebo-controlled Phase III trial that enrolled 101 patients aged 2–21 years with a confirmed disease-related CDKL5 gene variant (Section B.2)**.
- **The modelling approach, assumptions, and inputs used have been validated with a UK clinical key opinion leader (KOL) (Section B.3.3.3)**

Adding GNX to ECM is cost-effective relative to ECM alone in patients with CDD

- **The base case incremental cost-effectiveness ratio (ICER) for GNX as adjunctive therapy vs ECM alone is £22,200 per quality-adjusted life-year (QALY) gained using the Patient Access Scheme (PAS) price for GNX (Section B.3.9)**
- **The cost-effectiveness of GNX as adjunctive therapy persists under a wide range of scenarios and sensitivity analyses (Section B.3.10).**

B.3.1 *Published cost-effectiveness studies*

B.3.1.1 *Identification of studies*

A systematic literature review (SLR) was conducted to identify cost-effectiveness studies in the published literature relevant to the decision problem (Section B.2.1).

Electronic databases were searched on 9th August 2022 via the OVID platform pre-determined search strategies, and included MEDLINE®, MEDLINE® In-Process, Embase, EconLit, and the Cochrane Library. Supplementary searches of public registries and databases, reference lists, previous health technology assessment, appraisals, and conference proceedings were performed to identify data not captured in the database searches. Full details of the searches are provided in Appendix D.

However, no published cost-effectiveness studies of relevance to this submission were identified about ganaxolone (GNX) or healthcare resource utilisation in CDD.

B.3.1.2 *Description of identified studies*

No relevant studies were identified for inclusion.

B.3.1.3 *Quality assessment of identified studies*

No relevant studies were identified for inclusion.

B.3.2 *Economic analysis*

As the SLR did not identify any existing economic evaluations of GNX for treatment of CDD, a de novo economic model was built in Microsoft® Excel to address the decision problem. The main features of the economic analysis are outlined in Table 28.

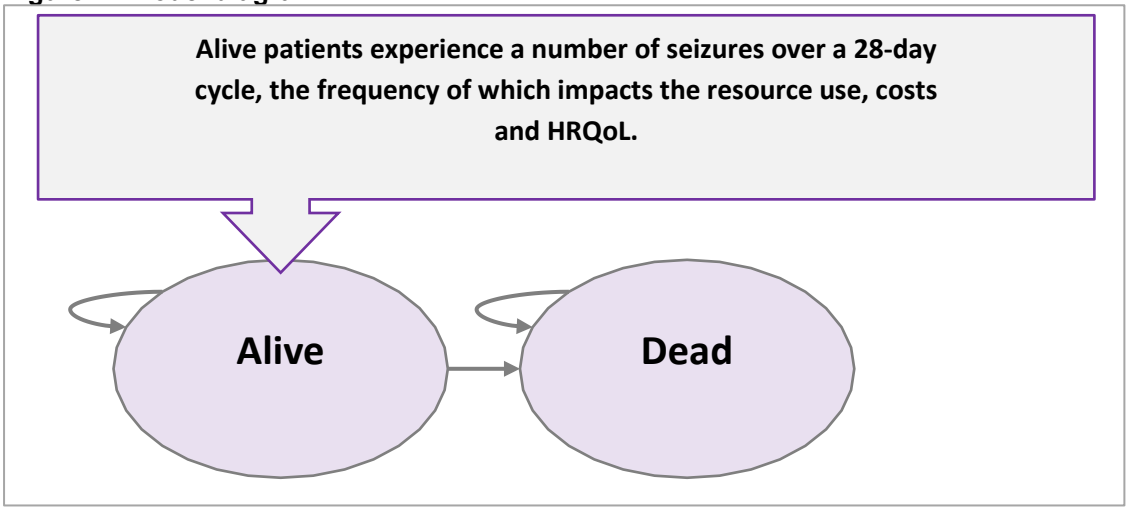
B.3.2.1 *Patient population*

The patient population for which the economic analysis was undertaken corresponds to a hypothetical cohort of 1,000 patients with CDD aged [redacted] (average age of patients likely to be starting GNX), with 20.8% of patients being male, in line with the descriptive statistics of the patient population in the Marigold study (Section B.2.3.3).

B.3.2.2 *Model structure*

The cost-effectiveness model is a two-state unidirectional Markov state-transition model. The structure of the model is shown in Figure 14.

Figure 14 Model diagram



Abbreviations: HRQoL, health-related quality of life.

B.3.2.3 *Health states*

The model is structured around two health states: Alive and Dead. Alive patients experience an average number of seizures per cycle, which impact on their health-related quality of life (HRQoL) and healthcare resource use.

B.3.2.4 *Perspective*

Analyses were conducted from the perspective of the National Health Service (NHS) and of the Personal Social Services (PSS) in England, as per NICE guidance (84).

B.3.2.5 *Time horizon*

CDD is a progressive, lifelong, life-limiting condition requiring extensive care and treatment throughout the patient lifetime. NICE guidance states that model time horizons should be long enough to capture all benefits of the treatment (84); therefore, a lifetime time horizon was applied to the model.

B.3.2.6 *Cycle length*

The model uses a 28-day cycle length (with half cycle correction applied) in line with seizure frequency outcomes from the Marigold study.

B.3.2.7 *Discounting*

The model assumed an annual discount rate of 3.5% for the UK setting in the base case.

Table 28: Features of the economic analysis

	Current evaluation	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime	NICE guidance states that model time horizons should be long enough to capture all benefits of the treatment (84). As CDD is a progressive, lifelong, life-limiting condition, a lifetime time horizon is required to capture all benefits of treatment.
Treatment discontinuation	A general discontinuation rate of [redacted] per 28-day cycle was applied	Estimates derived from the double-blind phase and the open label extension phase data from the Marigold study
Source of utilities	Utility values from the general population (Ara and Brazier 2010 (85)) to which an overall disutility value related to the frequency of seizure experienced was applied. Seizure-related decrement in utility was proxied with data for patients with TSC. Utilities were derived from general public (86).	NICE guide to the methods of technology appraisal 2022 (84). The proxy condition/data used is justified by the lack of CDD-specific HRQoLdata and has been validated in discussions with a clinical KOL.
Source of costs	Cost were sourced from a UK HCRU study (11), the NHS	NICE guide to the methods of technology appraisal 2022 (84).

	Current evaluation	
Factor	**Chosen values**	**Justification**
	Schedule of Reference Costs 2020/2021 (87), Personal Social Services Research Unit Costs (88) and inflated to 2021/22 values where necessary). Healthcare resource use was proxied by data for patients with LGS (11).	The proxy condition/data used is justified by the lack of CDD-specific cost and resource use data and has been validated in discussions with a clinical KOL.

Abbreviations: CDD, CDKL5 Deficiency Disorder; CDKL5, cyclin-dependent kinase-like 5; HCRU, healthcare resource use; KOL, key opinion leader; LGS, Lennox-Gastaut syndrome; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TSC, tuberous sclerosis complex; UK, United Kingdom.

B.3.2.8 *Intervention technology and comparators*

B.3.2.8.1 Intervention

The intervention considered was GNX as adjunct therapy (on top of the established clinical management [ECM]), with the same dosing schedule used in the Marigold study: up to a target dose of 63 mg/kg in patients weighting 28 kg or less, and up to a target dose of 1,800 mg/kg per day in patients weighting more than 28 kg.

B.3.2.8.2 Comparator

The comparator considered was ECM as defined in the Marigold study: up to 4 ASMs without GNX. Ketogenic diet or vague nerve stimulation (VNS) were also allowed, if started previously and stable at randomisation.

B.3.3 *Clinical parameters and variables*

B.3.3.1 *How are clinical data incorporated into the model?*

The clinical effectiveness of treatments was evaluated based on their impact on seizure frequency at baseline.

B.3.3.1.1 Seizure types

Seizures are typically categorised between primary vs secondary or tertiary types and generalised vs focal types, as described in Table 29.

Primary seizures (“major motor seizures” in Marigold) – which include all seizures of the generalised type – are considered as the most impactful seizures in terms of resource use and HRQoL, represent the vast majority of seizures recorded in the Phase III Marigold study, and also were the basis of the primary outcome measure in this pivotal

trial. Therefore, it was regarded most relevant to focus on primary seizures/major motor seizures in the base case analysis, with secondary and tertiary seizures being only considered for the scenario analysis on all seizure types. This assumption, and the approach for modelling were validated by a clinical key opinion leader (KOL; Section B.3.3.3).

The decision to focus on primary seizures (i.e., "major motor seizures" in Marigold) as part of the base case analysis was also guided by the fact that, in the Marigold study, the incidence of secondary and tertiary seizures was very low when compared with the incidence of primary seizures. The high uncertainty associated with a low number of secondary and tertiary seizure types would thus make comparative effectiveness estimates potentially unreliable.

Table 29. Seizure types and classification

Primary Seizures (Major motor seizures†)	Secondary Seizures (Countable focal-onset seizure types)	Tertiary Seizures (Hard to count seizure types)
Bilateral tonic	Focal motor with intact awareness or altered awareness	Focal non-motor with intact awareness
Generalised tonic-clonic	Focal nonmotor with altered awareness	Absence
Atonic/drop		Myoclonic
Bilateral clonic		Epileptic spasms
Focal to bilateral tonic-clonic seizures		

Generalised seizure type

Focal seizure type

†Note: The term "primary seizures" was used in the Marigold study protocol to refer to the seizure types evaluated for the primary endpoint; the more commonly accepted clinical term "major motor seizures" is used for those seizure types in Section B.2. of this document. Major motor seizures include bilateral tonic (sustained motor activity ≥3 seconds), generalised tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic seizures. The terms "primary seizures" and "major motor seizures" are synonymous.
Source: Marigold Study (72).

B.3.3.1.2 Distribution of seizure frequencies under ECM and GNX as adjunctive therapy

The model is populated with the distribution of seizure frequencies in patients enrolled in the Marigold study. Seizures in patients receiving ECM were modelled based on the 28-day seizure frequency distribution of all patients (n=100) in the trial at baseline. To

model this baseline and the uncertainty around it most appropriately, a statistical distribution was fitted to patients' seizure frequency data collected at baseline.

The lognormal distribution was chosen to model the baseline frequency of seizures in the cost-effectiveness model based on the Akaike information criterion/BIC statistics (provided in Table 30) and visual inspection of the curves' fit to the data (provided in Figure 15). All distributions tested were rejected by a test of goodness of fit, except for the lognormal.

Table 30. Statistical measures of goodness of fit for distributions

Distribution	AIC	BIC	GOF test p-value
Gamma	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Logistic	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; GOF, goodness of fit

Figure 15. Statistical distribution density functions plotted over the baseline distribution of seizure frequency

Abbreviations: exp, exponential

The seizure frequency distribution among the modelled patient cohort on GNX as adjunctive therapy was constructed by applying to the mean of the baseline seizure frequency distribution – modelled via the lognormal distribution – the estimated reduction in seizure frequency from baseline (Hodges-Lehmann estimate of location shift, a robust estimation method to determine the difference between values in two or mor data sets)

associated with GNX as adjunctive therapy. This location shift estimate (27.08%) was adjusted for the mean reduction in seizure frequency from baseline experienced by patients in the placebo (PBO) arm.

This approach was preferred to the alternative of modelling GNX separately to avoid introducing bias (in either direction) through heterogeneity of CDD in general, and thus between individual patients in the Marigold study. Indeed, due to the small number of patients; any variance between the baseline and final seizure frequency could artificially impact the magnitude of difference between the two modelled curves, whereas our model aims to estimate the impact of GNX in a hypothetical identical cohort of patients.

The estimates of treatment-related reduction in seizure frequency for primary, secondary and all seizure types are provided in Table 31. The resulting seizure frequency distribution for both ECM and GNX as adjunctive therapy are depicted in Figure 16.

Table 31. Seizure frequency parameters

Parameter	Value	Source
Mean seizure frequency per 28-day cycle with ECM alone, Log Mean (Log SD)	[redacted]	Marigold study (48) and PLD analysis
Reduction in seizure frequency from baseline with GNX, adjusted for PBO*, Mean (95% CI)	−27.08% (−47.92%, -9.95%)	

Abbreviations:CI, confidence interval; ECM, established clinical management; GNX, Ganaxolone; PBO, placebo; PLD, patient level data; SD, standard deviation
* Estimated using the Hodges-Lehmann estimate of location shift

Figure 16. Modelled distribution of seizure frequency (major motor seizures)

Abbreviations: ECM, established clinical management; Gan, ganaxolone

B.3.3.1.3 Treatment adherence and discontinuation

The model assumed a [redacted] discontinuation rate per cycle to reflect the proportion of patients who were found to discontinue GNX for all causes in the open-label extension (OLE) of the Marigold study (**Error! Reference source not found.**).

Table 32.Treatment discontinuation rate

Parameter	Default value	SE	Source
Discontinuation rate per cycle (all causes)	[redacted]	[redacted]	Analysis of Marigold PLD (3001) and OLE data

Abbreviations: PLD, patient-level data; OLE, open label extension; SE, standard error

B.3.3.2 *Transition probabilities*

In the absence of direct mortality data available for patients with CDD, the mortality rates in the model were estimated using those for the general UK population, uplifted based on the mortality rates reported for patients with Lennox-Gastaut syndrome (LGS) by Chin et al, 2021 (11).

LGS is a type of epileptic encephalopathy with multiple different types of seizures, and particularly tonic and atonic seizures. Intellectual development is usually delayed and often worsens over time (89). Given these characteristics, LGS was considered a viable proxy for the clinical outcomes of patients with CDD.

The appropriateness of proxying survival in patients with CDD with survival outcomes in patients with LGS was confirmed by the clinical KOL consulted and deemed conservative as there are only very few known patients above the age of 30 years.

The standardised mortality ratio in patients with LGS (compared with the general population) was derived from the crude mortality rate in patients with LGS reported by Chin et al, 2021 (4–6 per 1,000 person-year) (11) and that in the general population in England (0.6 per 1,000 person-years) (Table 33).

Mortality rate projections for patients with CDD derived by applying the standardised mortality ratio to the general UK population mortality rates are shown in Figure 17. In the base case analysis, no difference was assumed in baseline mortality between ECM alone and ECM + GNX.

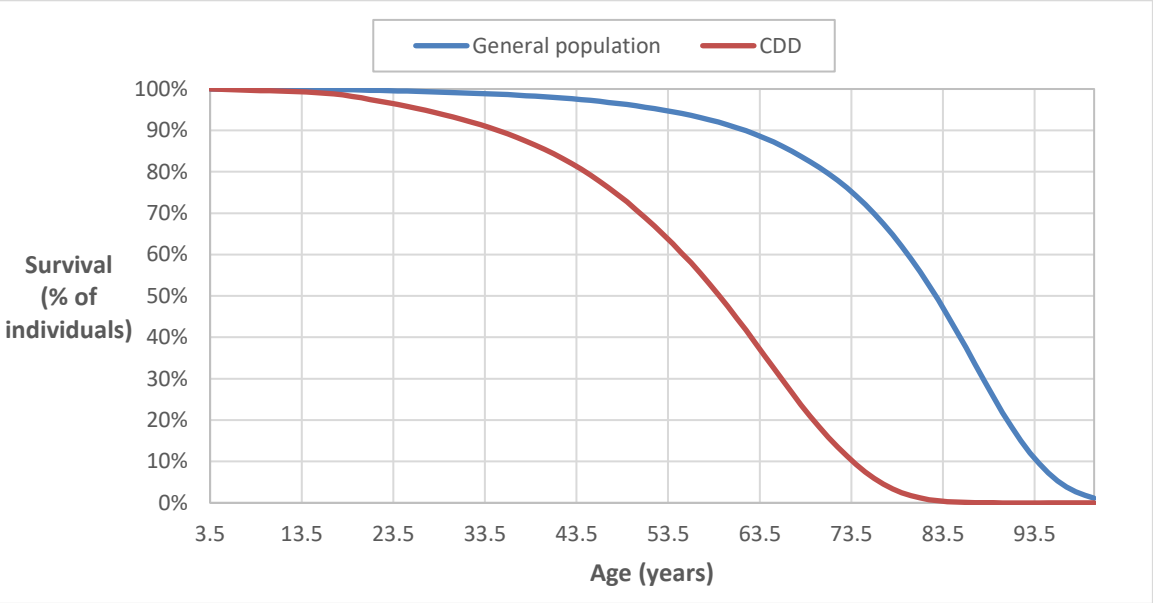
Table 33.Standardised mortality ratio in LGS patients (compared with the general population)

Parameter	Default value	SE	Source
Standardised mortality ratio in LGS patients (compared with the general population)	8.33*	0.85	Chin et al, 2021 (11)
Mortality inflation – ECM alone versus GNX + ECM	1.00	0	Assumption – no difference in mortality between arms.

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; LGS, Lennox-Gastaut syndrome; SE, standard error

* Patients with LGS were found in Chin et al, 2021 (11) to have a crude mortality rate of 4–6 per 1,000 person-years (over a follow up consisting of ~1,700–1,800 patient-years) that is higher than that reported for the general population in England (0.6 per 1,000 person-years).

Figure 17. Projected survival rates for patients with CDD based on estimated standardised mortality ratios in patients with LGS and general population mortality rates



Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5; LGS, Lennox-Gastaut syndrome

B.3.3.3 *Clinical expert assessment of applicability of clinical parameters*

Clinical expert opinion was used to assess the applicability of values in the model. One clinical KOL from the [redacted] was interviewed via web-conference for the purpose of presenting and validating the applicability of model values used (specifically proxy values derived from data relating to similar conditions).

The KOL was provided with an overview of health economic modelling, and specifically the health economic model used in this submission. He provided insights as to:

- Whether our modelling approach reflects CDD course, treatment pathways, clinical practice, and the key drivers of morbidity and mortality.
- Which data sources would be the most appropriate to use, especially regarding data specific to other similar conditions to fill evidence gaps related to CDD, specifically.
- Key questions focussed on:
    - Does the model structure accurately reflect the natural history of CDD?
    - Are the mortality estimates produced by the model comparable with what would be expected in the real world?
    - Is the approach used to model seizure frequency appropriate?
    - In terms of the type and frequency of seizures, which conditions offer the most appropriate comparison with CDD?
    - What would be the most appropriate source of resource use and cost data?
    - How is a reduction in seizure frequency expected to impact the resource use and hospitalisation patterns in patients with CDD?
    - What would be the appropriate standard of care in CDD?

The KOL selection criteria included: experience in the treatment of epileptic encephalopathies and CDD within NHS England [redacted] having extensive practical care expertise, research and publication activity in the area of CDD; still actively managing patients with CDD and working with their families.

B.3.4 *Measurement and valuation of health effects*

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

No relevant HRQoL data were captured in any clinical trials of patients with CDD, thus necessitating the use of proxy indications (e.g., Tuberous Sclerosis Complex [TSC]) to fill HRQoL-related evidence gaps.

B.3.4.2 *Mapping*

No relevant HRQoL mapping studies were identified for CDD.

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

No relevant HRQoL studies were identified for CDD, thus necessitating the use of proxy conditions with similar seizures (e.g., TSC) to fill HRQoL-related evidence gaps.

B.3.4.4 *Key differences*

No relevant HRQoL studies were identified for CDD.

B.3.4.5 *Adverse reactions*

The model did not incorporate any effect of adverse event (AE) on patients' HRQoL. Since data from the Marigold study demonstrated no significant difference in the incidence of AEs between the PBO and GNX arms of the model, it was assumed that their impact on both cost and QoL would be the same in both arms.

B.3.4.6 *Health-related quality-of-life data used in cost-effectiveness analysis*

In the absence of HRQoL data in patients with CDD, seizures frequency was used as the key driver of HRQoL in patients. To achieve this, a baseline utility value representing the general population was generated, from which an estimated disutility was subtracted based on the frequency of generalised/focal seizures experienced. The model then applied a proportional decrement to the baseline (general population) utility value based on the number of seizures experienced. This approach was validated by the clinical KOL.

B.3.4.6.1 Baseline utility values

The QoL of both patients with CDD and their caregivers is greatly affected by seizure frequency and severity, besides developmental issues and disability (Section B.1.3.2.2). However, with no CDD-specific utility values available to represent HRQoL in these patients, we employed general population utility values derived using the widely-used and validated regression coefficients reported by Ara and Brazier, 2010 (85) – provided in Table 34 – to represent the “baseline” utility value of patients with CDD of the same age and gender. These utility scores were then adjusted by decrements based on seizure frequency to model reduced QoL due to seizure frequency. It should be noted that this approach is likely to be highly conservative in nature, as it cannot fully capture seizure severity in addition to the impact of CDD on childrens’ long term development and disability in later life, and, irrespective of seizures, patients with CDD would be expected to have lower QoL than individuals of equivalent age in the general population.

Table 34. Baseline utility value parameters

Parameter	Default value	SE	Source
General population utility – constant	0.9508566	0.19017132	Ara and Brazier, 2010 (85)
General population utility – male coefficient	0.0212126	0.00424252	
General population utility – age coefficient	-0.0002587	-0.00005174	
General population utility – age-squared coefficient	-0.0000332	-0.00000664	

Abbreviations: SE, standard error

B.3.4.6.2 Seizure-related disutility

In the absence of data specific to patients with CDD, the disutility associated with seizure was proxied by the disutility experienced by patients with TSC, a similar condition. This approach was validated by the clinical KOL.

Seizure-related disutility in patients with TSC was informed by data from a Vignette study in general public by Lo et al, 2022 (86). The study provides disutility estimates for both patients and caregivers of patients with TSC, based on the frequency of generalised and focal seizures per day. Clinical expert opinion was sought to validate the applicability of data from patients with TSC as a proxy for patients with CDD, with regard to the similarity between the seizure types generally experienced (and those reported in the study), the impact these seizures would have on patients and caregivers, and the general comparability of QoL for patients with the two conditions and their caregivers.

Given the potential discrepancy in seizure categorisation between the patients/condition considered in this study and our seizure model based on the Marigold study, we used the modelled frequency of seizures (Figure 16) stratified by generalised and focal based on the distribution/categorization of seizures from the Marigold study (Table 29) to determine the frequency of generalised and focal seizures in the ECM and GNX arms. From this, we then determined the weighted average utility based on the proportion of patients falling into relevant generalised and focal seizure frequency categories per the modelled frequency distribution (Figure 16). This ensured that the categories of seizure modelled based on Marigold were similar to the categories used to derive differential states in the proxy Vignette study. This value was then applied as a proportion of general population utility to adjust utility values for age and gender.

Seizures are the only element of CDD considered to impact HRQoL in the model, although patients' HRQoL may be impaired due to other aspects of the condition (e.g., developmental impairment or disability). However, given the potential overlap between seizures and these aspects of CDD in terms of clinical progression of the condition and related impact on patient/caregiver HRQoL, the impact of these other aspects on HRQoL was not modelled to ensure the analysis remained conservative.

Also, it is worth noting that in the base case analysis, only primary seizures (i.e. major motor seizures) were modelled using generalised seizure utility decrements from TSC as the basis. This was also warranted as the frequency of secondary and tertiary seizures was comparatively very low, with a median frequency of zero for the former in the Marigold population.

Utility parameters used in the model for patients and caregivers are shown in Table 35 and Table 36, respectively.

Patients aged less than 18 years are assumed to require support from an average of 1.8 caregivers, while patients aged 18 or over are assumed to require support from an average of 1 caregiver over the remainder of their lifetime.

Table 35. Patient utility values* based on seizure frequency (base case)

Parameter	Default value	SE	Source
Utilities associated with generalised seizures (focus of the base case analysis)			
Patient utility (1 generalised and 0 focal seizures per day)	0.1830	0.0570	Lo et al, 2022 (86)
Patient utility (2 generalised and 0 focal seizures per day	0.0890	0.0540	
Patient utility (3–14 generalised and 0 focal seizures per day	−0.1130	0.0590	
Patient utility (3–14 generalised and 5–14 focal seizures per day	−0.2340	0.0560	
Utilities associated with focal seizures (scenario analysis)			
Patient utility (0 generalised and 0 focal seizures per day)	0.7250	0.0250	Lo et al, 2022 (86)
Patient utility (0 generalised and 1–2 focal seizures per day)	0.5040	0.0370	
Patient utility (0 generalised and 3–4 focal seizures per day)	0.2820	0.0530	
Patient utility (0 generalised and 5–14 focal seizures per day)	0.0740	0.0550	

* Values used in the model are adjusted for age and gender.
Abbreviations: SE, standard error

Table 36. Caregiver utility values* based on seizure frequency (base case)

Parameter	Default value	SE	Source
Utilities associated with generalised seizures (focus of the base case analysis)			
Caregiver utility (1 generalised and 0 focal seizures per day)	0.5460	0.0390	Lo et al, 2022 (86)
Caregiver utility (2 generalised and 0 focal seizures per day	0.4760	0.0450	
Caregiver utility (3–14 generalised and 0 focal seizures per day	0.3190	0.0480	
Caregiver utility (3–14 generalised and 5–14 focal seizures per day	0.2210	0.0530	
Utilities associated with focal seizures (scenario analysis)			
Caregiver utility (0 generalised and 0 focal seizures per day)	0.9050	0.0080	Lo et al, 2022 (86)
Caregiver utility (0 generalised and 1–2 focal seizures per day)	0.7910	0.0170	
Caregiver utility (0 generalised and 3–4 focal seizures per day)	0.6380	0.0370	
Caregiver utility (0 generalised and 5–14 focal seizures per day)	0.4310	0.0490	

* Values used in the model are adjusted for age and gender.
Abbreviations: SE, standard error

Since there is significant uncertainty associated with the use of alternative conditions to model HRQoL in patients with CDD, the model allows an alternative approach to proxy seizure-related utility decrements, based on the survey-based study by Auvin et al, 2021 (90), estimating HRQoL in patients (and their caregivers) with LGS and DS.

In patients with LGS and their caregivers, HRQoL was stratified based on the number of drop seizures per month (130, 110, 80, 60, 45, 20, 0) and the number of seizure-free days in an average month (1, 3, 6, 9, 12, 15, 18, 30). In patients with DS and their caregivers, HRQoL was stratified based on the number of convulsive seizures per month (32, 25, 16, 8, 6, 4, 0) and the number of seizure-free days in an average month (4, 8, 12, 18, 21, 24, 28, 30). As with the default approach, a proportional utility value was calculated and applied to the utility value for the general population to ensure that the modelled HRQoL was age- and sex-adjusted.

The model also accommodated for user-defined utility values (e.g., based on response rates) for the purpose of scenario analyses.

B.3.4.7 *Clinical expert assessment of applicability of health state utility values*

The clinical KOL consulted validated both the proxy condition used and the type of seizures to quantify the impact of seizure on HRQoL in patients with CDD.

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

In the absence of relevant studies reporting healthcare resource use and cost data in patients with CDD, available evidence in patients with LGS was used as a proxy to model healthcare resource use and costs in patients with CDD. These studies providing evidence in patients with LGS are described in Appendix I.

B.3.5.1 *Resource identification, measurement and valuation studies*

In the absence of data from patients with CDD, the healthcare resource use was proxied with data available for patients with LGS in the base case scenario. The use of such data was validated by the clinical KOL, to ensure the resource use and costs associated with CDD and LGS were comparable and suitable for use in the model.

B.3.5.2 *Appropriateness of NHS Reference costs/Payment by Results tariffs*

Unit costs were applied to resource use estimates, based on the latest values reported in the National Health Service (NHS) reference costs and the Personal Social Services Research Unit (PSSRU) (88) in the UK.

B.3.5.3 *Clinical expert assessment of applicability of cost and healthcare resource use values*

The clinical KOL validated the use of LGS as a proxy for quantifying the healthcare resource use and associated costs in CDD, given the level of similarity between the two conditions. Importantly, this proxy relationship is not expected to overestimate the healthcare resource use in CDD.

B.3.5.4 *Intervention and comparators' costs and resource use*

B.3.5.4.1 Treatment and administration costs

It was assumed that there was no incremental administration cost associated with the use of GNX, nor the use of ECM with or without GNX.

The model used an assumed unit cost to generate base case results. The average dosing data from the Marigold study were then used to calculate the average cost per patient per cycle. Per the Marigold study, the dosing schedule of GNX is up to 63 mg/kg in patients weighing 28 kg or less, and up to 1,800 mg/kg per day in patients weighing more than 28 kg. This stratification was used to define two different dosage parameters, applied based on whether the patients' weight was above or below 28 kg. Patient weight was assumed to increase with age, using weight data stratified by age from the Marigold study.

Acquisition cost and dosing and other related parameters are shown in Table 37. Average weight projections are shown in **Error! Reference source not found.**.

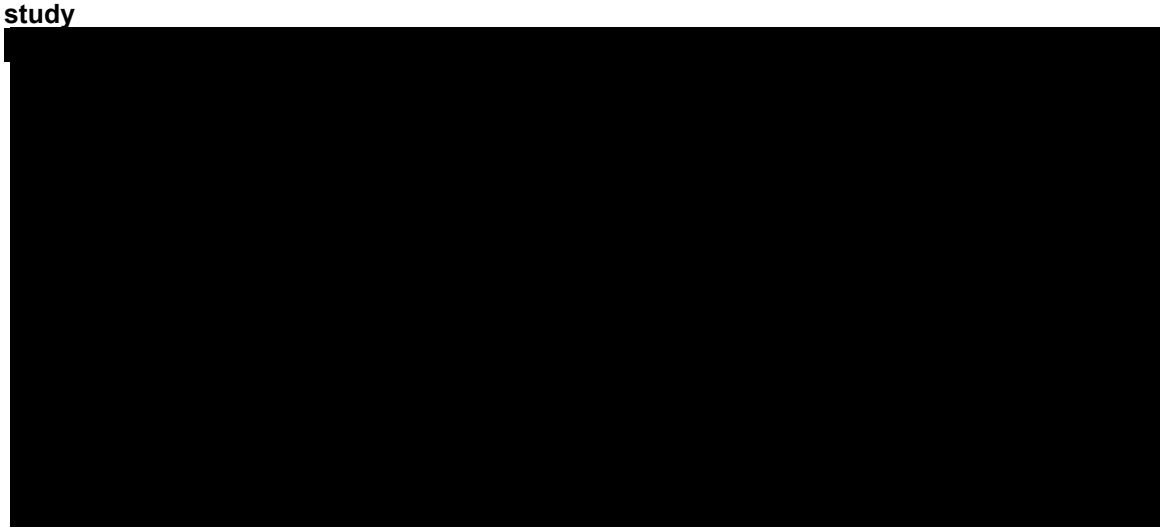
Table 37. Treatment cost parameters

Parameter	Default value	SE	Source
Unit cost per pack GNX (110 mL/5,500 mg)	[redacted]	[redacted]	Data on File, Orion Pharma (UK) Limited.
Average dose GNX in patients ≤28 kg (mg/kg/day)	[redacted]	[redacted]	Marigold study
Average dose GNX in patients >28 kg (mg/day)	[redacted]	[redacted]	
Daily acquisition cost - ECM	£15.00	£0.00	Assumption based on Marigold study data, as patients could receive a broad range of medications and other treatments concomitantly; received by both patients on ECM alone and ECM + GNX, no difference between arms.
Daily acquisition cost - rescue medication – ECM alone	£359.91	£71.98	Assumed reduction in rescue medication based on adapted approach and data from ID1211

Daily acquisition cost - rescue medication – ECM + GNX	£280.58	£56.12	(91); the proportion of patients in each arm experiencing 0–27 seizures per cycle incurred £204 in medication costs, while others experiencing more incurred £408 in medication costs.

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; SE, standard error; UK, United Kingdom.

Figure 18. Patient weight projections based on age, determined based on the Marigold study



Source: Marigold study

B.3.5.5 *Health-state costs and resource use*

B.3.5.5.1 Base case approach

The healthcare resource use in patients with CDD was proxied with the healthcare resource use in patients with probable LGS reported by Chin et al (11), based on the relative annual frequency of resource use in terms of primary and secondary healthcare contacts and visits (Table 38). Differential costs were available for patients aged under 12 and those aged 12 or over and were thus applied in the model accordingly.

It was assumed that the incidence of these contacts is the same in patients treated with GNX as adjunctive therapy and those treated with ECM alone, with the exception of epilepsy-related hospital admissions.

For consistency, the incidence of epilepsy-related hospital admissions was lowered by the same equivalent mean reduction in seizure frequency reported in the Marigold study (27.08%). This assumption was validated by the clinical KOL consulted.

Unit costs for primary and secondary healthcare contacts and visits from the NHS reference costs and the PSSRU (88) in the UK are provided in Table 39. The cost of

epilepsy hospitalisation was assumed to be the average of codes related to long stay hospitalisations of various severities, given an average of 29 days reported in real-world registry data (19), validated by clinical expert opinion indicating that patients with CDD experience extensive hospital stays.

Table 38. Healthcare resource use parameters

Parameter		Default value (annual)	SE	Source
Patients aged <12 years	GP consultation	5.54	0.06	Chin et al, 2021 (11)
	GP home visit	0.27	0.01	
	GP phone call	0.83	0.02	
	Nurse consultation	0.66	0.02	
	Nurse home visit	0.03	0.00	
	Nurse phone call	0.24	0.02	
	Number of hospital outpatient visits	10.04	0.46	
	Number of hospital inpatient admissions (all cause)	0.57	0.21	
	Number of hospital inpatient admissions (epilepsy related)	3.04	0.19	
	Number of A&E visits	0.96	0.07	
Patients aged ≥12 years	GP consultation	5.97	0.05	
	GP home visit	0.29	0.01	
	GP phone call	0.54	0.01	
	Nurse consultation	0.96	0.01	
	Nurse home visit	0.06	0.00	
	Nurse phone call	0.02	0.00	
	Number of hospital outpatient visits	7.13	0.16	
	Number of hospital inpatient admissions (all cause)	0.37	0.04	
	Number of hospital inpatient admissions (epilepsy related)	0.89	0.03	
	Number of A&E visits	1.04	0.05	
	Reduction in epilepsy-related admissions* with GNX	27.08%	–	Assumption based on Marigold study

Abbreviations: A&E, accident and emergency; GNX, Ganaxolone; GP, general practitioner; SE, standard error.
*Assumed to be hospital inpatient stays and A&E visits

Table 39: Unit costs of care

Parameter	Default value	SE	Source
Cost per GP consultation	£34.40	£3.42	PSSRU. Unit costs of care 2020 (88) inflated to 2021 costs
Cost per GP home visit	£78.45	£7.80	
Cost per GP phone call	£8.46	£0.84	
Cost per Nurse consultation	£5.87	£0.58	
Cost per Nurse home visit	£0.00	£0.00	
Cost per Nurse phone call	£1.45	£0.14	
Cost per hospital outpatient visit	£244.00	£24.40	NHS reference costs 2020/21 (87). Service code 223; Paediatric Epilepsy (outpatient)
Cost per hospital inpatient admission (all cause)	£1,182.00	£118.20	NHS reference costs 2020/21 (87); Total healthcare resource groups currency Code PX57A, PX57B, PX57C; Paediatric, Examination, Follow-up, Special Screening or Other Admissions
Cost per hospital inpatient admission (epilepsy-related)	£6,545.75	£654.58	NHS reference costs 2020/21 (87); Non-elective long-stay; currency Code PRO2A, PRO2B, PRO2C; Paediatric Epilepsy Syndrome. Assumed long-stay due to length of hospitalisation (27.4 days) reported in Mangatt et al, (21)
Cost per A&E visit	£170.00	£17.00	NHS reference costs 2020/21 (87). Service code 170; Accident and Emergency (outpatient)

Abbreviations: A&E, accident and emergency; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SE, standard error.

B.3.5.5.2 Alternative sources of direct healthcare costs

Given the uncertainty associated with the use of data from patients with a similar condition, such as LGS, to proxy the healthcare resource use and costs in patients with CDD, an alternative costing method based on another condition was provided.

This second method used DS as a proxy disease; the healthcare resource use and costs are reported in Lagae et al, 2019 (92).

The authors reported the cost per patient per year of:

- Seizure related symptoms: emergency visits, ambulance calls, epilepsy specialist visits, drug costs
- Non-seizure-related symptoms: physiotherapy, speech therapy, therapy for learning difficulties, therapy for autism, therapy for attention deficit hyperactivity disorder, behavioural therapy

Direct costs of the above healthcare resource use categories were reported in the paper itself and were used directly under this method. Therefore, this alternative approach directly replaces both the resource use estimates reported by Chin et al, 2021 (11), and the unit cost data reported by the PSSRU.

It was assumed that there was no difference in the healthcare resource use between GNX as adjunctive therapy and ECM alone arms when using this method based on the costs from Lagae et al, 2019 (92).

Table 40. Alternative annual costs of care

Parameter	Default value	SE	Source
Emergency visits	£635.14	£63.51	Lagae et al, 2019 (92), inflated to 2021 costs
Ambulance calls	£1,089.38	£108.94	
Epilepsy specialist visits	£1,143.73	£114.37	
Physiotherapy	£1,361.12	£136.11	
Speech therapy	£1,431.69	£143.17	
Therapy for learning difficulties	£378.00	£37.80	
Therapy for autism/autism-like symptoms	£389.36	£38.94	
Therapy for ADHD	£82.74	£8.27	
Behavioural therapies	£155.74	£15.57	

Abbreviations: ADHD, attention deficit hyperactivity disorder; SE, standard error.

B.3.5.6 *Health-state costs and resource use*

The costs described above apply to the Alive state of the model.

B.3.5.7 *Adverse reaction unit costs and resource use*

There was no significant difference in treatment-related AEs in the PBO and GNX arms in the Marigold study. Nevertheless, the cost of hospitalisation due to adverse events is included in the model and assumed equal in both arms. The proportion of patients experiencing any AE requiring or prolonging hospitalisation in the overall study population from Marigold [redacted] were applied to an average annual cost of (all-cause) hospitalisation reported in 2020/21 NHS reference costs (87) (Table 39).

B.3.5.8 *Miscellaneous unit costs and resource use*

No miscellaneous unit costs and resource use are included.

B.3.6 *Severity*

Based on estimates of proportional and absolute quality-adjusted life-year (QALY) shortfall in patients with CDD (vs age- and sex-matched individuals from the general population), the technology qualifies for a severity modifier weighting of 1.7 for QALYs (Table 41), with a QALY shortfall of over 18 QALYs.

The model was used to estimate the total discounted QALYs accrued for patients with CDD vs the average QALYs accrued in counterparts without the condition, using general population survival (ONS life tables (93)) and QoL (Ara and Brazier 2010 (85)) data at a similar starting age and time horizon.

Table 41. QALY shortfall estimates and severity weighting

QALYs		QALY Shortfall with CDD		Implied severity weighting
CDD (ECM)	**General population**	**Absolute**	**Proportional**	
[redacted]	[redacted]	20.75	83.23%	1.7

Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinalse-like 5; ECM, Established clinical management; QALY, quality-adjusted life-year.

Table 42. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	20.8% male	Section B.2.3.3
Starting age	[redacted]	

Abbreviations: QALY, quality-adjusted life-year

No previous evaluations of CDD are available. The model contains two states, in which weighted average utilities are accrued – therefore, for patient-specific QALY shortfall analysis, no disaggregation by state was feasible.

Table 43. Summary of QALY shortfall analysis

Comparator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with model treatments	QALY shortfall	
			Absolute	**Proportional**
ECM alone	[redacted]	[redacted]	20.75	83.23%
GNX + ECM	[redacted]	[redacted]	19.78	79.35%

Abbreviations: ECM, established clinical management; GNX, ganaxolone; QALY, quality-adjusted life-year

B.3.7 *Uncertainty*

Due to the rare nature of CDD, its exact epidemiology is largely unknown (Section B.1.3.1.1). Therefore, there is a paucity of data on survival, HRQoL and healthcare resource use and costs in patients with CDD. All these important components of the cost-effectiveness analysis were therefore proxied using outcomes reported for a similar condition to CDD, namely LGS for survival and healthcare resource use (base case analysis) and TSC for HRQoL.

A further source of uncertainty is the data available from the clinical study itself – our model does not assume differences between treatment arms in terms of the AEs experienced (and requiring management), nor does it capture differences in concomitant medication use and so forth. Throughout, we have sought to use a consistent approach where no difference could be inferred from trial data; for example, assuming similar AE rates and rescue medication usage between arms and similar resource use except that which would specifically be impacted by seizure frequency.

B.3.8 *Summary of base-case analysis inputs and assumptions*

B.3.8.1 *Summary of base-case analysis inputs*

A list of all variables used in the economic analysis is provided in Table 44.

Table 44. Summary of base case inputs

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Discounting				
Discount rate (costs)	3.5%	0– 5% used in additional scenario analyses	NICE guide to the methods of technology appraisal 2022	B.3.2.7
Discount rate (outcomes)	3.5%	0– 5% used in additional scenario analyses		
Clinical parameters (primary i.e., generalised seizure only)				
Average (log-transformed) seizure frequency per cycle	[redacted]	[redacted] (lognormal)	Marigold Study	B.3.3.1.
Reduction in seizure frequency with ganaxolone (versus baseline)	27.08%	[redacted]	Marigold Study	
Reduction in epilepsy-related admissions* with ganaxolone	27.08%	-	Marigold Study	B.3.5.2.
Discontinuation rate/cycle	[redacted]	[redacted]	Marigold Study and OLE data	B.3.3.1.

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Survival				
Survival in the general population	Lifetable England	-	ONS	B.3.3.2.
Standardised mortality ratio in patients with LGS vs general population in the UK	8.33	0.85 (gamma)	Chin et al, 2021 (11)	
Baseline utility and disutility for primary i.e., generalised seizure only				
Baseline utility of the general population	Age- and gender-specific values for the UK general population	Multinormal distribution fitted to regression coefficients	Ara and Brazier 2010 (85)	B.3.4.6.
Patient disutility (1 generalised and 0 focal seizures per day)	0.1830	0.0570 (beta)	Lo et al, 2022 (86)	
Patient disutility (2 generalised and 0 focal seizures per day	0.0890	0.0540 (beta)		
Patient disutility (3–14 generalised and 0 focal seizures per day	−0.1130	0.0590 (beta)		
Caregiver disutility (1 generalised and 0 focal seizures per day)	0.5460	0.0390 (beta)		
Caregiver disutility (2 generalised and 0 focal seizures per day	0.4760	0.0450 (beta)		
Caregiver disutility (3–14 generalised and 0 focal seizures per day	0.3190	0.0480 (beta)		
Average number of caregivers per patient aged <18 years	1.80	0.36	Assumption	
Average number of caregivers per patient aged ≥18 years	1.00	0.20		
Costs				
Drug acquisition costs (no administration costs are considered in the model)				
Unit cost per pack ganaxolone (110 mL/5,500 mg)	[redacted]	[redacted]	Orion Pharma (UK) Limited.	B.3.5.2.

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Average dose ganaxolone in patients ≤28 kg (mg/kg/day)	[redacted]	[redacted]	Marigold study	
Average dose ganaxolone in patients >28 kg (mg/day)	[redacted]	[redacted]		
Daily acquisition cost - ECM	£15.00	£0.00	Assumption based on Marigold data	
Daily acquisition cost - rescue medication (ECM alone)	£359.91	£71.98	Assumption based on NICE ID1211 data (91)– difference based on seizure frequency	
Daily acquisition cost - rescue medication	£280.58	£56.12		
Healthcare resource use				
GP consultation (patients aged <12 years)	5.54	0.06	Chin et al, 2021 (11)	B.3.5.2.
GP home visit (patients aged <12 years)	0.27	0.01		
GP phone call (patients aged <12 years)	0.83	0.02		
Nurse consultation (patients aged <12 years)	0.66	0.02		
Nurse home visit (patients aged <12 years)	0.03	0.00		
Nurse phone call (patients aged <12 years)	0.24	0.02		
Number of hospital outpatient visits (patients aged <12 years)	10.04	0.46		
Number of hospital inpatient admissions (all cause) (patients aged <12 years)	0.57	0.21		
Number of hospital inpatient admissions (epilepsy related)	3.04	0.19		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
(patients aged <12 years)				
Number of accident and emergency (A&E) visits (patients aged <12 years)	0.96	0.07		
GP consultation (patients aged ≥12 years)	5.97	0.05		
GP home visit (patients aged ≥12 years)	0.29	0.01		
GP phone call (patients aged ≥12 years)	0.54	0.01		
Nurse consultation (patients aged ≥12 years)	0.96	0.01		
Nurse home visit (patients aged ≥12 years)	0.06	0.00		
Nurse phone call (patients aged ≥12 years)	0.02	0.00		
Number of hospital outpatient visits (patients aged ≥12 years)	7.13	0.16		
Number of hospital inpatient admissions (all cause) (patients aged ≥12 years)	0.37	0.04		
Number of hospital inpatient admissions (epilepsy related) (patients aged ≥12 years)	0.89	0.03		
Number of accident and emergency (A&E) visits (patients aged ≥12 years)	1.04	0.05		
Unit costs				
Cost per GP consultation	£34.40	£34.40	PSSRU. Unit costs of care 2020 (88) inflated to cost year 2021	B.3.5.2.
Cost per GP home visit	£78.45	£78.45		
Cost per GP phone call	£8.46	£8.46		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Cost per Nurse consultation	£5.87	£5.87		
Cost per Nurse home visit	£0.00	£0.00		
Cost per Nurse phone call	£1.45	£1.45		
Cost per hospital outpatient visit	£244.00	£244.00	NHS reference costs 2020/21 (87)	
Cost per hospital inpatient admission (all cause)	£1,182.00	£1,182.00		
Cost per hospital inpatient admission (epilepsy-related)	£6,545.75	£6,545.75		
Cost per A&E visit	£170.00	£170.00		

Abbreviations: A&E, Accident and Emergency; CI, confidence interval; ECM, established clinical management; GP, general practitioner; LGS, Lennox-Gastaut syndrome; NHS, National Health Service; ONS, Office of National Statistics; PSSRU, Personal Social Services Research Unit; SD, standard deviation; SE, standard error; UK, United Kingdom.

B.3.8.2 *Assumptions*

The key overarching assumptions relevant to the model are as follows:

- Our model assumes lifelong duration of effects for those patients who remain on treatment (i.e. no treatment habituation), and, similarly, immediate loss of treatment effect to those discontinuing treatment (as a conservative approach).
- Data from patients with LGS were used to proxy survival and healthcare resource use in patients with CDD (base case analysis), and data from patients with TSC were used to proxy seizure-related decrement in HRQoL in patients with CDD. Data from other conditions were tested in scenario analyses.
- The model used seizure distributions modelled using mean values and uncertainty estimates to parameterise a lognormal distribution given the skewness of data and the limitations this inferred on parametric modelling of trial data directly. This assumption and alternative methods were tested in scenario analyses.

When assumptions were made, all were validated by a clinical KOL consulted.

B.3.9 *Base-case results*

B.3.9.1 *Base-case incremental cost effectiveness analysis results*

Under the base case analysis, when applying the PAS price, the use of GNX as adjunctive therapy vs ECM alone is associated with an incremental cost effectiveness ratio (ICER) of £22,200 per quality-adjusted life-year (QALY) gained. Disaggregated cost and utility results are shown in Table 45 and Table 46, respectively. The net health benefits (NHB) associated with adjunctive GNX treatment vs ECM alone are presented in Table 47.

Table 45: Disaggregated per patient costs by treatment arm

	ECM alone	Ganaxolone + ECM	Incremental
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Rescue medication	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Other direct healthcare costs	[redacted]	[redacted]	[redacted]
Total costs (undiscounted)	[redacted]	[redacted]	[redacted]
Total costs (discounted)	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, established clinical management

Table 46: Disaggregated per patient utility by treatment arm

	ECM alone	Ganaxolone + ECM	Incremental
Patient QALYs	[redacted]	[redacted]	[redacted]
Caregiver QALYs gained	[redacted]	[redacted]	[redacted]
Total QALYs (undiscounted)	[redacted]	[redacted]	[redacted]
Total QALYs (discounted)	[redacted]	[redacted]	[redacted]
Total QALYs (discounted and weighted)	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, established clinical management; QALYs, quality-adjusted life years.

Table 47: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
ECM alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ganaxolone + ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, established clinical management; QALYs, quality-adjusted life years; NHB, net health benefit

B.3.9.2 *Clinical outcomes from the model*

A density plot of the lognormal distribution vs clinical data is shown in Figure 19. An assessment of various distributions vs the available data from the Marigold study identified the lognormal distribution as the best fitting curve and was therefore selected to model seizure frequency.

Figure 19: Histogram and theoretical densities – lognormal vs clinical data from Marigold

B.3.10 *Exploring uncertainty*

B.3.10.1 *Probabilistic sensitivity analysis*

B.3.10.1.1 Inputs

In order to assess the overall effect of parameter uncertainty on the model outcomes, a probabilistic sensitivity analysis (PSA) was conducted. Key model parameters were assigned to statistical distributions based on the parameter type and the expected uncertainty around the default parameter values. The distributions used are presented in Table 48.

Table 48: Distributions used for model parameters in PSA

Model parameter	Distributions used	Distributions used
Patient baseline characteristics	Starting age	Normal distribution
	Percent male	Beta distribution
Clinical parameters	Seizure frequency	Gamma distribution
	Proportional reduction in seizure frequency	Beta distribution
	Discontinuation rate per cycle	Beta
	Ganaxolone dose	Gamma
Utilities	General population utility regression parameters	Normal distribution
	Average number of caregivers per patient	Gamma distribution
	Mortality odds ration	Gamma distribution

Model parameter	Distributions used	Distributions used
	Patient utility values (Lo et al, 2022) (86)	Beta distribution
Costs and resource use	Resource use frequency (Chin et al, 2021) (11)	Gamma
	Reduction in epilepsy admissions with ganaxolone	Beta
	Resource use unit costs (PSSRU/NHS)	Gamma

Abbreviations: NHS, National Health Service; PSA, probabilistic sensitivity analysis; PSSRU, Personal Social Services Research Unit.

B.3.10.1.2 Results

Mean probabilistic cost-effectiveness estimates are provided in Table 49. The scatterplot of costs and benefits is shown in Figure 20, while the cost-effectiveness acceptability curves are shown in Figure 21.

Table 49. Base-case results (probabilistic analysis)

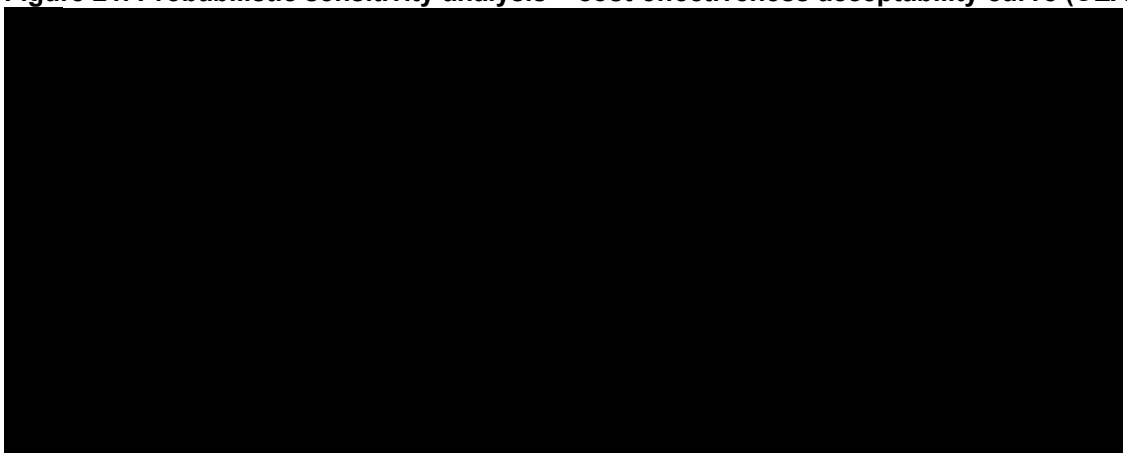
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
ECM alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GNX + ECM	[redacted]	[redacted]	[redacted]	[redacted]	**26,828**

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Figure 20. Probabilistic sensitivity analysis – cost-effectiveness plane

Abbreviations: ECM, established clinical management; GNX, ganaxolone; QALY, quality-adjusted life year

Figure 21. Probabilistic sensitivity analysis – cost-effectiveness acceptability curve (CEAC)



Abbreviations CEAC, cost-effectiveness acceptability curve; ECM, established clinical management; GNX, ganaxolone.

B.3.10.1.3 Discussion of variation between base case and PSA results

The CEAC indicates that GNX becomes the most cost-effective option at a willingness to pay threshold of approximately [redacted] and, similarly, the average probabilistic ICER of £26,828. We suggest this slight rightward shift is due to a 'floor effect' introduced by attempts to conservatively model the left-skewed seizure frequency data from the Marigold study. The Gamma distribution limits the minimum seizure frequency to zero (as is logical); however, this limits the potential of both seizure reductions (i.e., the maximum amount these reductions can impact seizure frequency) and the potential for seizure frequency to spread evenly either side of the median value. Therefore, this somewhat limits the potential for the costs, QALYs and ICER to reduce vs the base case, while the scope to increase is less limited. We feel, however, that this limitation does give the benefit of better estimates in the base case with regard to conservative modelling of seizure frequency from the source data.

B.3.10.2 *Deterministic sensitivity analysis*

B.3.10.2.1 Inputs

Deterministic sensitivity analyses (DSAs) were conducted to explore the impact of changing assumptions concerning the key model parameter values on the plausible ICER. Tornado diagrams, in which a numerical variable is varied over a specified range in order to measure its impact on cost-effectiveness, were generated. Parameters included in the tornado diagrams were varied by ± 20% of the base case to assess the relative impact of these parameters on the cost-effectiveness estimates.

The parameters that varied in the univariate sensitivity analysis were:

- Patient baseline characteristics
- Clinical parameters including seizure frequency and reductions
- Drug acquisition costs
- Adverse events
- Direct resource use and costs
- Utilities
- Mortality

B.3.10.2.2 Results

Results from one-way (deterministic) sensitivity analyses indicate that the model remains robust under variation of all parameters. The ten most impactful parameters are presented in Figure 22. The model was most sensitive to the impact of XXXXXXXXXXXXX; no scenario increased the ICER above £36,000 per QALY gained.

Figure 22: One-way (deterministic) sensitivity analysis results

Abbreviations: FS, focal seizures; GS, generalised seizures; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year.

B.3.10.2.3 Scenario analysis

Testing the model using alternative data sources yields similar ICERs to the one in the base case, indicating that the range of conditions chosen as proxy does not impact the model's results significantly. The tested key scenarios are shown in Table 50.

Table 50: Scenario analysis results

Scenario	Incremental costs	Incremental QALYs gained	ICER
Base case: resource use/costs from Chin et al, 2021(11) utilities from Lo et al, 2022 (86)	[redacted]	[redacted]	£22,200
Scenario A: resource use/costs from Lagae et al, 2019 (92), utilities from Lo et al, 2022 (86)	[redacted]	[redacted]	£26,314
Scenario B: resource use/costs from Chin et al, 2021(11)., utilities from Auvin et al, 2021 (90)	[redacted]	[redacted]	£26,957

Scenario C: resource use/costs from Lagae et al, 2019 (92), utilities from Auvin et al. 2021 (90)	[redacted]	[redacted]	£31,953
Scenario D: Alternative seizure frequency and reduction parameters based on **all seizures** vs primary seizures alone (Log mean seizure frequency [redacted], Log SD [redacted], seizure frequency reduction 17.38%)	[redacted]	[redacted]	£35,920
Scenario E: Marigold study maintenance period seizure frequency and reduction parameters based on **primary seizures alone** (Log mean seizure frequency [redacted], Log SD [redacted], seizure frequency reduction 29.31%)	[redacted]	[redacted]	£20,327
Scenario F: Marigold study maintenance period seizure frequency and reduction parameters based on **all seizures** (Log mean seizure frequency [redacted], Log SD [redacted], seizure frequency reduction [redacted] %)	[redacted]	[redacted]	£29,600
Scenario G: Hypothetical 50% increase in mortality with ECM alone to model impact of seizure-related mortality risk	[redacted]	[redacted]	£20,860

Abbreviations: ECM, established clinical management; ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SD, standard deviation.

B.3.11 *Subgroup analysis*

No subgroup analysis was undertaken.

B.3.12 *Benefits not captured in the QALY calculation*

Due to paucity of utility and cost data, indirect treatment benefits beyond the direct impact of seizure frequency on healthcare resource use and QoL were not captured. One such benefit is reduction in seizure severity: in the Marigold trial, a substantially higher proportion of patients in the GNX group experienced improvements in seizure intensity and duration compared with ECM alone (62% vs 36%), as reported by the caregivers on the CGI-CSID. In addition, quality of life impact on siblings was not captured. Also, factors such as long-term disease progression, disability and developmental impairment cannot be modelled, although these indirect impacts contribute to shape the patient journey in CDD. As such, our model is conservative in that it cannot capture the holistic QoL and cost impact of the condition. Furthermore, the model does not reflect the full societal costs and impact of CDD, especially considering potential productivity losses through missed work time.

B.3.13 *Validation*

B.3.13.1 *Validation of de novo cost-effectiveness analysis*

Currently, there are no available treatments for CDD; thus, no published economic evaluations of treatments for CDD were identified in the SLR.

B.3.14 *Interpretation and conclusions of economic evidence*

Ganaxolone is a cost-effective treatment option in CDD; using a validated conservative approach to parameterisation, the model yields robust ICERs across a range of different scenarios and under probabilistic and deterministic sensitivity analyses.

The relative lack of impact on the ICER when using different conditions as a proxy for CDD (e.g. the use of data from patients with LGS or DS to represent utility values in patients with CDD, or the use of QoL estimates for patients with LGS or TSC to represent utility values for patients with CDD) is encouraging, as this would be a key area of potential uncertainty in the model. Under all scenarios tested, the ICER remained within a relatively small range of variance, suggesting that the choice of proxy condition does not undermine the model, and aligns well with clinical expert opinion that these conditions are valid for use as a proxy in the absence of data specific to CDD.

The model is simple and conservative in nature, in that it does not seek to capture benefits outside the scope of direct seizure frequency-related costs and outcomes. Long-term disease progression, disability and developmental impairment are key factors in the patient journey in CDD; however, these elements (or the impact of GNX on these) cannot be modelled in the absence of robust data. Thus, the model does not include these elements so as to avoid introducing bias toward GNX. Indeed, by assuming GNX does not impact these areas of CDD, our approach is demonstrably conservative.

The model is associated with some limitations. Firstly, the lack of available data specific to CDD has required the use of data for other related conditions as a proxy in numerous places. This approach, while not ideal, has been implemented as pragmatically and conservatively as possible. Steps were also taken to test the proposed data and conditions used as proxies; firstly, via validation with a clinical KOL and, secondly, through scenario testing. The former confirmed the validity of the chosen proxy conditions and approach used, while the latter highlighted that the use of different conditions as proxy does not undermine the model's results.

A further limitation arises from the data available from the Marigold study itself. With regard to the number of seizure-free days, although these data were provided in Marigold, nothing meaningful could be inferred from modelling them alone versus taking them into account indirectly, via the change of average of major motor seizures. Moreover, our model does not assume differences between treatment arms in terms of the adverse events experienced (and requiring management), nor does it capture differences in concomitant medication use. However, the total number of TEAS were similar between the Marigold treatment groups with or without GNX. In addition, the proportion of patients using ASMs, non ASM, and

nonpharmacological therapies prior or during the study were similar for both the GNX and ECM alone cohorts. Throughout, we have sought to use a consistent approach where no difference could be inferred from trial data; for example, assuming similar adverse event rates and rescue medication use between arms, and similar resource use except that which would specifically be impacted by seizure frequency. Importantly, where assumptions were made, these were validated by clinical KOL opinion.

B.4. References

1. ZTALMY (ganaxolone). Summary of Product Characteristics. Version 10.2. rev.1. February 2021.
2. Weaving LS, Christodoulou J, Williamson SL, Friend KL, McKenzie OL, Archer H, et al. Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. Am J Hum Genet. 2004 Dec;75(6):1079-93.
3. Olson HE, Demarest ST, Pestana-Knight EM, Swanson LC, Iqbal S, Lal D, et al. Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review. Pediatr Neurol. 2019 Aug;97:18-25.
4. International Foundation for CDKL5 Research. Living with CDKL5 deficiency disorder. Available from Accessed: Nov 2021.
5. Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 2019;142(8):2303-18.
6. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:125-7.
7. Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, et al. Incidence of Dravet Syndrome in a US Population. Pediatrics. 2015 Nov;136(5):e1310-5.
8. Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. Epilepsia. 1997 Dec;38(12):1283-8.
9. Office for National Statistics. Births in England and Wales: 2021. [cited]; Available from: .
10. Orion Pharma. Systematic literature review (SLR) of clinical and burden of illness (BOI) evidence in patients with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder. August 2022. Data on file.
11. Chin RFM, Pickrell WO, Guelfucci F, Martin M, Holland R. Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: retrospective linkage cohort study. Seizure. 2021 Oct;91:159-66.
12. Schubert-Bast S, Kay L, Simon A, Wyatt G, Holland R, Rosenow F, et al. Epidemiology, healthcare resource use, and mortality in patients with probable Dravet syndrome: A population-based study on German health insurance data. Epilepsy Behav. 2022 Jan;126:108442.
13. Friedman D. Sudden unexpected death in epilepsy. Curr Opin Neurol. 2022 Jan 31.
14. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol. 2016 Sep;15(10):1075-88.
15. Trinka E, Bauer G, Oberaigner W, Ndayisaba JP, Seppi K, Granbichler CA. Cause-specific mortality among patients with epilepsy: results from a 30-year cohort study. Epilepsia. 2013 Mar;54(3):495-501.
16. Bahi-Buisson N, Kaminska A, Boddaert N, Rio M, Afenjar A, Gerard M, et al. The three stages of epilepsy in patients with CDKL5 mutations. Epilepsia. 2008 Jun;49(6):1027-37.
17. Frullanti E, Papa FT, Grillo E, Clarke A, Ben-Zeev B, Pineda M, et al. Analysis of the Phenotypes in the Rett Networked Database. Int J Genomics. 2019;2019:6956934.

18. Loulou Foundation IFfCR. The Voice of the Patient Report: CDKL5 Deficiency Disorder (CDD). June 17, 2020. Accessed November, 2021. .
19. Leonard H, Junaid M, Wong K, Demarest S, Downs J. Exploring quality of life in individuals with a severe developmental and epileptic encephalopathy, CDKL5 Deficiency Disorder. Epilepsy Res. 2021 Jan;169:106521.
20. Fehr S, Wilson M, Downs J, Williams S, Murgia A, Sartori S, et al. The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy. Eur J Hum Genet. 2013 Mar;21(3):266-73.
21. Mangatt M, Wong K, Anderson B, Epstein A, Hodgetts S, Leonard H, et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. Orphanet J Rare Dis. 2016 Apr 14;11:39.
22. Demarest ST, Olson HE, Moss A, Pestana-Knight E, Zhang X, Parikh S, et al. CDKL5 deficiency disorder: Relationship between genotype, epilepsy, cortical visual impairment, and development. Epilepsia. 2019 Aug;60(8):1733-42.
23. Fehr S, Wong K, Chin R, Williams S, de Klerk N, Forbes D, et al. Seizure variables and their relationship to genotype and functional abilities in the CDKL5 disorder. Neurology. 2016 Nov 22;87(21):2206-13.
24. Mori Y, Downs J, Wong K, Anderson B, Epstein A, Leonard H. Impacts of caring for a child with the CDKL5 disorder on parental wellbeing and family quality of life. Orphanet Journal of Rare Diseases. 2017 2017/01/19;12(1):16.
25. Cutri-French C, Armstrong D, Saby J, Gorman C, Lane J, Fu C, et al. Comparison of Core Features in Four Developmental Encephalopathies in the Rett Natural History Study. Ann Neurol. 2020 Aug;88(2):396-406.
26. Greene C DC, Love-Nichols J, Swanson L, Drew J, Smith L, editor. Clinical features of CDKL5 Deficiency Disorder compared to other infantile onset genetic epilepsies; 2020.
27. Amin S, Majumdar A, Mallick AA, Patel J, Scatchard R, Partridge CA, et al. Caregiver's perception of epilepsy treatment, quality of life and comorbidities in an international cohort of CDKL5 patients. Hippokratia. 2017 Jul-Sep;21(3):130-5.
28. Amin S, Monaghan M, Aledo-Serrano A, Bahi-Buisson N, Chin RF, Clarke AJ, et al. International Consensus Recommendations for the Assessment and Management of Individuals With CDKL5 Deficiency Disorder. Front Neurol. 2022;13:874695.
29. Jakimiec M, Paprocka J, Smigiel R. CDKL5 Deficiency Disorder-A Complex Epileptic Encephalopathy. Brain Sci. 2020 Feb 17;10(2).
30. Muller A, Helbig I, Jansen C, Bast T, Guerrini R, Jahn J, et al. Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with CDKL5-related epilepsy. Eur J Paediatr Neurol. 2016 Jan;20(1):147-51.
31. Rusconi L, Salvatoni L, Giudici L, Bertani I, Kilstrup-Nielsen C, Broccoli V, et al. CDKL5 expression is modulated during neuronal development and its subcellular distribution is tightly regulated by the C-terminal tail. J Biol Chem. 2008 Oct 31;283(44):30101-11.
32. Zhu YC, Xiong ZQ. Molecular and Synaptic Bases of CDKL5 Disorder. Dev Neurobiol. 2019 Jan;79(1):8-19.
33. Katayama S, Sueyoshi N, Inazu T, Kameshita I. Cyclin-Dependent Kinase-Like 5 (CDKL5): Possible Cellular Signalling Targets and Involvement in CDKL5 Deficiency Disorder. Neural Plast. 2020;2020:6970190.
34. Lux AL, Osborne JP. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. Epilepsia. 2004 Nov;45(11):1416-28.
35. Leonard H, Junaid M, Wong K, Aimetti AA, Pestana Knight E, Downs J. Influences on the trajectory and subsequent outcomes in CDKL5 deficiency disorder. Epilepsia. 2022 Feb;63(2):352-63.

36. Demarest S, Marsh R, Treat L, Fisher MP, Dempsey A, Junaid M, et al. The Lived Experience of Parents' Receiving the Diagnosis of CDKL5 Deficiency Disorder for Their Child. J Child Neurol. 2022 Feb 23:8830738221076285.
37. Orphanet. [cited]; Available from: .
39. ICD-10-CM-Code. [cited]; Available from: .
40. Kobayashi Y, Tohyama J, Kato M, Akasaka N, Magara S, Kawashima H, et al. High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders. Brain Dev. 2016 Mar;38(3):285-92.
41. Boston Children Hospital. CDKL5 Disorder Treatment. Available at: Accessed: February 2022.
42. Downs J, Jacoby P, Saldaris J, Leonard H, Benke T, Marsh E, et al. Negative impact of insomnia and daytime sleepiness on quality of life in individuals with the cyclin-dependent kinase-like 5 deficiency disorder. J Sleep Res. 2022 Oct;31(5):e13600.
43. Downs J JP, Reddihough D, Whitehouse A, Leonard H, Benke T, Demarest S, Saldaris J, Williams K. Can latent profiling inform how we understand quality of life in intellectual disability? Developmental Medicine & Child Neurology. 2022;64(S2):5-41.
44. Marinus Pharmaceuticals. Ganaxolone. Clinical study 1042-3001. Statistical analysis plan. 18 May 2021.
45. Telethonkids Organization. QI-disability fact sheet. Available at: .
47. Orion Pharma. The CDD patient journey in Europe. Data on file. 2022.
48. Pestana-Knight EM, Amin S, Bahi-Buisson N, Benke TA, Cross JH, Demarest ST, et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. The Lancet Neurology. 2022;21(5):417-27.
49. Bjurulf B, Reilly C, Sigurdsson GV, Thunström S, Kolbjer S, Hallböök T. Dravet syndrome in children-A population-based study. Epilepsy Res. 2022 May;182:106922.
50. Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. Epilepsy Res. 2016 Dec;128:43-7.
51. Cross JH, Galer BS, Gil-Nagel A, Devinsky O, Ceulemans B, Lagae L, et al. Impact of fenfluramine on the expected SUDEP mortality rates in patients with Dravet syndrome. Seizure. 2021 Dec;93:154-9.
52. Johannesen KM, Gardella E, Scheffer I, Howell K, Smith DM, Helbig I, et al. Early mortality in SCN8A-related epilepsies. Epilepsy Res. 2018 Jul;143:79-81.
53. Owen Pickrell W, Guelfucci F, Martin M, Holland R, Chin RFM. Prevalence and healthcare resource utilization of patients with Dravet syndrome: Retrospective linkage cohort study. Seizure. 2022 Jul;99:159-63.
54. Strzelczyk A, Schubert-Bast S. Expanding the Treatment Landscape for Lennox-Gastaut Syndrome: Current and Future Strategies. CNS Drugs. 2021 Jan;35(1):61-83.
55. Symonds JD, Elliott KS, Shetty J, Armstrong M, Brunklaus A, Cutcutache I, et al. Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. Brain. 2021;144(9):2879-91.
56. Office for National Statistics. Death registrations, populations and age standardised rates, England. [cited]; Available from: .
68. Care DoHaS. NHS Outcomes Framework 2016 to 2017. 2016.
69. European Medicines Agency (EMA). Epidyolex EPAR. Available at : Accessed on: 15th September, 2022.
70. Rogawski M, Masuoka L, Specchio N, Chez M, Tarquinio D. Abstracts of 20th Annual ASENT Meeting. Neurotherapeutics. 2018 Jul 9:819-35.
71. Devinsky O, Verducci C, Thiele EA, Laux LC, Patel AD, Filloux F, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Epilepsy Behav. 2018 Sep;86:131-7.

72. Marinus Pharmaceuticals. Clinical study report for 1042-CDD-3001. A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in children and young adults with cyclin-dependent kinase-like 5 (cdkl5) deficiency disorder (cdd) followed by long-term open-label treatment. 28 May 2021.
73. Olson H, Moosa AN, Rybak E, Aimetti A, Hulihan J, Pestana Knight H. Extended Duration Safety and Efficacy of Adjunctive Ganaxolone Treatment in Patients with CDKL5 Deficiency Disorder: 8-Month Minimum Open-Label Extension Follow-up. Abstract S13.005. . Americal Academy of Neurology. 2022;98.
74. Marinus Pharmaceuticals. Ganaxolone. Summary of clinical efficacy. Final EMA submission. November, 2021.
75. Marinus Pharmaceuticals. Ganaxolone. Clinical study report for 1042-0900. A multicenter, 26 Week open-label proof of concept trial of ganaxolone in children with PCDH19 female pediatric epilepsy and other rare genetic epilepsies followed by 52-week open label treatment. 2021.
76. Marinus Pharmaceuticals Inc. Post-hoc responder analysis. Marigold study. Data on file. 2022.
77. Demarest S, Aimetti A, Rybak E, Li D, Hulihan J, Downs J. AES abstract. Effect of ganaxolone on quality of life in children with the CDKL5 Deficiency Disorder. 2021.
78. Carter RB, Wood PL, Wieland S, Hawkinson JE, Belelli D, Lambert JJ, et al. Characterization of the anticonvulsant properties of ganaxolone (CCD 1042; 3alpha-hydroxy-3beta-methyl-5alpha-pregnan-20-one), a selective, high-affinity, steroid modulator of the gamma-aminobutyric acid(A) receptor. J Pharmacol Exp Ther. 1997 Mar;280(3):1284-95.
79. Nik AM, Pressly B, Singh V, Antrobus S, Hulsizer S, Rogawski MA, et al. Rapid Throughput Analysis of GABA(A) Receptor Subtype Modulators and Blockers Using DiSBAC(1)(3) Membrane Potential Red Dye. Molecular pharmacology. 2017;92(1):88-99.
80. Saporito MS, Gruner JA, DiCamillo A, Hinchliffe R, Barker-Haliski M, White HS. Intravenously Administered Ganaxolone Blocks Diazepam-Resistant Lithium-Pilocarpine-Induced Status Epilepticus in Rats: Comparison with Allopregnanolone. J Pharmacol Exp Ther. 2019 Mar;368(3):326-37.
81. Specchio N, Amin S, Aimetti A, Hulihan J. Extended duration safety and efficacy of ganaxolone for the treatment of cdkl5 deficiency disorder: Preliminary open label extension analysis (Marigold study). Poster. American Epilepsy Society, Virtual, December 4-8, 2020.
82. Rees CA, Pica N, Monuteaux MC, Bourgeois FT. Noncompletion and nonpublication of trials studying rare diseases: A cross-sectional analysis. PLoS Med. 2019 Nov;16(11):e1002966.
83. Perucca E. What clinical trial designs have been used to test antiepileptic drugs and do we need to change them? Epileptic Disord. 2012 Jun;14(2):124-31.
84. National Institute for Health and Care Excellence (NICE). Health technology evaluations: the manual. Process and methods. Published: 31 January 2022. Available at Accessed: October 2022.
85. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010 Aug;13(5):509-18.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

January 2023

File name	Version	Contains confidential information	Date
ID3988 ganaxolone – Updated company SIP 200123 no ACIC-clean	**V0.3.1**	**No**	**Revision Jan 20, 2023***

*version 0.3 accidentally contained some confidential information that we have removed from this version 0.3.1. No other changes.

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Ganaxolone Brand name: Ztalmy® Branding:

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The population under evaluation in the current NICE appraisal includes people 2 years of age or older with seizures caused by CDKL5 Deficiency Disorder (CDKL5[§]) who require an additional treatment on top of their prescribed therapies already in use to help control their seizures better. [§] Please note that in all other documents submitted as part of this NICE appraisal (ID3988) CDKL5 Deficiency Disorder is abbreviated to and referred to as CDD. In this document, however, we call it CDKL5, as that is the most commonly used term by patient communities when referring to the condition.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

EMA
Submission date: 28 October 2021
Marketing authorisation date: EMA approval pending

MHRA
Submission date: Pending
Marketing authorisation date: MHRA authorisation pending

Further information related to the marketing authorisation of ganaxolone can be found in the company submission, Document B, Section B.1.2.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

CDKL5 UK (https://curecdkl5.org.uk/)

CDKL5 UK is a charity organisation run by parents caring for a child with CDKL5 who fund research worldwide into the genetic causes and treating symptoms of CDKL5, support participation into clinical trials relevant to treating CDKL5 and raise public awareness of CDKL5.

Orion has collaborated with CDKL5 UK on two occasions to date:

- Orion Pharma (UK) Ltd provided a grant of £11,760 [on 27th June 2022] to be used to support the educational activities organised by CDKL5 for the families of people caring for a child with CDKL5. Orion Pharma (UK) Ltd was not involved in the delivery of the activities.
- Orion Corporation (Finland) retained CDKL5 UK as a consulting organisation to provide insights and opinion in relation to the development of resources and support to be offered by Orion to the community and people living with CDKL5 Deficiency Disorder (CDKL5) in Europe. CDKL5 UK was compensated €2,500 (£2,494) for this collaboration on 29th June 2022.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Cyclin-**d**ependent **k**inase-**l**ike **5** Deficiency Disorder (CDKL5) is a rare, genetic condition which belongs to a group of conditions called **d**evelopmental **e**pileptic **e**ncephalopathies (DEEs). CDKL5 is characterised by severe seizures which begin in the first weeks and months of life often not controlled by currently available treatments, severe developmental delays, and a wide range of coexisting symptoms (e.g., disorders affecting the stomach & intestine, breathing and sleep, as well as nutritional problems). People with CDD require life-long treatment and extensive care. CDKL5 is caused by loss-of-function mutations in the CDKL5 gene on the X-chromosome, resulting

in the body being unable to produce the CDKL5 protein, which is essential for normal brain development.

CDKL5 was only identified as recently as 2004 and due to its rarity, the exact number of people affected by CDKL5 is unknown. It is estimated that CDKL5 affects between 1.7–2.5 in 100,000 children.[1,2] With so few people being born each year with CDKL5, it is estimated that between 11 and 16 people are born with CDKL5 in England and Wales each year, with clinician opinion approximating 60 cases overall in England in 2022. With so few people born each year, it is considered a rare disease. [3] For context these numbers mean that CDKL5 is still a much rarer condition than other developmental epileptics encephalopathies, such as Dravet syndrome or Lennox Gastaut syndrome. Among every five children with CDKL5, there are typically four girls and only one boy affected because CDKL5 is caused by a mutation of a gene on the X-chromosome.

CDKL5 has a profound impact upon the quality of life of affected people. Most children suffer from seizures occurring within the first 3 months of life, and up to 9 out of 10 will experience daily seizures. Sadly, as many as 84–95% of patients suffer from seizures that do not adequately respond to treatment, which further affects their quality of life.[4-5] Seizures have been reported by a majority of CDKL5 patients' carers as in the top three most burdensome symptoms.[6]

Severe development delay is observed in CDKL5 with significant impact on patients' abilities to walk, talk and feed themselves, all of which require constant specialised care. Most patients also suffer from coexisting symptoms affecting the stomach & intestine, breathing, and sleep, as well as nutritional problems, further impacting their quality of life and the dependency on caregivers.

The impact on the caregiver(s) of a person affected by CDKL5 is considerable. It has been reported that caregivers experience substantially reduced emotional wellbeing, linked to the condition and associated financial worries.[7] For example, when people with CDKL5 experience a greater seizure frequency, the impact on caregivers worsens. Similarly, poorer physical and mental health tends to be reported by the caregiver(s) of those people, who are totally dependent on being fed. In addition, seizures and other debilitating symptoms of CDKL5 (such as respiratory problems) increase the likelihood of hospital admission for patients and increase costs to the healthcare systems.[7, 8]

In summary: CDKL5 is characterised by early-onset difficult to treat seizures. Seizures present in varying types over time, with a very high proportion of patients having daily seizures, or weekly seizure clusters. The response to current anti-seizure medications may be limited, with the initial benefit usually reducing over time (6-12 months), as the seizures become unresponsive to treatment Alongside the seizures, CDKL5 also involves severe developmental delays and multiple coexisting symptoms. Overall, people with CDKL5 therefore require life-long treatment and care. Along with the level of developmental delays, high seizure frequency has been associated with poorer quality of life and increased health care service needs. Thus, CDKL5 imposes a substantial clinical and social burden on the patients and their caregivers, and a considerable financial burden on healthcare systems.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
CDKL5 was identified as a distinct condition only relatively recently and it shares many similar features and symptoms with other conditions, and it is very rare. Due to this background, CDKL5

has been historically difficult to diagnose, although the more recent implementation of genetic testing has helped to achieve a timelier diagnosis.

Diagnosis via genetic testing often follows when it is suspected that an infant or child has CDKL5 based on the presence of clinical symptoms associated with the disease, most commonly early onset seizures.[9] In NHS England, genomic testing is generally offered to patients with rare early onset or syndromic epilepsy[10].

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The management for people with CDKL5 is focused on controlling symptoms (e.g., seizures), while also providing supportive care for the other impairments people experience. At present, there are no treatments addressing the underlying genetic cause of CDKL5.

In June 2022 an international panel of expert clinicians and researchers issued guidance on the assessment and management of patients with CDKL5.[11] There was no consensus around which treatments should be used as first-, second-, third- or fourth treatments options. Nevertheless, the standard treatments of vigabatrin, steroids and the combination of these featured most strongly as first treatment option among these experts, each supported as a first treatment option by around one third of the experts.

Indeed, various anti-seizure medications, are in practice the main treatment for CDKL5 associated seizures.[12] However, none of these have been developed or approved by regulators specifically for CDKL5, and, in most cases, their efficacy is limited by response rates decreasing over time.[12, 13]

Other than anti-seizure medications, non-drug treatments are sometimes used as additional options in people with CDKL5, including a special, low-carbohydrate diet known as ketogenic diet, and vagus nerve stimulation or other surgical interventions. This is chosen by some, if seizures are not well-controlled by medication, or there are issues with the side effects.[12] Among a choice of steroids, vigabatrin, combination of these or the ketogenic diet, nearly a quarter of experts in the international panel stated they would offer the ketogenic diet as a second-line therapeutic option for patients with CDKL5.[11]

Whilst not specific to CDKL5, clinical guidelines for the management of epilepsies in children, young people and adults are available from NICE in England and Wales, where the choice of treatment is based on seizure type.

Currently, there is an unmet need for an effective, well tolerated treatment specific for CDKL5-related seizures that can improve and maintain clinical outcomes and thereby reduce the disease burden.

In the setting of CDKL5, ganaxolone (in combination with currently available treatment options) has demonstrated to be an effective and well tolerated treatment for the associated epileptic seizures in the Marigold trial. The Marigold was a multi-country, Phase III double-blind randomised, placebo-controlled trial [14]. Marketing authorization application for ganaxolone is based mainly on this trial in CDKL5, and is currently under review by European regulators. Therefore, in England, it is anticipated that ganaxolone will be offered as an add-on to other anti-seizure medications to improve seizure control in patients with CDKL5 that are 2 years of age and older.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Over time the effects of anti-seizure medicines have been reported to decline. For example, a study of caregivers for people with CDKL5 published in 2017 indicated that 95.2% had tried at least two anti-seizure medications, and still reported experiencing poor seizure control. Furthermore, 62.0% had received at least five anti-seizure medications.[15]

In the study by Leonard et al, 2021, parents of 129 children with CDKL5 (aged >3 years) in Europe, North America, Australia, and New Zealand reported the quality of life of their children using a recognised questionnaire (Quality-of-Life Inventory [QI]-Disability), which has been specifically developed for children and adolescents with intellectual disability.[16] Overall, impairments and limitations caused by CDKL5, including lack of ability to sit, use hands, and communicate had the greatest adverse impact on children's quality of life. Also, people with a higher seizure frequency tended to have a poorer quality of life.

In line with the study by Leonard et al, a survey among 52 caregivers of children with CDKL5 in the US, revealed that seizures are one of the most burdensome symptoms affecting patients, second only to development delay. Caregivers in the survey also reported that the profound multisystem complications of CDKL5 had a devastating impact on their family life.[6]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Ganaxolone works in the brain to reduce the number of seizures.

Ganaxolone works by regulating brain activity through interactions with a type of receptor (the site on the nerve cells on which drug molecules can bind to) called gamma-aminobutyric acid type-A ($GABA_A$) receptors. These $GABA_A$ receptors are responsible for controlling excessive activity in the brain which leads to abnormal electrical pulses, resulting in seizures.

Some of the other anti-seizure medications also act via the $GABA_A$ receptors. However, there are different types and locations in the brain, where these receptors are found. Ganaxolone binds to a unique type of $GABA_A$ receptors which are located not only within, but also on the surface the nerve cells, which the current medications do not affect. As a result of acting also on these additional receptor sites, ganaxolone has the potential to improve the control of seizures that are not well-controlled by the current treatments, and potentially maintain the effect better.

Ganaxolone has been shown in the phase 3 Marigold study to have a significant and clinically meaningful impact on CDKL5 by reducing the monthly major motor seizure frequency (Marigold study – see below), with a manageable side effect burden.

The effect of ganaxolone in reducing seizure frequency appears to be maintained in patients who receive long-term treatment, as suggested by interim results from the extension phase of the study, where all patients are treated with ganaxolone.

As noted above, there are currently no approved CDKL5-specific treatments to control the epileptic seizures patients experience. Ganaxolone has the potential to provide substantial health-related benefits to patients through significant reduction in seizure frequency, improvements in seizure intensity and duration, and subsequently, quality of life of both patients and the families affected. Published evidence suggests that early optimal seizure management may positively influence the future outcomes for a child with CDKL5.[17]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

The intended use for ganaxolone is for it to be taken as an add-on treatment to other anti-seizure medications with a view to controlling CDKL5-related seizures better. Due to the mechanism of action and the difference in the $GABA_A$ binding site (*see section 3a*), ganaxolone is believed to provide additional benefits beyond existing anti-seizure medications.

The treating physician should check the dosing and whether it is advisable to use ganaxolone with the medications already in use. With certain other medications the efficacy of ganaxolone may be reduced to an extent due to interactions, or there could be excessive somnolence (sleepiness) or sedation. Also, alcohol may increase the risk of somnolence and sedation.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Ganaxolone is provided as an oral suspension (an off-white, cherry flavoured liquid containing undissolved particles of ganaxolone) in a 110 mL bottle at a strength of 50 mg/mL. Packs of 1 and 5 bottles are planned, which will contain a suitable oral syringe or a set of syringes, and an adaptor that are used to administer the medication. Ganaxolone should be administered three times daily with food. The bottle is shaken for at least 1 minute and rested for a further 1 minute before measurement and administration of the dose. An oral syringe is used to measure the recommended dose. The recommended dose is based on the weight of the patient and is built up over four weeks from the start of treatment until the required dose is reached (titration). Dosages should not be increased more than every 7 days, based on how well the patient is able to tolerate the treatment. The titration schedule for patients is split out into two groups, those weighing 28kg or less, and those weighing more than 28kg. For example, for a child of 15 kgs the dose would be 6.3 ml three times daily. Beyond 28 kg weight all patients target at 12 ml three times daily, which is no more frequent than many of the current treatments.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
Name: Marigold **Population:** Patients aged 2–21 years with a pathogenic or probably pathogenic CDKL5 variant and at least 16 major motor seizures (defined as bilateral tonic, generalised tonic-clonic, bilateral clonic, atonic, or focal to bilateral tonic-clonic) per 28 days in each 4-week period of an 8-week historical period **Study size:** Number of participants = 101 **Comparators:** Placebo (non-active substance) + other anti-seizure medications. Patients were randomised to receive either ganaxolone or a placebo (non-active substance), in addition to their standard anti-seizure medications. The drug was administered as either a drinkable liquid or as a capsule, and it was taken with food. Patients had to maintain stable background medications while in the clinical trial. **Started:** 30 June 2018 **Completed:** 28 May 2021 **Study publication:** https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(22)00077-1/fulltext **National Clinical Trials link:** https://clinicaltrials.gov/ct2/show/NCT03572933 **Name:** Marigold open-label extension **Population:** All eligible patients from double-blind phase

Study size: Number of participants = 88

Comparators: All patients enrolled into the open-label extension receive ganaxolone. This is a single-arm study with no comparator treatment.

Started: May 2021

Completed: Study is ongoing and planned to complete when marketing authorisation received in Europe

Study publication: https://cms.aesnet.org/abstractslisting/extended-duration-safety-and-efficacy-of-adjunctive-ganaxolone-treatment-in-patients-with-cdkl5-deficiency-disorder--8-month-minimum-open-label-extension-follow-up

National Clinical Trials link: https://clinicaltrials.gov/ct2/show/NCT03572933

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Marigold

The Marigold study demonstrated that ganaxolone, as an add-on treatment to other anti-seizure medications, provides effective seizure control in patients with CDKL5 compared with placebo

In the Marigold study, the primary efficacy endpoint (i.e., percentage change from the start of the study in 28-day major motor seizure frequency during the 17-week study period) was met. Patients treated with ganaxolone experienced a statistically significant, 4.5-fold reduction from the start of the study in median 28-day major motor seizure frequency compared with patients receiving placebo (30.7% vs 6.9%). Reduction in seizures was the primary therapeutic aim of the study, and these results show that ganaxolone is more effective in reducing seizures compared with placebo.

In Marigold, patients treated with ganaxolone experienced overall improvements compared with those receiving placebo, as assessed by caregivers and clinicians

Caregivers rated 62.5% of ganaxolone treated patients as improved, compared with 43.8% in the placebo group. Clinicians rated 54.2% of ganaxolone treated patients as improved, compared with 41.7% in the placebo group.

Caregiver reporting in the Marigold study suggests improvements with ganaxolone in seizure intensity and duration

A substantially higher proportion of patients in the ganaxolone group experienced improvements in seizure intensity and duration compared with placebo (62% vs 36%), as reported by the caregivers on the CGI-CSID (a caregivers' questionnaire to assess changes in seizure intensity/duration).

Patients on ganaxolone tended to also have more seizure-free days compared to placebo

There was increase of 4.91% in the percentage of major motor seizure-free days with ganaxolone, compared with 0.17% on placebo.

The Marigold study also showed that treatment with ganaxolone has the potential for quality of life improvements in both patients and caregivers

Trends of quality-of-life improvement were observed in patients treated with ganaxolone compared with placebo. Ganaxolone treated patients had a greater improvement from the start of the study to week 17 in 4 of the 6 domains in the quality of life-inventory (QI) disability scale, with an overall mean change from the start of the study of 4.28 in the ganaxolone group and 1.84 in the placebo group. Adjunctive treatment with ganaxolone also resulted in numerically higher proportions of patients in attention and in several aspects of behaviour, compared with placebo. Moreover, treatment with ganaxolone has a potential for quality-of-life improvements in both patients as well as caregivers. For example, parents of patients in the ganaxolone group had a greater improvement on the 'Parenting Stress Index' score at the end of the 17-week double-blind period compared with parents of patients in the placebo group.

Marigold open-label extension

During the open-label extension phase of the Marigold study (interim results cut-off date 24th February 2021), ganaxolone showed continued effectiveness in reducing seizure frequency in patients who received long-term treatment. Patients treated with ganaxolone for ≥12 months experienced a sustained reduction in 28-day major motor seizure frequency, suggesting a maintained effect.

In patients who switched from placebo to ganaxolone treatment, reductions in major motor seizure frequency observed over the first 4 weeks continued up to Months 19 to 20. In patients who continued treatment with ganaxolone, reductions in major motor seizure frequency were maintained up to Months 19 to 20. Additionally, patients who switched from placebo to ganaxolone reached similar response rates (20%) within one month as the original ganaxolone group (24.5%). At week 17 of the open-label extension, patients were reported as improved by 68.0% and 73.6% of clinicians and caregivers, respectively, following the same trend as the double-blind phase of the trial (see Section B.2.6.2 of Document B in the company submission).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used, does it sufficiently capture quality of life for this condition? Are there other disease specific quality-of-life measures that should also be considered as supplementary information?

Please outline in plain language any quality-of-life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The Marigold study highlighted an improvement in patient and carer quality of life when treated with ganaxolone plus anti-seizure medications compared with placebo plus anti-seizure medications. In the study, patients' quality of life was assessed using the QI-Disability scale, a parent/caregiver reported quality of life rating scale specifically developed for children and adolescents with intellectual disability. Parents/caregivers' quality of life was assessed using the Parent Stress Index scale which is designed to evaluate the magnitude of stress in the parent-child system (*please see section 3e above for further details*).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Consistent with other treatments that act on the $GABA_A$ receptors, the most frequent adverse event experienced by patients treated with ganaxolone are sleepiness (somnolence), along with dizziness and fatigue (tiredness). However, ganaxolone has been shown to be generally well-tolerated in clinical studies, to date.

During the double-blind phase the Marigold study, ganaxolone was generally well tolerated in patients with CDKL5 with most side effects following treatment categorised as mild or moderate in severity. Reports of side effects occurring following treatment were similar between patients receiving (on top of other anti-seizure medications) either ganaxolone or placebo (86.0% vs 88.0%). The most commonly reported side effects in ganaxolone-treated patients related to the central nervous system and were of mild to moderate intensity. Mild or moderate sleepiness (somnolence) was the most common side effect reported by ganaxolone treated patients (36.0% vs 16% for placebo). Of note, fewer patients on ganaxolone experienced vomiting (10% vs 20%) when compared to those taking a placebo (non-active substance). Overall, medicine discontinuations due to side effects did not increase with ganaxolone, compared to placebo. Only 4% of patients who received ganaxolone discontinued from the study because of side effects occurring following the start of treatment, while in those who received placebo the rate was 7.8%.

During the open-label extension phase of the Marigold trial, ganaxolone was generally well tolerated, with no new safety signals identified. Overall, side effects occurring following the start of treatment were similar to those in the double-blind phase with seizure, somnolence, pyrexia, and vomiting being the most frequently observed. Based on the long-term open-label extension data, somnolence seemed to settle over time to a rate similar to that reported on placebo in the double-blind study period (14–22% vs 16%).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Currently, there are no approved treatments specifically for seizures caused by CDKL5, and available anti-seizure medications have a suboptimal effectiveness in CDKL5, with response rates decreasing over time.[12,13, 18] Thus, efficacious treatments developed for CDKL5-related seizures are urgently needed to improve clinical outcomes in both short and long term and reduce the disease burden on patients and their families.

The clinical benefits of ganaxolone, demonstrated in the Marigold study (and its open-label extension), are of high relevance to patients in real-world clinical practice, and can help address this unmet need in CDKL5.

In real-world practice, the primary outcome Marigold (i.e., change from the start of the study in 28-day major motor seizure frequency) and other key outcomes assessed in this trial can indeed translate into important clinical benefits to a considerable number of patients including:

- Significant reduction in seizure frequency
- Improvements in seizure intensity and duration
- Potential increase in seizure-free days
- Sustained efficacy and tolerability in the long-term (open-label interim results)

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Mild or moderate sleepiness (somnolence) was the most common side effect reported by ganaxolone treated patients during the Marigold study. This is something that caregivers may need to take into account in their daily activities.

The administration frequency is 3 times daily, which means a dose will be needed in the middle of the day as well. Assistance with administration will be required at home and in educational facilities, as with most of their other medications too. There are no data currently to suggest significant issues with compliance.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- What is the structure of the model? Explain how the model reflects the experience of having the condition over time.

For CDKL5, little data is published on the impact major motor seizures have on patients' quality of life and healthcare resources due to the rarity and the fairly recent identification of the condition. However, based on data published related to other severe epileptic syndromes similar to CDKL5, major motor seizures are thought to be the most impactful seizures in terms of NHS resource use and quality of life. It is for this reason that major motor seizure frequency data from the Marigold study has been used to reflect the experience of CDKL5 patients in the health economic model.

The health economic model for ganaxolone uses medication information (doses, duration of use) and the seizure frequency data from the Marigold study to inform the effectiveness estimates over the life span of CDKL5 patients. The model estimates the impact on NHS resources when add-on ganaxolone is introduced compared to current therapies alone ("established clinical management") and considers the impact of the patients' and caregivers' quality of life using a measure called quality-adjusted life years (QALYs).

- Does the treatment extend life? If so, please explain how (for example. by delaying disease progression, reducing disease severity or complications, reducing disease relapses or life-limiting side effects).

Generally, people with epilepsy and severe persistent seizures have a somewhat increased mortality rate compared to people with no seizures[19, 20]. Ganaxolone is not expected to impact upon patients' survival. Thus, no difference in life expectancy was assumed between patients treated with current care vs those using ganaxolone. As ganaxolone reduces seizures, it could potentially impact positively the developmental delay of the children affected; however, in the model, this was not assumed.

- Describe briefly which trial outcomes feed into the economic model. If trial data used for a certain length of time followed by extrapolation, please note how long the trial data was used for and briefly how the data has been extrapolated.

The clinical effectiveness of ganaxolone, with regards to reduction in major motor seizures, is modelled using data reported from the Marigold study.

Clinical inputs based on the Marigold study and their respective chapters in the Company Submission are summarised in the below table:

Primary seizures clinical inputs based on the Marigold study (Chapter in Company Submission)
Average major motor seizure frequency per cycle (B.3.3.1.)
Reduction in seizure frequency with ganaxolone, as compared to before start of the study treatment (Placebo-adjusted) (B.3.3.1.)
Reduction in epilepsy-related admissions with ganaxolone (B.3.5.2.)
Discontinuation rate/cycle from the long-term extension of the Marigold study (B.3.3.1.)

Modelling how much a treatment improves quality of life

- How is the treatment modelled to change a person's quality of life compared with the treatments already in use? This should include after stopping treatment if relevant. For example, say if the treatment improves quality of life because of improving symptoms or decreases quality of life because of side effects.

In the economic model major motor seizures are the sole driver of treatment impact on patients' and caregivers' quality of life (QoL). Due to lack of QoL data in CDKL5, that would be in an applicable format for the model, data on how seizures impact on quality of life was taken from a similar epileptic syndrome (tuberous sclerosis complex, TSC) as a substitute. The impact of seizures on the QoL ("disutility") of both the patients as well as caregivers was described in the study[21] and was applied in the model on CDKL5, based on the seizure frequency and type.

The estimated disutility from the above was then subtracted from the numerically described quality of life values of the general population, to provide an estimate of "how bad" it feels, the more seizures are experienced daily. This approach was also supported by a clinical expert.

The difference in impact between treatment with ganaxolone and currently available anti-seizures medications is estimated using the difference in effectiveness (seizure reduction) shown in the Marigold study.

- Which quality of life measure(s) did you use to estimate a person's quality of life over time and on treatments? Are there any aspects of the condition or its treatments affecting quality of life which may not have been fully captured by the methods used to estimate quality of life?

The above-mentioned study assessed the impact that type and frequency of seizure had on various aspects of life quality in people with CDKL5 and their caregivers' lives including psychological and social wellbeing, health and daily life. Although the study focussed on people with TSC, the impact which seizures have on people with CDKL5's lives is estimated to be similar. The model may not however fully capture all the impacts to quality of life associated with CDKL5.

Modelling how the costs of treatment differ with the new treatment

- Does the medicine lead to any cost implications (positive or negative) for the health service (e.g., drug costs, number of days in hospital)?

Based on the evidence available and the company's economic analysis, ganaxolone would be considered as offering a good use of NHS resources as a treatment for patients with CDKL5. The results in the cost-effectiveness analysis suggest that outside of the costs for medications, treatment with ganaxolone can lead to some reduction in other direct healthcare costs to the NHS including A&E visits and epilepsy-related inpatient hospitalisations.

Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?

Assistance with administration will be required in educational facilities. However, these would be indirect costs which do not directly impact the NHS and therefore are not accounted for in the health economic model. Furthermore, most patients would likely need assistance with the other medications as well.

Uncertainty

- Are there any key assumptions you have made in your model about the medicine's benefits or costs because of lack of data?

The most uncertain data comes from the TSC study as studies in CDKL5 have not been published.[21] This informs the estimated impact that the type and frequency of seizures can have on people with tuberous sclerosis complex, which shares similarities with CDKL5, but may not fully reflect the real-world impact seizures have on people with CDKL5. However, the approach of using data from TSC in place of CDKL5 was supported by expert clinical opinion.

The results predicted by the model are based on clinical data from the Marigold study, which has a relatively short treatment duration of up to 2 years, considering that CDKL5 is a lifelong condition. The results of the model have been tested to assess the reliability of the model's data and the assumptions made.

- Did you test using alternative assumptions or data in your model? Which had the largest effect on your cost effectiveness estimates?

Key model input values were varied by ±20% versus the values at the start of the model ("base case"). Model results remain relatively at the same range under variation of all input assumptions.
Are there any data you have presented to support your modelled outcomes being plausible?

Please see section B.3.10 of Document B in the Company Submission.

- What is the modelled benefit in overall survival, quality adjusted life years and the incremental cost effectiveness ratio?

Based on the model, more quality-adjusted life years (QALYs) will be gained when ganaxolone is added to the current anti-seizure therapies ("established clinical management"). At the proposed price and given the typical 'willingness-to-pay threshold' of NICE, the treatment with ganaxolone appears to represent a cost-effective use of NHS resources.

- Have you made a case for a severity modifier being relevant for this condition? If so, please summarise the data presented

A severity modifier is a multiplication factor applied in some cases on the basic QALY gain which the cost effectiveness model would otherwise show for a new treatment. NICE allows this method in certain situations, to improve the cost effectiveness and provide some leeway for therapies meant for very serious, severe, usually life-long conditions, with a pronounced negative impact on quality of life.

In the economic analysis of ganaxolone the use of a severity modifier is based on the estimated improvement in quality of life relating to the major motor seizure reduction achieved by treatment with ganaxolone, as demonstrated in the Marigold study, and taking into account the estimated life expectancy of people with CDKL5, which tends to be shorter than those in the general population.

- Are there any benefits or disadvantages of the treatment not captured in the modelling?

The model cannot quite capture the holistic quality of life and cost impact of the condition. Due to lack of adequate evidence, potential indirect treatment benefits beyond the direct impact of seizure frequency on healthcare resource use and quality of life, such as long-term disease progression, disability and developmental impairment are not captured in the model, although these indirect impacts contribute to shape the patient journey in CDKL5. QoL impact on siblings is not taken to consideration either, nor does the model reflect the full societal costs and impact of CDKL5, considering potential productivity losses through missed work.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Ganaxolone is a step forward in the treatment of CDKL5 in as much as when licensed, it will be the only treatment intended for the treatment of people with CDKL5. It has been shown to significantly reduce seizure frequency as an add-on medication in patients for whom other anti-seizure medications do not adequately control the seizures.

Unlike other anti-seizure medications, ganaxolone binds with $GABA_A$ receptors at two different receptor sites. This binding mechanism is unique, decreasing excessive activity in the brain which

leads to abnormal electrical pulses, resulting in seizures. This helps to explain why ganaxolone may prove an important treatment option for CDKL5 patients whose seizures have not been adequately controlled by previous or existing treatments.

The ability of ganaxolone to reduce major motor seizure frequency has been demonstrated in a relatively large, randomised-controlled trial in a study population of interest (CDKL5 patients), which is not always possible in rare conditions. The study met its primary aims in demonstrating an effective and well-tolerated treatment option.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
N/A

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:
Response:

1. Olson HE, Demarest ST, Pestana-Knight EM, Swanson LC, Iqbal S, Lal D, et al. Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review. Pediatr Neurol. 2019 Aug;97:18-2
2. Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 2019;142(8):2303-18
3. House of Commons. 'NICE appraisals of rare diseases'. 12 March 2019. Accessed online at: https://researchbriefings.files.parliament.uk/documents/CDP-2019-0022/CDP-2019-0022.pdf. Accessed on 21 October 2022
4. Frullanti E, Papa FT, Grillo E, Clarke A, Ben-Zeev B, Pineda M, et al. Analysis of the Phenotypes in the Rett Networked Database. Int J Genomics. 2019;2019:6956934
5. Greene C DC, Love-Nichols J, Swanson L, Drew J, Smith L, editor. Clinical features of CDKL5 Deficiency Disorder compared to other infantile onset genetic epilepsies; 2020
6. Loulou Foundation IFfCR. The Voice of the Patient Report: CDKL5 Deficiency Disorder (CDD). June 17, 2020. Accessed November, 2021. https://www.cdkl5.com/wp-content/uploads/2020/06/CDD-VoP-REPORT.pdf
7. Mori Y, Downs J, Wong K, Anderson B, Epstein A, Leonard H. Impacts of caring for a child with the CDKL5 disorder on parental wellbeing and family quality of life. Orphanet Journal of Rare Diseases. 2017 2017/01/19;12(1):16
8. Mangatt M, Wong K, Anderson B, Epstein A, Hodgetts S, Leonard H, et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. Orphanet J Rare Dis. 2016 Apr 14;11:39
9. Lindy AS, Stosser MB, Butler E, et al. Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. Epilepsia. 2018;59(5):1062-1071
10. NHS England. 'National genomic test directory'. Updated 11 August 2022. Accessed online at: https://www.england.nhs.uk/publication/national-genomic-test-directories/
11. Amin S, Monaghan M, Aledo-Serrano A, Bahi-Buisson N, Chin RF, Clarke AJ, et al. International Consensus Recommendations for the Assessment and Management of Individuals With CDKL5 Deficiency Disorder. Front Neurol. 2022;13:874695
12. Jakimiec M, Paprocka J, Smigiel R. CDKL5 Deficiency Disorder-A Complex Epileptic Encephalopathy. Brain Sci. 2020 Feb 17;10(2)
13. Muller A, Helbig I, Jansen C, Bast T, Guerrini R, Jahn J, et al. Retrospective evaluation of low long-term efficacy of antiepileptic drugs and ketogenic diet in 39 patients with CDKL5-related epilepsy. Eur J Paediatr Neurol. 2016 Jan;20(1):147-51
14. Pestana-Knight EM, Amin S, Bahi-Buisson N, Benke TA, Cross JH, Demarest ST, et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. The Lancet Neurology. 2022;21(5):417-27

15. Amin S, Majumdar A, Mallick AA, Patel J, Scatchard R, Partridge CA, et al. Caregiver's perception of epilepsy treatment, quality of life and comorbidities in an international cohort of CDKL5 patients. Hippokratia. 2017 Jul-Sep;21(3):130-5
16. Leonard H, Junaid M, Wong K, Demarest S, Downs J. Exploring quality of life in individuals with a severe developmental and epileptic encephalopathy, CDKL5 Deficiency Disorder. Epilepsy Res. 2021 Jan;169:106521
17. Leonard H, Junaid M, Wong K, Aimetti AA, Pestana Knight E, Downs J. Influences on the trajectory and subsequent outcomes in CDKL5 deficiency disorder. Epilepsia. 2022 Feb;63(2):352-63
18. Fehr S, Wong K, Chin R, Williams S, de Klerk N, Forbes D, et al. Seizure variables and their relationship to genotype and functional abilities in the CDKL5 disorder. Neurology. 2016 Nov 22;87(21):2206-13
19. Friedman D. Sudden unexpected death in epilepsy. Curr Opin Neurol. 2022 Jan 31.
20. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol. 2016 Sep;15(10):1075-88
21. Lo SH, Marshall J, Skrobanski H, Lloyd A. Patient and Caregiver Health State Utilities in Tuberous Sclerosis Complex. Pharmacoecon Open. 2022 Jan;6(1):105-21

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

July 2023 (confidentiality marks updated only)

File name	Version	Contains confidential information	Date
ID3988 Ganaxolone for CDD_Update of Response to EAG clarification questions_21-12-2022_Fully redacted -conf marks updated 24072023	**Final updated version**	**Yes**	**24 July 2023**

Only Confidentiality marks checked 24/7/2023 – no further changes.
All confidentiality marks AIC/CIC updated throughout the document.
UPDATED CONFIDENTIALITY CHECKLIST PAGE NUMBERS REFER TO THIS VERSION.
Please note; all separately uploaded Appendices + model are CIC – indefinitely.

Section A: Clarification on effectiveness data

Literature searching

A1. Please could the company provide the search terms used to search ClinicalTrials.gov?

The primary population of interest for the clinical section of our systematic literature review was CDKL5 deficient patients. However, we extended our searches of the trial registry to the broader populations. The search terms used along with the hits returned are shown in Table 1.

Table 1. Search terms used to search ClinicalTrials.gov for the different populations of interest and related hits

#	Population of interest	Search terms used	Hits
1	CDD	CDKL5	60
2	Rett syndrome	Rett	63
3	Dravet syndrome	Dravet	60
4	Lennox-Gastaut Syndrome	Lennox-Gastaut	47
5	Epileptic Encephalopathy Syndrome	Epileptic Encephalopathy	28

Abbreviations: CDD, CDKL5 deficiency disorder; CDKL5, cyclin-dependent kinase-like 5

CDD – CDKL5
Rett – Rett
Dravet – Dravet
LGS - Lennox-Gastaut
EE - Epileptic Encephalopathy

A2. Please could the company explain the decision to search for myoclonic epilepsy using controlled vocabulary (e.g. MeSH in MEDLINE) but not as a free-text term (e.g. in title or abstract fields)?

We would like to thank you for bringing this to our attention. Our searches do contain both controlled vocabulary and free text terms for Dravet syndrome. As you point out, we do not have free text term for myoclonic epilepsy of infancy. However, Dravet syndrome was previously known as myoclonic epilepsy of infancy. Thus, we feel that the inclusion of the controlled vocabulary for Dravet and the free text for Dravet, as well as some of the more general free text terms, would make it very unlikely to miss any studies of interest with the current search strategy. Nonetheless, we have since

tested our searches by adding this term and reviewing the difference, and, although we do find a slightly higher number of studies with the inclusion of free text terms for myoclonic epilepsy, none of these were deemed to be relevant for inclusion in the current review after screening.

Clinical effectiveness data

A3. In Table 10 it is stated that 3 people discontinued ganaxolone before the end of the study, but reasons for discontinuation in the table and in section B.2.3.2 are only provided for 2 people. For clarity, can the company please confirm why the 3rd person discontinued?

The "3rd patient" discontinued the study treatment before the final week-17 visit (end of double blind [DB] period) due to a treatment-emergent adverse event (somnolence), but regardless of this, the patient *stayed in the trial* until the end of the DB period. This is consistent with the Marigold clinical study report (see sections 10.1. and 12.2.3.2). Also visible from the main publication of the Marigold trial results by Pestana-Knight EM et al. Lancet 2021 (Table 3, footnote).

A4. In Table 15 of the company submission it is stated that when quality appraising the MARIGOLD trial all demographic and baseline characteristics "known to influence clinical outcomes" were balanced between trial arms. Please can the company confirm which characteristics were included in this definition?

We acknowledge that, in the current form, the statement can be confusing. Therefore, we would like to rephrase it as "overall, the demographic and baseline characteristics were balanced between trial arms".

A5. Figure 9 showing the rate of response across participants in MARIGOLD (p. 59) is very useful. Can you please either extend the x-axis of the graph to show the proportion of participants with increases in seizure frequency in each arm (i.e. >0% increases in seizure frequency at corresponding units), or present this information as a separate graph?

Figure 1 illustrates the cumulative response curve in 10% increments for patients with seizure worsening within the 17-week double-blind period for each treatment arm, as requested. Differences between GNX and PBO with percent reductions that have nominal p-values <0.05 are marked with an asterisk.

Figure 1. Full 17-week double-blind period: Cumulative response curve of worsening in 28-day major motor seizure frequency vs baseline period (ITT)

Abbreviations: ITT, intent-to-treat
Source: Data on File Marinus Pharmaceuticals Inc.

In the Marigold trial, the primary end point was defined as the percentage of change in 28-day major motor seizure frequency in the 17-week double-blind treatment period (including a 4-week dose titration at start), compared with the baseline period. However, the “European regulatory guidance on clinical investigations of medicinal products in the treatment of epileptic disorders” recommends that efficacy endpoints should be based on the changes in seizure frequency in the treatment maintenance dose phase, thus, excluding the titration period. Therefore, we also present the respective information from the maintenance phase, with both improvement and worsening (Figure 2) compared with baseline.

As shown in the figure, the percentage of patients who worsened is numerically greater for PBO than for GNX at each response level, while the percentage of patients improved is greater for GNX. Differences are statistically significant at several points, marked with an asterisk.

Figure 2. Cumulative Curves of change in 28-Day Seizure Frequency for Primary Seizure Types (13-Week Maintenance Phase, ITT Population)

Abbreviations: ITT, intent-to-treat
Source: Data on File Marinus Pharmaceuticals Inc.

A6. The caption to Table 16 (p.56-57) states that 'Summaries are based on the sum of the individual seizures, the countable seizures, and the clusters with uncountable seizures (each cluster with uncountable seizures counts as 1 seizure)', while Table 29 appears to indicate that secondary seizures were countable, and tertiary seizures were considered "Hard to count". Please could the company:

- Confirm that the analysis in Table 16 shows results for major seizures only, or explain otherwise
- Confirm which seizure types were considered countable and which were uncountable
- Describe how uncountable clusters of seizures were defined and dealt with?

Yes, Orion confirm Table 16 reports major motor seizures (MMS) only.

Change in major motor seizure frequency was chosen as the primary end point of the Marigold trial, since these seizure (MMS) types were both the most consequential, and most clearly "countable", i.e., identifiable, and more often

occurring clearly as separate seizures, so that the number of daily seizures can be counted by the caregivers who kept a seizure diary within the trial. These “countable” MMS types were defined to include bilateral tonic (sustained motor activity = 3 secs), generalized tonic-clonic, atonic or drop, bilateral clonic, and focal to bilateral tonic-clonic seizures. The secondary and especially tertiary seizures such as absence seizures can be by nature harder to detect in general, and thus also more often “uncountable”.

The study protocol states that individually occurring seizures are “countable”. When seizures occur in clusters where one seizure is rapidly followed by another one in such a pace that it is not possible to separate the individual seizures, these seizures are considered “uncountable”. One such seizure cluster was conservatively counted only as 1 MMS, if there was a major motor element involved. If no such element was present in the cluster, it was counted as 1 non-MMS seizure (and included in all seizures, but not MMS).

A7. In the table below the EAG presents means (standard deviations) as presented in company submission Table 16 (p.56-57). Please can the company clarify how change from baseline was calculated?

Table 2: Select data of 28-day seizure frequency for major motor seizures

	Baseline period	Double blind period	Mean %-change from baseline
Ganaxolone	115.4 (138.4)	93.7 (133.9)	-14
Placebo	103.9 (173.0)	151.0 (469.5)	64.6

Individual %-changes from baseline were calculated for each patient and then averaged by treatment group, ending with the mean %-change from baseline for each group. The underlying distribution of seizure frequency is highly skewed and, therefore, the mean change from baseline cannot be calculated directly from visit means.

A8. Also based on Table 2 above, could the company please comment on the noticeably higher coefficient of variation (CV; SD/mean) in the placebo arm during the double-blind period compared to the other cells?

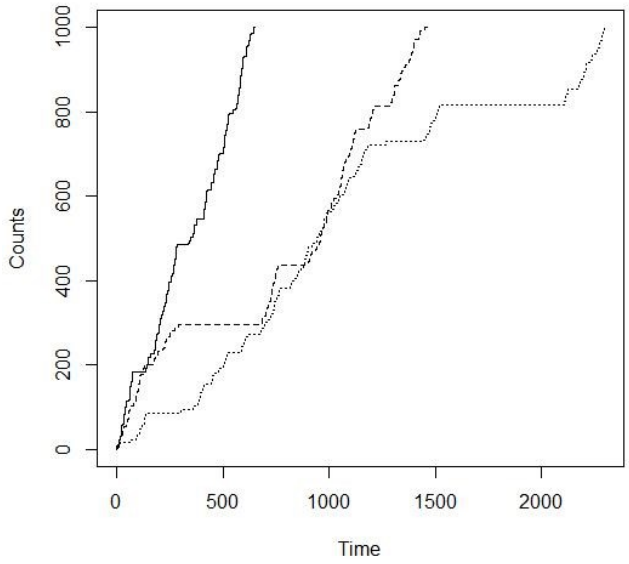
The value range in the placebo group (week 17) is very wide (Table 3), ranging from a minimum of [redacted] to a maximum of [redacted] which yields a large standard deviation (SD). In both treatment arms there were few outliers with extremely high seizure counts (see also response to question B5).

Table 3. Extreme values of 28-day seizure frequency at week 17

Placebo				Ganaxolone			
Lowest		Highest		Lowest		Highest	
Value	SUBJID	Value	SUBJID	Value	SUBJID	Value	SUBJID
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							

A9. The EAG would like to better understand temporal variation in seizures (which has not been presented in the company submission and is not visible in Figure 15 in the company submission, p.98), in particular, variability between individuals and the constancy of the rate of seizures. Data or figures that provide this information might be in the appendix of the clinical study report which has been requested (clarification question C4). However, if not, the EAG requests plots (one for each arm) showing the accumulation of seizures with time for each individual over their complete follow-up (baseline, double blind and extended open label periods) of MARIGOLD. The following figure shows an example of this type of plot for three individuals made by

the EAG with artificial data. (If individual figures are cluttered the results could be distributed across several graphs.)



Seizure frequency was collected as diary entries, where parent/caregiver provided the number of seizures occurring per day. Based on the raw diary entries, a cumulative count of seizures was calculated for each patient. The clinical study report does not contain the type of figure requested and currently there is no access to individual data from the ongoing OLE study. Therefore, we have provided a figure containing cumulative seizure frequency during the 17-week double-blind part (please see below).

The longest data collection time for few individual patients [redacted] and [redacted]) was from baseline up to [redacted] days ([redacted] weeks). Highest cumulative count (see also question A8) was [redacted] seizures for one patient [redacted]. Plotting the data with the entire range shown is not helpful for detecting any patterns on individual data. Therefore, the graph below is truncated [redacted] seizures and [redacted] days (Figure 3). Both treatment arms [redacted] of the data. Most of the patients [redacted]. Cumulation of the seizures over time is [redacted] and in both treatment arms the cumulative seizure frequency is less than [redacted] over the entire 17-week period, with exception of the few outliers.

Figure 3. Marigold study – cumulative number of primary seizures per day by patient and treatment

The detailed seizure information is available in the clinical study report (CSR) Appendix Listing 16.2.5.2.4. that has been provided now, along with all other CSR Appendixes.

A10. Please can the company confirm the dates of all planned data cuts for the MARIGOLD open-label extension (OLE) following the latest data cut on February 24th 2021?

The OLE is still ongoing in some countries and Marinus Inc is planning for the final Data cut off in [redacted], with the analyses/report anticipated to be available by the end of [redacted]

In addition to what was provided in the Orion evidence submission (Marigold CSR), data from a slightly more recent Data cut up to [redacted] has become now available (Data on File). In this data cut, all patients had passed the time point of [redacted] from the entry to OLE.

The available key results from the [redacted] data cut relating to changes in seizure frequency have now been summarised under question A12, as additional information to the outcomes requested.

A11. The population eligibility criteria for MARIGOLD requires that participants be experiencing ≥16 major motor seizures over a 28-day period, which seems a higher threshold compared to the inclusion criteria for the Phase IIa trial. Can you please confirm, and provide comment on whether that decision was driven by findings from the Phase IIa trial or by another rationale?

Orion do not have access to the exact details driving the decision. However, the phase IIa trial was an exploratory dose-finding, proof of concept trial that explored dosing, safety, and the potential for efficacy in several different difficult to treat epileptic conditions, with only 7 CDD patients among the total study population. As the phase II study population was more heterogenous, the seizure frequency criteria were also left more open to allow entry of patients with different conditions. The phase 3 Marigold trial criteria better reflect the pattern typical for CDD, in which a high proportion of patients have a high number of seizures refractory to most anti-seizure medications. At the time of the phase 3 study planning, this inclusion criterion (among the others) was also recommended by clinical CDD experts.

A12. PRIORITY QUESTION: Could the company please provide results of the analysis presented in Table 18 for the MARIGOLD OLE?

The analysis of the requested secondary outcomes for the OLE phase of Marigold is provided in Table 41. Data are presented up [redacted] from the entry to OLE [redacted] with all patients treated for at least [redacted] with ganaxolone (those randomised to ganaxolone in the DB phase were treated for at least 17 weeks + [redacted]

The median change from baseline in the percentage of seizure-free days in the OLE was [redacted] during the first [redacted] (see Table 4 below), the median (95% distribution free confidence interval [CI]) percentage of seizure-free days being [redacted] in patients treated with ganaxolone. Of note, variance in the change of the percentage of seizure-free days was large, with the upper quartile achieving [redacted] or better improvement in the seizure-free days, compared to their baseline situation.

The caregiver-rated secondary parameters also show continued improvement vs baseline, indicating that the benefits provided by ganaxolone are maintained in patients remaining on treatment.

Table 4. Summary of the secondary outcomes from the open-label extension phase

	GNX/GNX	PBO/GNX	GNX/GNX	PBO/GNX
Secondary seizure control endpoints				
Change vs baseline in percentage of seizure-free days, based on major motor seizure types	First [redacted] weeks (OLE)		First [redacted] (OLE)	
n	[redacted]	[redacted]	[redacted]	[redacted]
Median, (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
Caregiver Global Impression of Change vs baseline in Seizure Intensity/Duration score	[redacted]		[redacted]	
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved†, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Secondary behavioural/neuropsychiatric endpoints				
Caregiver Global Impression of Change vs baseline in Attention score	First [redacted] weeks (OLE)		First [redacted] (OLE)	
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved†, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Caregiver Global Impression of Change vs baseline in Parent or caregiver identified behavioural target score‡	First [redacted] weeks (OLE)		First [redacted] (OLE)	
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Secondary outcomes were measured at different time points. Here, we report data obtained at the time point closest to [redacted], as this was the longest duration of treatment all patients had the opportunity to have at the latest data cut-off date [redacted]
†Sum of the patients categorised as “Very much improved”, “much improved” and “minimally improved”.
‡Domains include sociability, communication, irritability, and hyperactivity
Abbreviations: IQR, interquartile range; OLE, open-label extension

As the above requested data is presented from the more recent Data cut off of [redacted], with complete data available to [redacted] for all subjects who entered the OLE, for consistency the company provide here an additional update on some of the key seizure response outcomes.

Following the DB phase, 88 of the 101 patients (87.1%) entered the OLE phase. At the time of the analysis, the duration of the OLE phase extended up to [redacted]. XXXXXXX patients were ongoing in the study and [redacted] patients had discontinued. The data is complete for all patients up to [redacted], beyond which point the decreasing patient numbers result from staggered entry into the OLE phase of the study.

Percent reduction in major motor seizure frequency

The [redacted] OLE data indicates that the efficacy of ganaxolone is well maintained for at least 2 years in patients who remain on treatment. Figure 4 below shows a median seizure reduction vs baseline of [redacted] on ganaxolone treatment in the OLE phase.

Figure 4. Percent reduction in 28-day major motor seizure frequency in the open label phase vs baseline

Footnote: As all patients in the OLE phase receive ganaxolone, the original PBO and GNX treatment groups have been combined. In those originally randomized to ganaxolone at the DB study start, who then continued to the OLE, the [redacted] equates to a total of [redacted] ganaxolone treatment duration ([redacted]). The data is presented only up to 24 months as the sample beyond that point is small and incomplete. Baseline for all patients in the OLE is the original Baseline in the DB phase.
Source: Data on file. Marinus Pharmaceuticals Inc.

While around [redacted] of patients per month discontinued the use of the medication, in those who remained on ganaxolone the median seizure reduction vs baseline ([redacted]). was higher than the reduction in the original ganaxolone group during the 17-week DB phase (absolute reduction with GNX at the end of week 17 was 30.7%, location shift 27.1% vs placebo) (Figure 4). The efficacy was similar and well maintained in both arms; in the placebo arm, after the patients had reached the maintenance dose of ganaxolone (Figure 5).

Figure 5. Percent Reduction in Major Motor (Primary) Seizure Frequency at the end of the Double-Blind Period and then at 2-month Intervals Within the Open-Label Extension (Intent-to-Treat Population)

Note: Only patients that completed a 2-month interval were included at the time point. Sample sizes varies due to subject discontinuation and due to subjects still ongoing within the OLE. Patients are grouped by their treatment assignment during the double-blind. All patients received open-label Ganaxolone in the OLE independent of their double-blind treatment assignment.
Abbreviations: GNX, Ganaxolone; OLE, open-label extension.
Source: Data on File, Marinus Pharmaceuticals Inc.

Responder rates

An increasing trend over time, similar to that observed for the median reduction in seizure frequency above, was reported also for the proportion of patients achieving the ≥50% response level ("50%-responder rate") over time. After [redacted] of ganaxolone treatment within the OLE phase, the 50%-responder rates were [redacted] respectively (Figure 6). Additionally, some patients [redacted] achieved seizure-freedom (i.e., 100% reduction) during some 3-month intervals. In comparison with the DB period, these response rates are considerably higher, independent of which response definition is used – the percentage of patients achieving ≥50% response at the DB phase was 24.5% and 14.9% in the ganaxolone and placebo groups, respectively.

Figure 6. Responder rates to open label ganaxolone over time, at 3 significant responder definitions

Source: Data on file. Marinus Pharmaceuticals Inc.

Overall, the updated findings from the OLE period presented above suggest consistency in antiseizure effects of GNX in CDD over time and corroborate the primary endpoint of the study.

A13. Please can the company provide variance data for continuous trial outcomes where these are missing from the company submission (e.g., QI-disability and response to parenting stress index)?

We have now provided the requested variance data for QI-disability and Parenting stress index, *adding them below* in a copy of the respective sections in the submission (document B, Section B.2.6.1.6).

B.2.6.1.6 Quality-of-life (QoL) – *(relevant parts of the section copied below to clarify this response only)*

"Response to QoL inventory – disability (QI-disability) scale

Responses to the QI-disability scale were recorded at Visit 3, Visit 4, Visit 5, and the taper visit (for patients who did not continue into the open-label phase or who discontinued early) and compared with responses recorded at baseline.

Overall, after the 17-week double-blind period, the mean (*SD*) change from baseline was [redacted] in the GNX group and [redacted] in the PBO group. The mean change from baseline in each domain of the QI disability scale for both treatment groups is provided in Table 5 (77). Compared with patients in the PBO group, patients in the GNX group had a greater improvement from baseline at the end of the 17-week double-blind period in [redacted]. For [redacted] QI-disability domains [redacted] patients in both treatment groups showed similar improvement from baseline.

Table 5: Summary of responses to the QI-disability scale† (17-week double blind phase)

QI-disability scale, mean change in score from baseline (*SD*)	Ganaxolone	Placebo
Positive emotions	[redacted]	[redacted]
Social interaction	[redacted]	[redacted]
Leisure and the outdoors	[redacted]	[redacted]
Independence	[redacted]	[redacted]
Physical health	[redacted]	[redacted]
Negative emotions	[redacted]	[redacted]

Abbreviations: QI, quality of life inventory; SD, standard deviation.
† The QI-Disability is a parent/caregiver reported quality of life scale specifically developed for children and adolescents with intellectual disability. The measure consists of 32 items that are rated on a five-point Likert scale (1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, or 5 = Very often). The items are grouped into six domains: physical health, positive emotions, negative emotions, social interaction, leisure, and the outdoors (leisure) and independence. The items are worded positively to measure well-being, except for the items related to the Negative Emotions domain, which are reverse scored before all items are transformed to a 100-point scale (19, 45). Specifically, domains are scored as follows: firstly, each of the Negative emotion raw scores are reversed (6 – raw score). Then each item's raw score (after reversing for Negative Emotions) is transformed as 25 x (raw score – 1), with never being scored as 0, rarely as 25, sometimes as 50, often as 75 and very often as 100. Finally, the converted scores are averaged over the items within the domains and over all the items (44).

Response to Parenting Stress Index

Responses to the PSI were recorded at Visit 3, Visit 4, Visit 5, and the taper visit (for patients who did not continue into the open-label phase or who discontinued early) and compared with responses recorded at baseline. Overall, parents of patients in the GNX group had a greater improvement on the PSI at the end of the 17-week double-blind period compared with parents of patients in the PBO group; the mean (*SD*) change from baseline was [redacted] and [redacted] for parents of patients in

the GNX and PBO groups, respectively."

Section B: Clarification on cost-effectiveness data

Positioning and Comparators

B1. On p. 34 of the company submission, it is stated that CBD was excluded as a comparator to ganaxolone as it is not currently approved for use in CDKL5 Deficiency Disorder (CDD) by either the EMA or MHRA. However, Epidiolex® use was allowed during the double-blind phase of MARIGOLD and on p.20 of the company submission it is stated that all anti-seizure medications administered for CDD are off-label. Is there further rationale for why a different approach was used for CBD than for other anti-seizure treatments?

The company acknowledges that the sentence on page 34 is somewhat misleading. The topic under consideration in submission ID3988 seeks to compare ganaxolone plus "established clinical management" (ECM) vs. ECM only, as the intended indication for ganaxolone is "adjunctive treatment of epileptic seizures associated with CDKL5 deficiency disorder in patients 2 years of age or older". The NICE scope defined the comparator to ganaxolone as ECM (e.g., without ganaxolone), which includes anti-seizure medications (ASMs), all of which are used "off-label" as they are unlicensed in CDD, specifically. The Marigold inclusion criteria allowed patients to have previously received or currently use any ASMs concomitantly, including Epidyolex® (cannabidiol), which aligns to the ECM stipulated as the comparator. A small number of patients indeed were on concomitant cannabidiol in the trial (1 in each treatment arm). Therefore, the same approach for cannabidiol has been taken as for all other ASMs.

Seizure frequency

B2. PRIORITY QUESTION: Please can the company confirm the EAG's understanding of the steps undertaken (and assumptions made) to derive and apply the Hodges-Lehmann (HL) estimate [redacted] % in the model (i.e., the

estimated change in seizure frequency for ganaxolone compared with placebo):

- **Derived the percentage change in seizures per 28 days for each individual at the timepoint (i.e. $(f(t1)_i-f(t2)_i)/f(t1)_i$ x 100 = percentage change for patient i)**
- **Applied the HL estimator of the difference in percentage change in frequency between arms**
- **Assumed that the seizure frequency distribution stays the same for a CDD cohort receiving established clinical management forever**
- **Applied the HL estimate as a percentage reduction without transformation when using X = ln(frequency data) to estimate a distributional impact e.g., LOGNORM.DIST(frequency values, mean(X)* (1-HL), SD(X), FALSE) in Excel**
- **Assumed this full treatment effect is instant and never reduces for a treated patient for the full time horizon.**

This is correct, the model assumes the reduction/shift is applied to the mean value within the modelled (lognormal) distribution to create a new distribution based on the new parameter. The effect is assumed to be present when patients are on treatment, so it is instant and does not reduce while on treatment, and similarly the effect is immediately removed when patients discontinue treatment (i.e., they revert immediately to the 'ECM alone' values and distribution).

For patients remaining on treatment in the long term, the OLE data indicate the benefit is maintained, and if anything, improved. Therefore, the assumption of constant treatment effect on patients on treatment can be considered quite conservative.

B3. Could the company please provide the analysis presented in Document B Table 19 (analysis of change in seizure frequency during weeks 5-17 in MARIGOLD) for the titration period (weeks 0-4)?

We have now provided the results of the change in seizure frequency for primary seizures and all seizure types for the titration period (weeks 0–4) of the Marigold DB phase in Table 6.

Table 6: Summary of 28-day seizure frequency for primary (major motor) seizures and all seizure types during the titration period of the double-blind phase (week 0–4) – ITT population

	Primary (major motor) seizure types		All seizure types	
Percent change from baseline in 28-day seizure frequency	Ganaxolone (n=49)	Placebo (n=51)	Ganaxolone (n=49)	Placebo (n=51)
Median (95% distribution-free CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Hodges-Lehmann Estimate of Location Shift (95% CI)†	[redacted]		[redacted]	

Abbreviations: CI, confidence interval; ITT, intent to treat; SD, standard deviation
Notes: Summaries are based on the sum of the individual seizures, the countable seizures, and the clusters with uncountable seizures (each cluster with uncountable seizures counts as 1 seizure). The primary seizure types include bilateral tonic (sustained motor activity ≥3seconds), generalised tonic clonic, atonic/drop, bilateral clonic, and focal to bilateral tonic-clonic. Within the baseline and postbaseline intervals, 28-day seizure frequency was calculated as the total number of seizures in the interval divided by the number of days with available seizure data in the interval, multiplied by 28. The baseline interval consists of the 6 weeks prior to the first dose. The maintenance portion interval consists of the 13 weeks following the 4-week titration portion of the double-blind post baseline phase.
†An estimate of how far the responses in the ganaxolone group are shifted from the placebo group. Duplicate seizure diary entries are not used in the analysis.
Source: Marigold study Clinical Study Report. Appendix Tables 14.2.5.4.1 and 14.2.5.4.2.

B4. PRIORITY QUESTION: Could the company please provide results of the analysis presented in Table 18, but for the OLE?

The analysis of the requested secondary outcomes for the OLE phase of Marigold is provided in Table 7. Data are presented up [redacted] from the entry to OLE [redacted] with all patients treated for at least [redacted] with ganaxolone (those randomised to ganaxolone in the DB phase were treated for at [redacted]

The median change from baseline in the percentage of seizure-free days in the OLE was [redacted] during the first [redacted] (see Table 7 below), the median (95% distribution free confidence interval [CI]) percentage of seizure-free days being [redacted] in patients treated with ganaxolone. Of note, variance in the change of the percentage of seizure-free days was large, with the upper quartile achieving [redacted] or better improvement in the seizure-free days, compared to their baseline situation.

The caregiver-rated secondary parameters also show continued improvement vs baseline, indicating that the benefits provided by benefits are maintained in patients remaining on treatment.

Table 7: Summary of the secondary outcomes from the open-label extension phase

	GNX/GNX	PBO/GNX	GNX/GNX	PBO/GNX
Secondary seizure control endpoints				
Change vs baseline in percentage of seizure-free days, based on major motor seizure types	First [redacted] weeks (OLE)		First [redacted]	
n	[redacted]	[redacted]	[redacted]	[redacted]
Median, (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
Caregiver Global Impression of Change vs baseline in Seizure Intensity/Duration score	First [redacted] weeks, OLE period		First [redacted]	
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved†, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Secondary behavioural/neuropsychiatric endpoints				
Caregiver Global Impression of Change vs baseline in Attention score	First [redacted] weeks (OLE)		First [redacted]	
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved†, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Caregiver Global Impression of Change vs baseline in Parent or caregiver identified behavioural target score‡	First [redacted] weeks (OLE)		First [redacted]	
n	[redacted]	[redacted]	[redacted]	[redacted]
Improved, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Secondary outcomes were measured at different time points. Here, we report data obtained at the time point [redacted], as this was the longest duration of treatment all patients had the opportunity to have at the latest data cut-off date of [redacted] †Sum of the patients categorised as “Very much improved”, “much improved” and “minimally improved”.

‡Domains include sociability, communication, irritability, and hyperactivity
Abbreviations: IQR, interquartile range; OLE, open-label extension

As the above requested data is presented from the more recent Data cut off of [redacted], [redacted] with complete data available to [redacted] for all subjects who entered the OLE, for consistency the company provide here an additional update on some of the key seizure response outcomes.

Following the DB phase, 88 of the 101 patients (87.1%) entered the OLE. At the time of the analysis, the duration of OLE extended up to [redacted]. Fifty-four (54) patients were ongoing in the study and 34 patients had discontinued. The data is complete for all patients [redacted] beyond which point the decreasing patient numbers result from staggered entry into the OLE phase of the study.

Percent reduction in major motor seizure frequency

The [redacted] OLE data indicates that the efficacy of ganaxolone is well maintained for at least 2 years in patients who remain on treatment. Figure 7 below shows a median seizure reduction vs baseline of [redacted] on ganaxolone treatment in the OLE phase.

Figure 7. Percent reduction in 28-day major motor seizure frequency in the open label phase vs baseline

Footnote: As all patients in the OLE phase receive ganaxolone, the original PBO and GNX treatment groups have been combined. In those originally randomized to ganaxolone at the DB study start, who then continued to the OLE, the [redacted]The data is presented up to 24 months as the sample beyond that point is small and incomplete. Baseline for all patients in the OLE is the original Baseline in the DB phase.
Source: Data on file. Marinus Pharmaceuticals Inc.

While around [redacted] of patients per month discontinued the use of the medication, in those who remained on ganaxolone the median seizure reduction vs baseline ([redacted]), was higher than the reduction in the original ganaxolone group during the 17-week DB phase (absolute reduction with GNX at the end of week 17 was 30.7%, location shift 27.1% vs placebo) (Figure 7). The efficacy was similar and well maintained in both arms; in the placebo arm, after the patients had reached the maintenance dose of ganaxolone (

Figure 8).

Figure 8. Percent Reduction in Major Motor (Primary) Seizure Frequency at the end of the Double-Blind Period and then at 2-month Intervals Within the Open-Label Extension (Intent-to-Treat Population)

Note: Only patients that completed a 2-month interval were included at the time point. Sample sizes varies due to subject discontinuation and due to subjects still ongoing within the OLE. Patients are grouped by their treatment assignment during the double-blind. All patients received open-label Ganaxolone in the OLE independent of their double-blind treatment assignment.
Abbreviations: GNX = Ganaxolone
Source: Data on File, Marinus Pharmaceuticals Inc.

Responder rates

An increasing trend over time, similar to that observed for the median reduction in seizure frequency above, was reported also for the proportion of patients achieving the ≥50% response level ("50%-responder rate") over time. After [redacted] of ganaxolone treatment within the OLE phase, the [redacted], respectively (

Figure 9). Additionally, some patients [redacted] achieved seizure-freedom (i.e., 100% reduction) during some 3-month intervals. In comparison with the DB period, these response rates are considerably higher, independent of which response definition is used – the percentage of patients achieving ≥50% response at the DB phase was 24.5% and 14.9% in the ganaxolone and placebo groups, respectively.

Figure 9.Responder rates to open label ganaxolone over time, at 3 significant responder definitions

Source: Data on file. Marinus Pharmaceuticals Inc.

Overall, the updated findings from the OLE period presented above suggest consistency in antiseizure effects of GNX in CDD over time and corroborate the primary endpoint of the study.

B5. PRIORITY QUESTION: In the company submission it is stated that seizure frequency decreased in the placebo arm of the MARIGOLD trial by week 17 (e.g., Sections B.2.6.1.1, Figure 8, B.2.6.1.2, B.3.3.1.2):

- **Given understanding of the trial methods and population, does the company have a view on why some participants in the placebo arm showed meaningful reductions in seizure frequency (e.g., 20% of participants saw >30% reduction in seizures)?**

- **Could the company please provide the distribution of seizure frequency in each trial arm at baseline, week 17 and the end of extension follow-up? This should take the form of two tables (one for each arm) with the below format and cell values equal to the number of observations. Due to the size of the expected table, please provide it in Excel:**

Table 8: Suggested format for company response to question B5

Seizures per 28 days	Baseline (N_0)	…	Week 17 (N_{17})	…	End of follow up (N_{EOFU})
0					
1					
2					
...					

No specific reason stands out from the data itself for some of the placebo-treated patients having ≥30% response, as far as the company are aware. It is not uncommon that in clinical trials fairly large placebo effects are seen, potentially due to e.g. more frequent physician/clinic contacts.

The requested Tables with Distribution of seizure frequency in the three time points are provided as a separate Excel file (“Distribution of seizure frequencies”), with the treatment arms described on separate sheets. EOFU was defined for this purpose as the end of the entire open-label phase, which varies by individual.

B6. Could the company provide evidence to suggest that seizure frequency is not related to mortality? Note that if higher seizure frequency is associated with higher mortality, then it follows that seizure frequency in the population will reduce over time irrespective of treatment, as those with higher seizure frequency will die at a higher rate, reducing the average seizure frequency as time passes.

While patients with epilepsy have a higher-than-expected risk of mortality, this risk results from a multitude of factors, of which seizure frequency is one. It is not possible, based on the current evidence, to robustly attribute what proportion of CDD mortality is uniquely related to seizure frequency rather than others such as long-term disability and developmental disorders.

As such, to ensure assumptions adopted were conservative, and avoid double counting or otherwise inflating mortality risk, mortality rates were assumed the same in both treatment arms. While a mortality benefit as suggested would potentially reduce seizure frequency through the moving average rate, it would also yield a loss of a large number of LYs and QALYs in the ECM arm, where patients survival is reduced.

B7. Can the company specify the ‘goodness of fit’ test reported in the company submission (Document B, Table 30)?

Goodness of fit tests was implemented via the goft package in R where available.

B8. Could the company please provide the following figures:

- An amended version of Figure 15 to (a) show the n of each non-zero bin included on the plot to allow assessment of outliers in the data (e.g., the small n with seizures > 1000 / 28-day period) and (b) with smaller bin widths to facilitate better visual comparison with the parametric fits (without labels for n))

- An amended version of Figure 16 separated by treatment arm (i.e. a separate figure for each arm) with the amended Figure 15 superimposed. This will allow visual assessment of the fit of the observed data to the values applied in the cost-effectiveness model.

- Separate box plots for each treatment arm showing seizure frequency by primary motor / secondary or tertiary at baseline and week 17. These will help us to understand the distributional impact of ganaxolone on seizure frequency by type of seizure, and to reconcile why the inclusion of all seizures increases the base-case ICER (company submission Table 50).

- Figure 16, with the smaller bin width histogram of the clinical data superimposed, by treatment arm (separate figure for each arm). This will allow visual assessment of the fit of the observed data to the values applied in the cost-effectiveness model.

Please find below, in
Figure 10**Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.**, an amended version of Submission Figure 15 with smaller bin widths and showing counts for each non-zero bin as requested. Note there [redacted] with 28-day seizure frequency >[redacted] as indicated in the figure below.

Figure 10: Submission Figure 15 amended using smaller bin widths with parametric fits

An updated figure showing the smaller bin widths as well as aligned density curves is shown below (Figure 11).

Figure 11: Submission Figure 16 amended, showing curves for ECM, with amended Submission Figure 15 superimposed (smaller bin width)

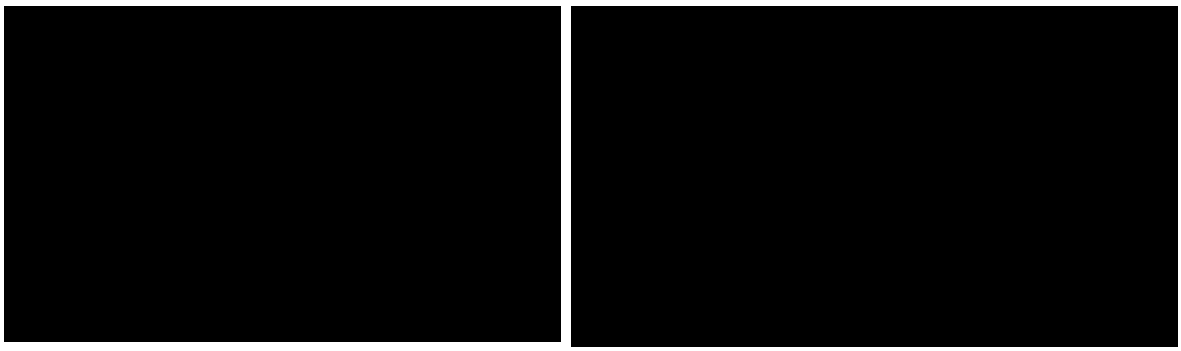
An updated figure showing ECM alone is provided below (Figure 12). An updated figure for ECM+GNX is not provided as the ECM+GNX curve was generated after applying the shift and cannot be directly overlaid on the data.

Figure 12: Lognormal curve for ECM alone.

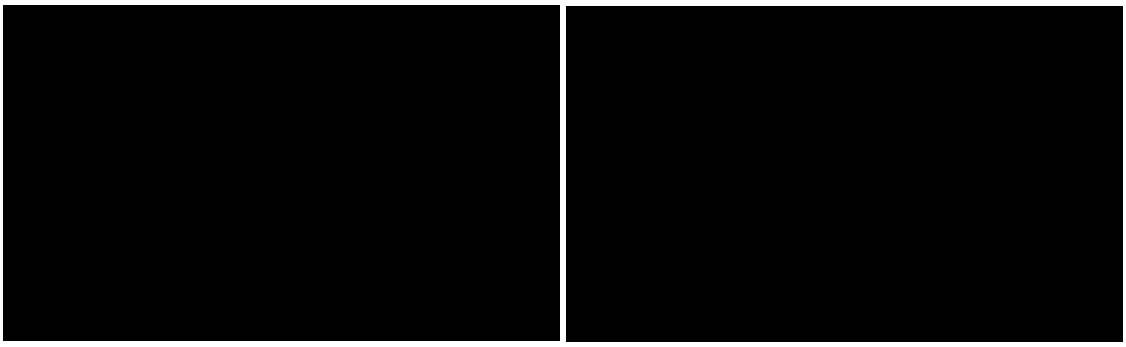
Boxplots for 28-day primary, secondary, and tertiary seizure frequency at baseline and endpoint (i.e., week 17) are provided in Figure 13.

Figure 13 a-c. Boxplots for seizure frequencies by treatment group at baseline and week 17 of the double-blind period.

13a) Primary



13b) Secondary



13c) Tertiary

B9. PRIORITY QUESTION: Could the company please explain why sensitivity analysis using alternative candidate distributional shapes for seizure frequency have not been presented (also see B10)? Can the company please include these in the cost-effectiveness model and clarification response?

The alternative candidate distributional shapes were not plotted directly in the model due to their rejection as suitable fits to the data – the lognormal was the only candidate that failed to be rejected at a 95% significance level. As such, we felt modelling the data using these unsuitable fits would give modelled seizure distributions that were not reflective of the actual data and would thus give seizure frequency estimates that are not informative and would in turn not give accurate outputs (given their impact on quality of life and costs).

B10. Several candidate distributions with potentially suitable characteristics (such as F, Johnson, Poisson, negative binomial, truncated normal, and so on) are excluded from the distributional analysis presented in the company submission in Section B.3.5., whilst distributions without the apparent features of the histogram in Figure 15

(like exponential and Weibull) are included. Further, the lognormal distribution is used in the base-case without alternative. Can the company please justify the selection of distributions included in the seizure frequency distributional analysis, explain the selection process, and justify the conclusion? Please refer back to the above request (B9) for figures which may be relevant to addressing this question.

Distributions were selected based on suitability for data (e.g., support) and visual inspection. The distributions listed above were not explored as they were not deemed suitable for the data type or did not meet the properties of visual inspection. Distributions were selected according to AIC and BIC, supplemented with results from goodness of fit tests where available.

B11. The Hodges-Lehmann estimate of location shift presented in company submission section B.3.3.1.2 is an estimate based on the median of differences between treatment arms (i.e., the median of the average difference between paired values within the dataset). Given the skewed non-normal distribution of the data and the associated issues with using mean values, could the company please justify the application of the Hodges-Lehmann estimated difference to the mean of the baseline frequency distribution, as described in section B.3.3.1.2 (page 98, bottom paragraph)?

We agree that the Hodges-Lehmann estimator is a suitable estimator of location shift given the skewed non-normal distribution data. We elected to apply the estimate by shifting the distribution via the mean as opposed to the median to allow for better approximation of distribution parameters used in the seizure frequency modelling (i.e., approximating parameters of lognormal distribution).

B12. In the cost-effectiveness model, the estimated reduction in absolute seizure frequency is applied to the mean of the baseline log-transformed seizure frequency in the established clinical management arm to model efficacy. However, the same reduction is not applied to the standard deviation, increasing the ratio of uncertainty to mean. Could the company please justify the assumption that the log-transformed mean seizure frequency would change whilst the standard error in that mean would remain the same?

We have assumed that the curves with a reduced mean via the approach applied would maintain a similar variance and thus the standard deviation would not be

reduced under the new parametric assumptions. Examination of trial results support there are generally similar standard deviations at endpoint and baseline timepoints.

Patient and caregiver utility impacts

B13. Please can the company provide evidence and/or justification to support its assumptions regarding the number of caregivers per patient, including why the number changes over time (i.e. age <18 [1.8 carers] vs. age≥18 [1 carer])?

We assumed 1.8 carers due to the contribution of parental care during childhood and reflecting the average number of parents would be less than 2; after which the average reduces at age 18 due to patients reaching adulthood. This assumption is indeed conservative, as it is possible that maintaining more than one carer beyond this point may be needed; we have modelled a scenario assuming 1.8 caregivers are maintained in adulthood.

B14. Tables 35 and 36 of the company submission refer to a scenario analysis in which utility values associated with focal seizures are included, though it is unclear which analyses in Table 50 of the company submission include these. Please can the company confirm which, if any, scenario analyses include the impact of focal seizures on patients and caregivers? Please provide sufficient information in your response so that the EAG can re-produce the results of this scenario analysis, including (for example) specific values used and affected cells in the cost-effectiveness model.

The scenarios on “all seizures” (rather than primary seizures only) included seizures of focal type. It should be noted that the incidence of focal seizures even amongst all seizures was by far the minority, making up a very small percentage of all seizures recorded.

B15. Please can the company provide the mean number of seizure-free days (SFD) for people categorised per the utilities identified from Auvin *et al.*, (2019) according to seizures per average month? Please ensure all necessary information is provided in

response so that the EAG can understand how people were assigned to each group (e.g., which category a patient with 120 seizures per month belongs to).

Table 9: Suggested table format for company response to question B15

Utility category	Description	SFD
"130"		
"110"		
"80"		
"60"		
"45"		
"20"		
"0"		

Patients were stratified into the number of seizures categories based on the proportion of patients falling into each per the modelled seizure curves. The categories were considered to be the minimum number experienced, i.e. a patient experiencing 120 would fall into the ≥110 category. While patients experienced on average [redacted], this did not vary significantly between treatment arms, and variance between patients within each arm was small. As such under all seizure categories, [redacted] number of seizure-free days was used to determine which SFD category was most appropriate to assign patients to – this was [redacted] where available, or the lowest available value otherwise.

The requested information is presented in Table 10.

Table 10: Utility category and description

Utility category	Description	# SFDs
"130"	Patients experiencing x ≥130 seizures per cycle	Assumed to be [redacted] all patients experiencing [redacted], assumed equivalent to a cycle
"110"	Patients experiencing 110 ≤ x < 130 seizures per cycle	
"80"	Patients experiencing 80 ≤ x < 110 seizures per cycle	
"60"	Patients experiencing 60 ≤ x < 80 seizures per cycle	
"45"	Patients experiencing 45 ≤ x < 60 seizures per cycle	
"20"	Patients experiencing 20 ≤ x < 45 seizures per cycle	Assumed to be [redacted] per month, in turn assumed to be equivalent to a cycle (lowest available)

"0"	Patients experiencing 0 ≤ x < 20 seizures per cycle	Assumed to be 30 per month, in turn assumed to be equivalent to a cycle (lowest available)

Abbreviations: SFD, seizure-free days

B16. In the patient flow sheets, an adverse event-related disutility of [redacted] is included for both treatment arms across all cycles, and is applied multiplicatively (i.e., the average utility value for the cohort at each cycle is multiplied by [redacted]) – see cell range BS15. Please can the company explain where the value of [redacted] was taken from, its relevance for inclusion at each cycle, and why it is applied multiplicatively (rather than additively)?

[redacted]

Mortality

B17. PRIORITY QUESTION: Can the company please explain why expected survival in the cost-effectiveness model is considerably lower than presented in company submission Figure 17 [redacted]?

[redacted]

[redacted]. From the EAG's initial investigation, it [redacted] (see VLOOKUP in column P of the patient flow sheets – refers to the 6th column of the life table in "ClinicalParams", which is labelled as [redacted]).

- Please can the company check and modify the application of mortality within the model to address this?
- In addition, please can the company provide the total estimated life-years from the model as an additional output on the 'BaseResults' sheet?

[redacted]

B18. Based on the provided reference, it appears that the life table data used to populate mortality in the model comes from the 2017-2019 life table and assumes all patients are male. Please can the company update mortality to use the latest

available life table (2018-2020, released 23 September 2021), and reflect the proportion of male and female patients per the MARIGOLD study?

We have amended the updated model provided to calculate a weighted average survival for males and females from the 2018-2020 UK ONS data source as requested.

B19. In applying a standardised mortality ratio (SMR) to capture the difference in mortality for a CDD population versus the general population, proportional hazards are assumed to hold. Please can the company provide any relevant evidence to support this assumption?

The company are not aware of existing evidence that would support whether a proportional hazards assumption does or does not hold; we have adopted an approach that requires the lowest level of assumption due to this lack of supportive data. Given this uncertainty, the projected survival curve for the CDD population was validated to ensure the projections did not appear inaccurate considering clinical experience of managing patients with CDD.

B20. The company derives an SMR for CDD versus the general population based on a study by Chin *et al.,* (2021), without any explicit justification for selecting this study instead of one of the other 7 studies described in Section B.1.3.4. Please can the company justify its choice of the study by Chin *et al.*, (2021), and explain why meta-synthesis was not pursued to account for the range of other estimates identified?

While an assumption, the use of this as a proxy was informed by 1) the source represented mortality rates in UK patients; 2) we maintained uniformity of sources in that it was also our base source of resource use assumptions; and 3) given the identical mortality rates between treatment arms in the model, the adjustment of mortality rates had little impact on the results produced.

B21. The company consulted a key opinion leader (KOL) on the appropriateness of using survival estimates from a patient population with Lennox-Gastaut syndrome (LGS). In Section B.3.3.2 of the company submission, the company states: *"The appropriateness of proxying survival in patients with CDD with survival outcomes in patients with LGS was confirmed by the clinical KOL consulted and deemed*

conservative as there are only very few known patients above the age of 30 years."
To ensure the EAG correctly understands the responses from the clinical KOL, please can the company:

- Confirm that the KOL supported the expected life years for CDD (Figure 17 and requested in clarification question B17)

- Clarify that statement from the KOL that there are few known patients over 30 years of age (section B.3.3.2) relates to people with CDD or LGS

- Confirm that the clinical KOL supported a median overall survival for CDD patients of around 60 years after initiation of ganaxolone (per Figure 17 in the company submission)?

- Present the exact data and lines of questioning on overall survival of CDD patients and life expectancy following initiation of ganaxolone (i.e., the model baseline) that were presented to the KOL?

The KOL was presented with the available options for data sources in the model, alongside the specific reported data, conditions/seizure types in source citations and the survival curves produced in the model under the mortality assumptions. They agreed the data sources and mortality curves presented were acceptable as a representation of CDD given the paucity of data available; however, they speculated that possibly the CDD mortality could be even somewhat higher. The same sources are still used; however, mortality curves were subsequently adjusted with the latest standard mortality rate as a base (UK ONS data, 2018-2020) and crude SMR data from Chin et al. (2021), which increased the survival. The approach was taken to ensure transparency/traceability of the data and it had nominal impact on model ICERs. The approach is also more conservative, not favouring ganaxolone.

Treatment effect, adherence, and discontinuation

B22. Can the company please provide a more detailed explanation of how the [redacted] per model cycle discontinuation rate was derived, and why the standard error is seemingly small in magnitude?

The number of patients discontinuing for all causes in the Marigold study over the double blind and long-term extension follow up extending [redacted] was used as the basis of the assumption; this was transformed to an instantaneous rate and subsequently a 28-day probability to create the cited [redacted] probability.

Costs and resource use

B23. PRIORITY QUESTION: In Table 2 of the company submission, the dosing of ganaxolone is described as follows: *"*[ganaxolone] *should be titrated gradually to achieve the recommended daily dose: 63 mg/kg/day in patients weighing ≤28 kg and 1800 mg per day in those weighing >28 kg."* However, in the model, a fixed dose of [redacted] mg is applied at each cycle. Please can the company check (and amend if applicable) the dosing of ganaxolone in the model to ensure it appropriately reflects the dose titration described in the company submission?

[redacted]

B24. PRIORITY QUESTION: The cost of ganaxolone in the model is based on an estimated total dose required per 28 days and is applied on a cost-per-mg basis. Consequently, no wastage costs are included within the model, yet the total size of a bottle (5,500mg suspended in 110 mL) is different to the 'target' dose required in a given day (maximum 1,800mg), and the dose used in the cost-effectiveness model. Please can the company explain if wastage costs are anticipated in practice, and if so, provide sensitivity analysis accounting for any drug wastage costs? Please also clarify the reasons why wastage may

or may not be expected in clinical practice, and how this would impact cost calculations

The oral suspension dose is administered via an oral syringe, and the required dose volume varies dependent on patient weight. Therefore, the number of full doses that a patient can receive from the 110 mL bottle will vary, as will the possible remainder in each bottle, when less than a full dose remains. However, there should be no drug wastage, as doses can be split between bottles (i.e. a dose started with the remainder of one bottle can be completed using a new bottle). As the product remains stable 30 days following opening, it does not require special storage and patients/ caregivers will be instructed to use the full contents of each bottle, zero or otherwise effectively zero wastage or minute is expected in chronic daily use. Thus, we consider the possible waste negligible in the life-time scenario.

B25. A daily acquisition cost of £15 is included in the model to account for established clinical management (ECM), whereas the daily acquisition cost of rescue medication is set to £0 (i.e., disabled in the base-case analysis). The company submission explains that no difference in ECM or rescue medication is assumed between treatment arms, and therefore neither of these costs affect the incremental model results. Within the company submission, results presented from the MARIGOLD study suggest similar use of anti-seizure medications (ASMs), though no specific data is presented concerning rescue medication specifically. Please can the company:

- Provide the basis on which an estimate of £15 was produced?
- Explain why no difference in use of rescue medication was assumed, while there is a modelled difference in the frequency of seizures?
- (If considered appropriate) provide a sensitivity analysis where rescue medication is linked with seizure frequency, and include a cost for this within the model?

The cost is an assumption due to the number, varying types and complex combinations of pharmacological and non-pharmacological treatment options, which included anti-epilepsy medications, nutritional support (including ketogenic diets)

amongst a large range of other management options. We considered £15 to be a conservative value to attached to what was a complex and nebulous range of options, which would in any case be assumed unchanged with and without ganaxolone (and thus non-impactful on the ICER).

[redacted]. However, as the company agree with the proposed logic, we have also modelled a [redacted] and attached to seizure frequency, to demonstrate the hypothetical impact of this assumption.

B26. In the model, the cost of an adverse event leading to hospitalisation was included (£1,182 per admission) for [redacted] % of patients on both arms, but this is costed per 28-day model cycle for the full modelled time horizon (i.e., a cost of £ [redacted] is applied for all surviving patients on both arms every 28 days). Please can the company explain why this cost is assumed to apply each model cycle? If this is an error, please re-submit the model with this corrected.

This is corrected in the updated model; events are assumed to be spread over the double-blind period (four cycles).

B27. In the company submission, it is noted that there was *"no significant difference in treatment-related AEs in the PBO and GNX arms in the MARIGOLD study"*, yet in Table 23 in Document B, there are considerable differences in treatment emergent adverse events (TEAEs) between arms (for example, TEAEs: ganaxolone 70%, placebo 43.1%, moderate/severe adverse events ganaxolone 54%, placebo 35.3%, serious TEAEs ganaxolone 12%, placebo 9%). Please can the company provide a full breakdown of adverse events by type, grade, and treatment arm, and then incorporate the differential impact (both costs and utility impacts) into the cost-effectiveness model?

The rates presented are those corresponding to categories of treatment-related rather than treatment-emergent adverse events. The incidence of treatment-

emergent adverse events was similar, and numerically lower with ganaxolone compared with placebo (86% versus 88%, respectively). Uncertainty around the definition of treatment-related within trials and with new treatments led the decision to assume equivalence based around a more robust measure of treatment-emergent adverse events. We have also only costed serious adverse events that would require admission to or prolongation of stay in hospital, as these would be the most impactful in terms of resource. Utility impact was not included to avoid risk of double counting of decrements in the model's day to day seizure-driven QoL estimation.
A breakdown of adverse events has been also attached in the attachment with the CSR Section 14 tables and figures (Table 14.3.2.4.1).

B28. Table 3 in Chin *et al.,* 2021 provides all-cause and epilepsy-related rates of hospital inpatient admissions (per patient-year). Please can the company explain why both all-cause and epilepsy-related rates are included in the model, without taking possible double counting into consideration?

We had assumed the study stratified hospitalisation by all-cause and epilepsy related based on the ICD-10 code, and that these were exclusive categories. However, if this is not the case, the number of all cause hospitalisations will reduce in both arms equally, since the reduction of hospital admissions with ganaxolone is assumed to impact only the epilepsy-related hospitalisations. Thus, the ICER would be unchanged.

B29. Values for patients under 12 years of age from Table 3 in Chin *et al.*, 2021 are applied to patients in the cost-effectiveness model irrespective of age, despite Table 3 in the article also providing values for patients ≥12 years old. Could the company please update the model to apply the rates in patients 12 years or older?

Our selection was based on the starting age of patients in the model, although we have run a scenario in which patients incur costs corresponding to the 12 years and older category when patients reach this age band and included inputs/functionality to allow the EAG to investigate this.

B30. In Chin *et al.*, 2021, “probable LGS” patients were defined as those with an EMR containing an ICD-10 code/Read Code for epilepsy (from HES/CPRD) and a formulary product code for rufinamide within a year of diagnosis. Further, according to Table 3 in Document B, a considerable proportion of CDD patients expected to be treated with ganaxolone are likely to have been pre-treated with rufinamide. Therefore, whilst none of the patients with confirmed LGS have CDD, some patients with probable LGS are likely to have CDD. Given this, could the company explain why ‘confirmed rather than probable LGS patients’ healthcare resource use has been used for the cost-effectiveness analysis?

The source has been selected as a proxy for CDD patients rather than to identify potential CDD patients within the patients not confirmed as LGS; we used LGS patients on the understanding that they have similarities and have selected the more homogenous population (rather than a population that includes unknown conditions). However, we understand the EAG’s argument and have run a scenario using updated model values corresponding to the ‘probable LGS’ values. (This is included in the provided updated model).

Section C: Textual clarification and additional points

C1. In describing the approach to account for treatment discontinuation with ganaxolone, the model file refers to a *“28-day discontinuation rate (*[redacted]*)”* (cell range B20 on the ClinicalParams sheet). Please can the company confirm that [redacted] is currently included within the model?

This error in the row title has been corrected in the updated model provided[redacted] was applied in the model.

C2. The code used to generate the cost-effectiveness acceptability curve (CEAC) does not appear to generate correct values. Please can the company check and then if required revise its programming for the CEAC within its model?

Apologies, but we could not reproduce this error – the code appears to work when we run the model. The CEACs produced appear to be as expected in our version.

C3. Is there an updated version of the Marigold clinical study report (CSR) that includes evidence for the Marigold open-label extension? If so, please can the company provide this with their response?

No, there is no updated report available. The OLE study part is still ongoing in some countries, and the OLE study is expected to be completed in [redacted]
Therefore, an updated analysis is likely to be available in [redacted]

C4. Please provide all appendices to the Marigold CSR, including tables and figures mentioned in the text of the CSR but not included in the reference pack

We have uploaded the requested Appendices and CSR section 14 tables, figures and narratives, as requested.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	CDKL5 UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Advocacy group funded by donations. Not a member organisation.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes Orion Corporation (UK). £11,760.00 Grant to fund vCreate Neuro, app based solution for sharing of seizure videos to clinicians by parents and caregivers. Orion Corporation (Finland). £2494.00
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Asked for feedback direct from parents of patients in a closed FB group specifically for parents of children with CDKL5. Copied verbatim in most cases given the impact of the views expressed.**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	For children and young people with CDKL5 they experience multiple seizures a day. There have additional co-morbidities and learning difficulties which means they can experience significant pain, recurrent infections, and in a lot of cases poor quality of life due to the medication regimes they are on. Carers described the living with the condition as : "I'm shattered. Emotionally and physically. I'm constantly on edge, waiting for the seizure that causes damage. Waiting to see if she makes any progress" "Any illness hits her hard and we have become frequent flyers at the hospital. Guilt. All the guilt all the time. Jealous of the life I thought she would have. Ecstatic anytime she makes a gain. Exhausted due to lack of sleep. I'm lucky if we get 5hours a night and she can go nights at a time on cat naps. Then the swings where she is so sleepy I can't feed her." "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. It's also constant. There is no letting up. The needs are constant AND constantly evolving" "Exhausting. All encompassing. Unpredictable. Poor sleep, poor quality of life. Constant juggling" "It feels like we live in a constant state of 'anxiety' just waiting for the next change in seizures (even when you are pretty calm and on top of life generally!!). Every little twitch could mean a new seizure type and you literally watch every little thing that your child does to determine whether it's something that needs attention/NHS input/or nothing at all. Sometimes you get sleep, sometimes you don't. Juggling work/business/other children is very hard but I feel like (we) just plow on through and tell everyone we are 'used to it' and 'used to being very busy' and 'everything is fine', even if you know it's not - although a lot of the time you have become so used to it that you can't imagine life any other way and everything is genuinely OK" "On the flip side, there's so much joy to be had when your child is well, seizure are minimal and you know that they are pretty settled (but as above, it's a constant question in your head of how long will this last?)."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**"**We have had decent care overall at GOSH and have been able to get all we needed from them (but we supplement privately). At the local hospital this was very different but at GOSH it feels they did all they could in terms of EEGs etc. and they listen to us as parents (e.g. re med choice and now support a no med approach actually). I rate them (and maybe that's our professor) highly. Of course it's very hard to get hold of people if you need anything outside the usual which is why is use private on top" "We have had excellent care. Our care is provided by the RCDN – CDKL5 due to where we live. The team around us have supported us and our daughter since she was 2 years old. The whole MDT have been instrumental in support our daughter to keep well. We respect them and their decisions which are always proportionate to her needs. She has been able to thrive directly because of the support available at Bristol. Allied to that, we have accessed a Personal Health Public through our ICB in Somerset for that last 8 years, this has meant our daughter has had individualised care and support in all aspect of her lifes. Due to the funding provided by the PHB for private physio this has reduced hospital admissions, and enable her to learn to walk just before her 7 birthday. She is now 17 and still has a adequate level of mobility on her feet." **"**I think it is so variable and very much luck on who becomes your consultant. If there was a standard protocol and training and the medical teams had joint training and coordinated better then I think there would be a significant improvement in care and opportunities. There should be some kind of flow chart for accessing therapies that all parties can access, parents and care teams."

8. Is there an unmet need for patients with this condition?	"Very high unmet need given there are no medications currently available for treatment of disorder and AEDs only treat the symptoms (ie seizures) with limited success and come with their own side effects" "I strongly feel that the care for CDKL5 should be more streamlined and appropriate in terms of medication and service/support. Also, parents and carers should be given lots of 'training' at every opportunity when it comes to what our children go through. For example, as soon as there is a need to services like physio, feeding solutions etc, children should be allocated sessions and parents helped with understanding and learning about what they will need to do on a daily basis." "There is no curative treatment - only symptomatic treatment at this point. Agree with other comments that there is no coordination of various medical disciplines and therapies that might be beneficial. Leaves the parents to co-ordinate (and often pay as well)" "Absolutely and most other complex neurological conditions. Lack of expert knowledge, lack of facilities (Eeg), lack of coordination of care." "Lack of adult neurologists in the UK and engagement with the disorder make for a difficult transition to adulthood"

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**"**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 . We are now on compassionate use and will stay on it for now . It will probably make your child sleepy but it's a case of adjusting the dose at lunch time and we give it at 2 o'clock so sleeps on the way home from school" **"**A new medication that could offer benefit to some children. Increasing the 'tools in the box'"

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	"Very highly advertised and gave a lot of us hope. But reality is different. Just another AED with strong side effects. Listening to parents feedback I would not say it had a great success to minimise seizures" "Another AED. Question if it's better than others but seems they chose CdKl5 and the other rare epilepsy after they couldn't get approval for wider epilepsy application. Question if this is really a great drug for cdkl5 or was is just easier to get this through FDA approval and now it's pushed to the cdkl5 community to monetise as a seemingly cdkl5 specific treatment." "Ganaxolone has been heavily promoted in the community Facebook groups, however, trials were relatively small in the grand scheme of things. People will always pick up on the negativity. It is important to take a balanced view and look at the results from the phase three trials. We all have hope when trying a new med whether it is ganaxolone or not. We take the chances as to whether it will work or not. If experiencing a decline in seizure control, we would trial this med if it were available over some of the standard protocol AEMs.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Boys seemed to have experienced more side effects of this drugs. It is worthwhile however, to be proportionate about his as there have not been expansive trials which have included boys who are a minority in the CDKL5 population.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• High unmet need for patients with CDKL5 across health and social care • If approval is given, education about CDKL5 should promoted across the NHS to all clinicians through the various professionals organisations, BPNA, GPs, Adult Neurology, Paediatrics • Experience of the condition varies depending on where you live this has direct impact on care • Impact on QoL for patients and carers is significant leading to carers being sceptical of the technology in the absence of other disease modifying treatments.

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Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists (ABN)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is a not-for-profit membership association for Neurologists whose mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The organisation is funded by membership fees.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Prevention of seizures and their consequences. There are many other comorbidities in people with CDKL5 deficiency disorder (CDD) including motor delay, intellectual disabilities and sleep disturbance, some of which may be partly influenced by seizure frequency. Patients with refractory epilepsy are also at risk of injury from seizures and falls and there is an increased risk of sudden unexpected death in epilepsy (SUDEP).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The ideal is freedom from seizures, but this is rarely achieved with current treatments for this group of patients. Cessation of generalised tonic-clonic seizures (one type of seizure seen in this condition) has benefits, for example in reduction of risk of sudden death (SUDEP). The commonly used measures of a 50% reduction in frequency of seizures, or types of seizures, though of undoubted help, should be acknowledged to be the arbitrary measure it is, and does not necessarily reduce risks (eg. of sudden death) or improve quality of life. A 30% reduction in major motor seizures, that is generalised tonic clonic seizures, tonic or atonic, was found in the large Phase 3 trial of ganaxolone in CDD and it would be reasonable to apply the same threshold for the current patient group.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Many patients with CDD do not become seizure-free with currently available antiseizure medications

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Primary treatments: currently licensed antiseizure medications (ASM) Ketogenic diet and vagus nerve stimulation are also considered

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CG137 (Epilepsies: diagnosis and management) for the general care of epilepsy, however CDD is not specifically mentioned in the childhood onset epilepsies section.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is not a well-defined pathway for all aspects of care. Patients will normally try several regularly used antiseizure medications. If seizures fail to respond to medication, patients should be referred for specialist review at a tertiary centre as per NICE guidelines. However, patients may often not continue to be seen at tertiary centres. Patients may be reviewed by a regional neurogenetics service, although at the current time this would be regarding wider impact of diagnosis for the family (eg counselling) rather than direct management of the condition
9c. What impact would the technology have on the current pathway of care?	An additional drug to be tried as adjunctive therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, as another antiseizure medication.
10a. How does healthcare resource use differ between the technology and current care?	I have no personal experience of its use, but the literature related to ganaxolone use do not identify any specific consideration compared with other anti-epileptic medications.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics for initiation at least
10c. What investment is needed to introduce the technology? (For example,	Increased support and systems for prescribing in hospitals, particularly if there is an increase in the number of patients referred for specialist follow-up and prescribing.

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Although not all patients will respond, studies have found improved seizure control (up to 30%) compared to placebo and it is likely that some patients will have a clinically meaningful improvement compared to current care.
11a. Do you expect the technology to increase length of life more than current care?	Yes, if seizure freedom or significant reduction in major seizure frequency is achieved.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, if seizure freedom or significant reduction in major seizure frequency is achieved.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not apparent

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	It will require additional time for issuing prescriptions from hospitals unless GPs are able to continue prescriptions after initiation and also blood monitoring may be required. Associated adverse effects associated with ganaxolone include upper respiratory infection, fatigue, and drowsiness.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Stopping criteria should be failure to achieve 30% reduction in disabling seizures, after stable dosage for 6 months, compared to baseline.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes by reducing seizure burden and associated seizure related risks for patients who are refractory to current treatment options.
16a. Is the technology a 'step-change' in the	No, it will provide an incremental change in the treatment of CDD

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	The population has medically refractory epilepsy and this is another medication to improve epilepsy outcome
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Associated adverse effects associated with ganaxolone include upper respiratory infection, fatigue, and drowsiness.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Mostly. The trial included patients if they were aged 2-21 years with a pathogenic or probably pathogenic CDKL5 variant and frequent major motor seizures. We would expect ganaxolone to be used predominantly in children, and adults with new diagnosis rarely.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Seizure reduction and adverse events. These were both measured.
18c. If surrogate outcome measures were used, do they adequately predict	N/A

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not to our knowledge
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	Not to our knowledge
21. How do data on real-world experience compare with the trial data?	As adult neurologists, there is very little real world data on adults with CDD for comparison

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No. Ganaxolone should be considered in CDD where other anti-epileptic treatments have failed
22b. Consider whether these issues are different from issues with current care and why.	Not different from current care issues.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Ganaxolone contributes to the treatment options for CDD • Freedom/reduction in motor seizures is a valuable achievement in this syndrome • Ganaxolone has only been compared with placebo in the population • Adverse effects associated with ganaxolone include upper respiratory infection, fatigue, and drowsiness. •

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Single Technology Appraisal

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

NHS organisation submission (ICBs and NHS England)

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes or **No** Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? **Yes** Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? Yes or **No** An expert in treating the condition for which NICE is considering this technology? Yes or **No** An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes or **No** Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national NHSE clinical commissioning policies for this condition or this treatment
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is not a nationally commissioned highly specialised service (HSS) for the treatment of CDKL5 deficiency disorder but there is a Rare Disease Collaborative Network (RDCN) with one member. RDCNs are made up of provider/s with an interest in a particular rare disease and are committed to working together to progress research, increase knowledge and improve patient experience and outcomes. TheCDKL5 RDCN but would provide a structure through which the drug could be distributed if it were approved by NICE. As the condition is so rare there is not widespread knowledge of treatment options outside the RDCN.
8. What impact would the technology have on the current pathway of care?	If the technology were recommended this would represent a step-change in the care of these patients.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	This therapy is not commissioned for routine use in England. Any use will have been in trials.
10. Will the technology be used (or is it already used) in the same way	

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	The technology would provide an important alternative treatment option for these patients.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology would be used in the RDCN.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment required
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Starting the treatment would require a confirmed genetic diagnosis
11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No equality issues
12b. Consider whether these issues are different from issues with current care and why.	

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Ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over [ID3988]: A Single Technology Appraisal

Produced by

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Ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over [ID3988]: A Single Technology Appraisal

Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU** 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; c.farmer@exeter.ac.uk
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Declared competing interests of the authors	Dr Amin was a trial manager for Marigold and provided advice to the company that informed their submission. He has never received money from the company. In his role as national lead for the CDKL5, Dr Amin has sought funding from industry on behalf of the organisation.
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
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Author Contributions:	
Darren Burns	Critical appraisal of the economic evidence and analysis submitted by the company, conducted additional economic analyses and drafted sections of the report
Zoe Phillips	Critical appraisal of the economic evidence and analysis submitted by the company, and drafted sections of the report
Justin Matthews	Critical appraisal of the statistical analyses conducted by the company throughout its submission, and drafted sections of the report
Ash Bullement	Critical appraisal of the economic evidence submitted by the company, conducted additional economic analyses and drafted sections of the report
Laura Trigg	Critical appraisal of the clinical trials of ganaxolone and drafted sections of the report
Simon Briscoe	Critical appraisal of the company's literature search strategies
Joseph Symonds	Expert clinical advice about CDKL5 deficiency disorder and its treatment

Author Contributions:	
Sam Amin	Expert clinical advice about CDKL5 deficiency disorder and its treatment
Dougal Hargreaves	Dr Hargreaves is a general paediatrician with expertise in epileptic disorders. He provided clinical advice about epilepsy amongst children and NHS services.
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input
Caroline Farmer	Project lead, critical appraisal of the company submission, writing and editorial input

Table of Contents

List of key issues

List of tables

List of Figures

Abbreviations

A&E	Accident and emergency
ADAMS	Anxiety, depression and mood scales
AE	Adverse event
ASMs	Anti-seizure medications
CDD	CDKL5 deficiency disorder
CDKL5	Cyclin-depended Kinase-like 5
CEAC	Cost-effectiveness acceptability curve
CGI	Clinical Global impressions
CGI-CSID	CGI of change in seizure intensity, duration and severity
CI	Confidence interval
CS	Company submission
CSHQ	Childrens sleep habit questionnaire
CSR	Clinical Study Report
CVI	Cortical Visual Impairment
DS	Dravet syndrome
DSU	Decision Support Unit
EAG	External Assessment Group
ECM	Established clinical management
EQ-5D	EuroQol five dimension
FS	Focal Seizures
GNX	Ganaxolone
GP	General practitioner
HL	Hodges-Lehmann
HRQoL	Health-related quality of life
HSUV	Health State utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IRQ	Inter Quartile Range
ITT	Intention-to-treat
KOL	Key opinion leader
LGS	Lennox-Gastaut Syndrome
MECP2	methly-CpG-binding protein 2
MHRA	Medicines and Healthcare products Regulatory Agency
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OLE	Open label extension
ONS	Office of National Statistics

A&E	Accident and emergency
OR	Odds Ratio
OWSA	One-way sensitivity analysis
PBO	Placebo
PCSF	Percentage change in 28 day seizure frequency
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QA	Quality assessment
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SF	Seizure frequency
SFD	Seizure-free days
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised Mortality Ratio
SUDEP	Sudden Death From Epilepsy
TA	Technology Appraisal
TEAE	Treatment emergent adverse events
USD	United States Dollar
VNS	Vagus Nerve simulation
VS	Versus
WTP	Willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on other issues identified by the EAG are in the main report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

Broadly speaking the key clinical issues related to the extent of a long-term treatment effect in the open-label extension of the pivotal trial.

In terms of cost effectiveness issues, the EAG noted several key issues. These have varying impacts on the cost-effectiveness of ganaxolone (GNX), though generally increase the ICER.

Table 1: Summary of key issues

ID	Summary of issues	Report section(s)
Long-term treatment effect	The EAG identified quality concerns with the OLE of Marigold, which increase uncertainty in the trial results beyond the double-blind period (>17 weeks). The concerns include a high rate of attrition that is associated with treatment outcome, and the risk that some reductions in SF may be driven by regression towards the mean.	3.2.2.5 and 4.2.6.1
Model structure	The company used a simple model structure, which limits its ability to represent the condition and likely treatment pathway. The potential impact of this on the results was unclear.	4.2.2
Seizure frequency	The company's model structure imposed many assumptions on the distribution and behaviour of seizure frequency, as	4.2.6.1

ID	Summary of issues	Report section(s)
	well as the effect of GNX. The net effect of these was likely to be an optimistic estimate of the clinical benefit of GNX.	
Consistency of disease proxies throughout the model	The company's base-case model used different diseases to proxy CDD mortality and healthcare resource use compared to patient HRQoL, creating inconsistency. Using the same disease to inform all of these considerably worsened the cost-effectiveness of GNX	4.2.7 and 4.2.8
Modelling errors	Correcting the errors in the company cost effectiveness model had a considerable impact on the ICER.	6.1.1; 6.1.2; 6.1.3; 6.1.4; 6.1.5; 6.1.6; and 6.1.7
Disease severity modifier and caregivers	The company base case included a severity multiplier of 1.7 for both incremental patient and caregiver QALYs. The NICE methods guidance is unclear about whether a severity multiplier should be applied to caregiver QALYs, though the EAG were of the view that this was not appropriate.	6.2.4.2

Abbreviations: CDD, CDKL5 deficiency disorder; EAG, external assessment group; GNX, ganaxolone; HRQoL, health-related quality of life; ICER, incremental cost effectiveness ratio; OLE, open-label extension; QALY, quality-adjusted life-year; SF, seizure frequency

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Discontinuation rate	This was calculated based on the number of participants and the number of discontinuations at the end of the Marigold OLE	This was calculated based on the exposure time in Marigold (i.e., time at risk of discontinuation) and the number of discontinuations	4.2.6.2 and 6.2.1
Health-related quality of life	Lo *et al.* vignette based on people with TSC	Auvin *et al.* based on people with LGS, which was consistent with inputs for HCRU and mortality	4.2.7; 4.2.8; 4.2.6.3; and 6.2.4
Dynamics of the treatment effect	The treatment effect from the end of the double-blind period of Marigold (17 weeks) applied from baseline with no transition or accumulation over time	The treatment effect was linearly interpolated based on half-cycle corrected data from the double-blind period of Marigold week 0-4 (titration period) and week 4-17 (maintenance period)	4.2.6.1 and 6.2.5
Cost of hospitalisation	Long-stay cost used based on Mangatt *et al.*	Short-stay cost based on the short average length of stay reported in Chin *et al.*	4.2.8

	Company's preferred assumption	EAG preferred assumption	Report Sections
Wastage	No wastage	10% wastage based on clinical expert advice	6.2.6
Severity modification for caregivers	Severity modifier applied to caregiver utilities, based on the QALY shortfall in patients (i.e., not based on caregiver QALY shortfall)	The EAG interpreted the NICE methods guide to exclude caregivers from disease severity modification. However, as this was unclear, this report presents the EAG preferred base case both with and without the severity modifier applied to caregivers	6.2.4.2

Abbreviations: EAG, external assessment group; HCRU, health care resource utilisation; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; QALY, quality-adjusted life-year; TSC, Tuberous Sclerosis Complex

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length of life (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by reducing the frequency of seizures experienced by patients. Given improvements in seizure frequency are associated with improved health-related quality of life, GNX is modelled to generate more QALYs compared to established clinical management.

Overall, the technology is modelled to increase costs due to the cost of GNX for as long as patients are assumed to remain on treatment (in addition to the costs of established clinical management), and leads to a reduction in costs associated with hospitalisation and the use of rescue medications.

The modelling assumptions that have the greatest effect on the ICER are:

- Assumptions affecting seizure frequency, and the ability of GNX to affect it
- Selection of an appropriate source for utility data, and the implementation of the data
- The baseline age of the cohort at initiation of GNX
- Assumptions relating to the average length of stay for epilepsy-related hospitalisations

1.3. The decision problem: summary of the EAG's key issues

The EAG did not identify any key issues with regard to the decision problem for this appraisal.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

Key Issue 1: Uncertainty surrounding clinical effects in the Marigold OLE

Report sections	**3.2.2.5 and 4.2.6.1**
Description of issue and why the EAG has identified it as important	The company argued that there was evidence of a sustained treatment effect of GNX in the Marigold OLE, however the EAG had concerns about the interpretation of these data. **1. Regression to the mean** Clinical experts to the EAG advised that people with CDD may initiate treatment for seizures following an exacerbation in seizure frequency. One expert described this as applicable to clinical trials also and would be like starting treatment at "the crest of a wave" of seizures. If this was the case, then a natural decline in seizure frequency would occur during trial follow-up, known as a 'regression towards the mean'. During the double-blind phase of Marigold, a significant minority of people in both treatment arms experienced reductions in seizure frequency, and it was unclear how many of these would have occurred naturally. However, relative effect sizes are able to generate an estimate of whether GNX delivered a benefit over and above ECM. In the OLE, however, there was no comparator arm, and it was therefore unclear to what extent reductions in seizure frequency were related to treatment. **2. Missingness due to treatment outcome** Participants receiving GNX in the double-blind phase of Marigold were permitted to discontinue treatment and not enter the OLE, and all participants in the Marigold OLE were permitted to discontinue at any time. Approximately 40% of participants receiving GNX withdrew from the trial before the latest data cut of the OLE, some of whom withdrew due to a lack of efficacy and some who withdrew for ambiguous reasons that the EAG considered could have been influenced by treatment efficacy (e.g. 'clinician decision'). The withdrawal of participants with a poor treatment response could cause an artificial drop in seizure frequency at follow-up timepoints.
What alternative approach has the EAG suggested?	It was not possible for the EAG to resolve this issue within its appraisal using the available data. Overall, the EAG considered the data from the double-blind phase of Marigold to be the highest quality data for decision-making, and that data from the OLE should be interpreted with extreme caution.
What is the expected effect on the cost-effectiveness estimates?	There was uncertainty surrounding the effect of GNX beyond the 17-week treatment period of the double-blind phase of Marigold, which had implications for modelling the long-term treatment effect within the lifetime horizon of the company model.
What additional evidence or analyses	There was limited information in the CS on the way in which participants in Marigold were recruited, though it is known that inclusion criteria included >16 major motor seizures per 28 days in a historical period. To assess the

Report sections	3.2.2.5 and 4.2.6.1
might help to resolve this key issue?	plausibility of a regression to the mean phenomenon: further trial details that indicate whether or not trial participants were more likely to be recruited when SF was intense; and longer term (>17 weeks) evidence (e.g. RWE or related disease) about stability/constancy of SF rates. Further data cuts from the Marigold OLE are expected (latest data cut to inform the CS was [redacted]). It would also be preferable to correct bias in the submitted SF analysis in the OLE phase using a missing data analysis which estimates SF for the full trial cohorts (i.e., analyses SF for all patients, including withdrawals).

Abbreviations: CDD, CDKL5 deficiency disorder; CS, company submission; EAG, External Assessment Group; GNX, ganaxolone; SF, seizure frequency; OLE, open-label extension; RWE, Real World Evidence

1.5. The cost effectiveness evidence: summary of the EAG's key issues

Key Issue 2: Model structure

Report sections	4.2.2
Description of issue and why the EAG has identified it as important	The company model was a simple Markov state- transition model with two primary health states (alive and dead) which may not have captured the full impact of the disease or treatment pathway, and may be considered atypical for NICE technology appraisals of genetic epileptic syndromes.
What alternative approach has the EAG suggested?	In its appraisal, the EAG suggested some alternative model structures which could (theoretically) be considered, though it is beyond the remit of the EAG to develop these further (and not possible with data the EAG was able to access).
What is the expected effect on the cost-effectiveness estimates?	The impact on the cost-effectiveness estimates was unclear.
What additional evidence or analyses might help to resolve this key issue?	Beyond re-developing the cost-effectiveness model using alternative structures, no additional analyses would help resolve this issue. However, provision of further justification for the choice of model structure (and dismissal of alternatives) may increase confidence in the structure chosen.

Abbreviations: EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence.

Key Issue 3: Application of seizure frequency

Report sections	4.2.6, 6.1, and 6.2.5
Description of issue and why the EAG has identified it as important	The company's overall approach to capturing SF for both treatment arms incorporated a large number of assumptions which had a considerable impact on cost-effectiveness results. For example, only primary seizures were considered in the base case model, while secondary and tertiary seizures were omitted. The company also assumed that the distribution of SF observed in the Marigold trial was representative of UK clinical practice, could best be represented with a lognormal distribution and would not change over time. The company assumed that treatment effects were instantaneous and maintained provided the patient remains on treatment, reverting to baseline immediately after discontinuation of treatment. They also assumed it was appropriate to apply a HL shift directly to distributional

Report sections	4.2.6, 6.1, and 6.2.5
	parameters to model the treatment effect, and that treatment did not impact seizure type or severity. Further, the EAG identified an error in the application of the treatment effect in that the treatment effect of GNX was applied as a percentage reduction directly to the mean [redacted] distribution fit, which was a mathematical error due to it violating the product rule of logarithms.
What alternative approach has the EAG suggested?	The EAG disagreed that only primary seizures were relevant to the decision problem. Some data suggested that the treatment effect of GNX may differ by seizure type and incorporating all seizure types may have therefore better reflected the scope of the appraisal. However, given that different types of seizure may be associated with different costs and utilities, the scenario analysis considering 'all seizures' may be considered conservative. The EAG implemented a ''fix' for the application error within its base-case analysis and explored a number of other scenarios related to the application of treatment effect, including interpolation of the effect to account for time-varying treatment effects within the observed period (per Marigold evidence at 4 and 17 weeks).
What is the expected effect on the cost-effectiveness estimates?	The ICER increased substantially when addressing this error in application, and again when interpolating the treatment effect. The ICER fell slightly when using the maintenance period efficacy for interpolation between weeks 4 and 17.
What additional evidence or analyses might help to resolve this key issue?	No further evidence needed for implementation errors. However, statistical analysis of the GNX/GNX cohort in the Marigold OLE could provide more up to date data with longer follow-up on GNX treated patients (acknowledging the need to address Key Issue 1). Clinical opinion may also help to resolve uncertainty relating to the generalisability of SF observed in the Marigold trial to UK clinical practice.

Abbreviations: EAG, External Assessment Group; GNX, ganaxolone; HL, Hodges-Lehmann; ICER, incremental cost-effectiveness ratio; SF, seizure frequency

Key Issue 4: Utility values

Report sections	4.2.7
Description of issue and why the EAG has identified it as important	The utility values used to populate the model were taken from published vignette studies and were subject to limitations. As there was no survival benefit associated with GNX, the utility values were important drivers of the cost-effectiveness results, applying to both patients and caregivers.
What alternative approach has the EAG suggested?	The EAG preferred the utility values reported by Auvin *et al.* as these were more granular with respect to SF and were based on the same proxy condition used for both medical resource use frequencies and mortality (LGS). [redacted]

Report sections	4.2.7
What is the expected effect on the cost-effectiveness estimates?	Depending on the choices made to populate the model, the cost-effectiveness results may improve or worsen. Implications are presented in Section 6.2 of this report. In the EAG's base-case analysis (Auvin *et al.,* correcting the implementation of these utilities to absolute values), the ICER is increased substantially – see Section 6.3.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion may be sought on the applicability of different proxy conditions, and whether the source condition should be consistent for resource use, mortality, and HRQoL

Abbreviations: CDD, CDKL5 deficiency disorder; EAG, External Assessment Group; GNX, ganaxolone; HL, Hodges-Lehmann; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; LGS, Lennox-Gastaut syndrome; SF, seizure frequency.

Key Issue 5: Miscellaneous model errors and unsubstantiated assumptions

Report sections	4.2.6, 4.2.8, 6.1, 6.2.6
Description of issue and why the EAG has identified it as important	The company model contained numerous errors. The errors with the largest impact on the ICER were: the incorrect application of the HL shift estimate to model treatment effect on SF distribution; not implementing age adjustment for caregivers (assuming them to be ageless); truncation of the SF distribution at 400 seizures; correction to incorrect age adjustment of patients; and correction of rescue medication cost estimates. In addition, the company's implementation of one-way sensitivity analyses was incorrect and the calculation of probabilistic ICERs, leading to an underestimation of the impact of individual parameter uncertainty on modelled outcomes. Key unsubstantiated assumptions included the instantaneous and infinitely durable nature of the treatment effect, a lack of any wastage of GNX.
What alternative approach has the EAG suggested?	The EAG corrected the objective errors in the modelling, and presented a base-case without the unsubstantiated assumptions made by the company
What is the expected effect on the cost-effectiveness estimates?	The EAG corrected company base case ICER was substantially higher than the company's base-case ICER. The EAG preferred base-case ICER was substantially higher than the willingness to pay threshold.
What additional evidence or analyses might help to resolve this key issue?	The EAG resolved a number of errors in the company model. To validate assumptions in the model with a large impact on the ICER, longer-term follow up data on the efficacy of GNX would be required.

Abbreviations: EAG, External Assessment Group; GNX, ganaxolone; ICER, incremental cost-effectiveness ratio; LGS, Lennox-Gastaut Syndrome; SF, seizure frequency.

1.6. Other key issues: summary of the EAG's views

Key Issue 6: Application of severity modifier

Report sections	6.2.4.2
Description of issue and why the EAG has identified it as important	The company applied a severity multiplier of 1.7 for both incremental caregiver and patient QALYs. The NICE methods guidance describes the severity modification applying to those "living with the disease", and the EAG was uncertain if this was also intended to applicable to caregivers.
What alternative approach has the EAG suggested?	The EAG explored scenarios with and without the severity modifier applied to caregiver QALYs.
What is the expected effect on the cost-effectiveness estimates?	The choice of severity modifier has a meaningful impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Not applicable.

Abbreviations: EAG, External Assessment Group; QALY, quality-adjusted life year(s).

1.7. Summary of EAG's preferred assumptions and resulting ICER

The EAG generated a base-case ICER of [redacted] with the implementation of the severity modifier for caregivers, and [redacted] without.

Table 3: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case	[redacted]	[redacted]	£22,200
Correction 1: Incorrectly implemented treatment effect	[redacted]	[redacted]	[redacted]
Correction 2: Implementation of Lo *et al.* utilities	[redacted]	[redacted]	[redacted]
Correction 3: Age adjustment for caregivers	[redacted]	[redacted]	[redacted]
Correction 4: SMR based on wrong values from Chin et al	[redacted]	[redacted]	[redacted]
Correction 5: Using EAG AUC function and increasing SF upper limit to 1000	[redacted]	[redacted]	[redacted]
Correction 6: Age adjust patients	[redacted]	[redacted]	[redacted]
Correction 7: Rescue medication	[redacted]	[redacted]	[redacted]
EAG corrected company base case	[redacted]	[redacted]	[redacted]
EAG 1: Discontinuation rate based on exposure time in Marigold study	[redacted]	[redacted]	[redacted]

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
EAG 2: Use of the Marigold maintenance HL	[redacted]	[redacted]	[redacted]
EAG 3: Use of Auvin *et al.* (with absolute values and caregiver utilities) (Key issue 4)	[redacted]	[redacted]	[redacted]
EAG 4: Interpolation of the treatment effect (Key issues 2 & 3)	[redacted]	[redacted]	[redacted]
EAG 5: Including 10% wastage	[redacted]	[redacted]	[redacted]
EAG 6: Hospitalisation short stay based on Chin *et al.*	[redacted]	[redacted]	[redacted]
EAG 7: Severity modifier applied to patients only (Key issue 6)	[redacted]	[redacted]	[redacted]
EAG's preferred base case (Caregiver severity 1.7x)	[redacted]	[redacted]	[redacted]
EAG's preferred base case (Caregiver severity 1x)	[redacted]	[redacted]	£868,980 (+£846,780)

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by Marinus Pharmaceuticals for an appraisal of ganaxolone (GNX) for the treatment of seizures in people with Cyclin-depended Kinase-like 5 (CDKL5) Deficiency Disorder (CDD).

2.2. Critique of the company's description of the underlying health problem

The company provided an overview of the burden of CDD in the target population in section B.1.2 and B.1.3 of the CS.

The CDKL5 gene, found on the X chromosome, encodes a protein responsible for normal brain function.[1] Estimated incidence is one in 40,000-60,000 live births, with a ratio of 1:4 males to females.[2] Though occurrence is more common in females, males commonly experience higher seizure frequency and increased brain atrophy.[3] A deficiency in the CDKL5 genes causes early onset seizures and developmental arrest.[4] Other symptoms include hypotonia, cortical visual impairments (CVI), sleep and gastrointestinal disturbance and autonomic dysfunction. Until recently (2005), CDD was considered to be a variant of Rett Syndrome, a neurological disorder resulting in similar symptoms.[5] However, those subsequently identified as having CDD were more severely affected and had a younger onset of seizures.

People with CDD experience a 90% onset of disease by the age of three months, and after a brief 'honeymoon' period where seizures temporarily remit, most people with CDD experience frequent seizures throughout their lives. Fehr et al (2016) reported that fewer than half of CDD patients experience a seizure free period of more than two months.[6] The most common seizure types experienced by people with CDD are epileptic spasms and tonic seizures, which are often clustered together. Many people with CDD are prescribed multiple anti-seizure medications (ASMs). However, polypharmacy has been identified as a risk of patients' wellbeing and is associated with an increased risk of adverse events.

People with CDD experience severe impairments to everyday functioning, and fewer than a quarter of people are able to walk independently or verbally communicate.[7] Clinical advice to the EAG was that it was difficult to determine if impairments experienced by people with CDD are caused by their development disorder, epilepsy, or other mechanisms of the condition.

However, seizures may cause harm to the brain and impair functioning ability and increase risk of sudden death from epilepsy (SUDEP).

Due to the severity of the condition, caregiver burden is very high. Mean mental health scores on the SF-12 were lower for CDD caregivers than the general population.Among CDD caregivers, those with children with gastrostomy feeding had better mental health scores but lower physical health scores. [8] Additionally, emotional wellbeing was significantly worse than for caregivers for children with Rett or Down's Syndrome. [9]

The EAG noted that the company provided an accurate summary of evidence on CDD and disease burden. The EAG considered the level of functional impairment to be a major driver of health-related quality of life (HRQoL). Clinical advice to the EAG highlighted that seizures vary in severity, meaning seizure frequency alone may not be a reliable marker or HRQoL. The company's description of CDD stages were reflective of the high level of uncertainty of CDD. Notably, due to the recent disease classification, there is no long-term natural history data showing the course of the disease and typical life expectancy of those with CDD. The EAG considered the company's description of the comorbidities well researched and to incorporate relevant evidence. There was less evidence presented on the impact of CDD on the mental health of people and their caregivers, which are likely to be significant.

2.3. Critique of the company's overview of current service provision

The company provided an overview of the current treatment options for people with CDD and the proposed treatment pathway with ganaxolone (GNX) in Section B.1.3.3 of the CS (Document B).

While NICE guidelines exist for epilepsies [NG217], including genetic epilepsies in children, there are no existing guidelines specifically for CDD. Currently, there is no curative treatment for CDD, relying on broad ASMs. CDD is classed as a drug-resistant epilepsy, which is defined by not achieving seizure control after two or more anti-seizure medications. [10]

Prior to a CDD diagnosis, children exhibiting seizures are treated with steroid medication. Diagnosis may take some months, after which treatment would switch to more specific ASMs. The median number of ASMs prescribed was six (0-33) across a person's lifetime, [11] more frequently levetiracetam, topiramate, clobazam and phenobarbital. NICE currently recommends the use of sodium valproate as a first line therapy for tonic and tonic-clonic seizures in those unlikely to have children in the future, followed by lamotrigine or levetiracetam, but the

prescription of lamotrigine in children under 13 was off-label. Due to the relatively new distinction of CDD from Rett syndrome, there is a lack of evidence on the impact and efficacy of ASMs.

A recent longitudinal study showed that around a quarter (82/312, 26%) of people with CDD reported cannabinoid use to aid seizure control, with around two-thirds reporting improvements in seizure control. [12] Caregivers also reported benefits of cannabinoid for cognition, sleep and mood, with most patients reporting no adverse effects, although the evidence from cannabinoid use for epileptic syndromes is uncertain. Currently, the NHS prescribes epidiolex, a highly purified CBD, for Lennox-Gastaut syndrome (LGS) (TA615) and Dravet Syndrome (DS) (TA614), both rare and severe forms of epilepsy. As some people with CDD are also diagnosed with LGS, this means that they would be eligible to receive epidiolex. Some people with CDD follow a ketogenic diet to aid seizure control, though evidence for the efficacy of this is also uncertain. Vagus nerve simulation (VNS) delivers electrical pulses to the vagus nerve and is an accepted form of treatment for refractory epilepsy. In a CDD specific study, two thirds of patients experienced an improvement in seizure activity. [13] Alternatively, surgical treatments for seizure control may also be used, with a significant, but short-lasting impact. Other symptoms of CDD are managed using treatments such as serotonin for sleep disturbances, or for patients with feeding difficulties, a gastrostomy tube may be used.

The EAG generally agreed with the company's description of current service provision for CDD. However, the EAG were unclear about whether GNX would be used as a first line treatment, or whether clinicians may only prescribe GNX if people had not responded to other treatments. The EAG were also unclear about the anticipated duration of treatment with GNX, for example whether a minimum treatment period is needed to determine if there will be a response, and whether those showing a response would be expected to receive the treatment for life. Clinical experts advised that any clinical response should be evident by 6 months, at which point, non-responders should be withdrawn. The EAG were concerned that this would not be the case if other treatment options were also not considered effective, increasing the risks associated with polypharmacy, but considered that due to safety and impact of HRQoL, withdrawal would typically occur for most non-responders.

2.4. Critique of company's definition of decision problem

The company statement regarding the decision problem was presented in Section 1 of the CS (Document B). The company position and the EAG response is provided in Table 4 below.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People 2 years of age or older with seizures caused by CDD	As per the scope	NA	The EAG agreed that the evidence submitted by the company was consistent with the NICE decision problem.
Intervention	Ganaxolone (ZTALMY®)	As per the scope	NA	The EAG agreed that the evidence submitted by the company was consistent with the NICE decision problem.
Comparator(s)	Established clinical management (ECM) without ganaxolone	Established clinical management, although restrictions were placed on use of cannabidiol.	NA	The EAG considered the decision problem submitted by the company was consistent with the NICE scope. ECM was considered to consist of ASMs and steroids as well as non-pharmacological treatments such as a ketogenic and vagus nerve stimulation. The EAG agreed with the company's descriptions of established clinical management, but highlighted the exclusion of cannabidiol, with the exception of epidiolex during the trial, which may not reflect real world use. However, did not consider this would have a major impact on trial findings.
Outcomes	The outcome measures to be considered include: • Seizure frequency (overall and by seizure type)	The clinical evidence was consistent with the NICE scope, though the company's economic model did not consider seizure severity or differences in adverse events	The company stated that there are no reliable methods for estimating the severity of seizures, and therefore this was not considered in the model.	The EAG agreed that the evidence submitted by the company was consistent with the NICE decision problem. However, the EAG noted that the use of seizure frequency as a primary outcome measure may not be entirely representative of disease severity, as advice from clinical experts suggested that impacts from seizures

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Proportion of people seizure-free (overall and by seizure type) • Seizure severity • Adverse effects of treatment • Health-related quality of life	between GNX and ECM.		are heterogeneous. The EAG agreed with the company that there are no reliable measures of the severity of seizures, though noted that this limits consideration of the potential effect of GNX. The company reported comparable rates of treatment-emergent adverse events between GNX and ECM in Marigold, and therefore assumed that the impact of AEs was equivalent in the model. However, the EAG noted that rates of drug-related AEs were higher in the GNX arm. There was no clear evidence that treatment with GNX increases the risk if AEs with significant resource implications, and so the EAG did not consider that differences in this assumption would have a major effect on the ICER.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the	No costs for genetic testing were included	The company analysis was consistent with the NICE reference case. The company stated that all people with CDD would receive a genetic test prior to starting ganaxolone, and therefore the availability of ganaxolone would not lead to a change in testing costs. However, the company	The EAG agreed with the company's rationale with respect to the testing costs, as CDD diagnosis was only able to be confirmed after genetic testing. The EAG understood that genetic testing for CDD is likely to have already occurred before ganaxolone is a administered. The EAG noted that the time horizon in the model was updated to 100 years at clarification from the original 75 years. This implied that people with CDD were able to exceed a life expectancy of 100 years, considering the mean starting age in the model is [redacted]. Despite

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The economic modelling should include the costs associated with diagnostic testing for CDKL5 gene mutations in people with CDD who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		also acknowledged that there are adults with CDD who have not received a genetic test and would not be likely to receive one in current practice.	the lack of long-term survival data in CDD, clinical advice to the EAG was that this was highly unlikely. Additionally, when considering a life-time horizon, the assumptions around the baseline age of caregivers became highly uncertain.
Subgroups	NA	NA	NA	NA
Special considerations including issues related to equity or equality	NA	NA	NA	NA

Abbreviations EAG, Evidence Assessment Group; NA, not applicable; NICE, National Institute for Health and Care Excellence

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify evidence for the clinical effectiveness of GNX. A single search was conducted to identify relevant evidence, along with all evidence required to inform the company's economic model (see Section 4.1). The EAG assessment of the company's SLR for clinical effectiveness is presented in Table 5.

Table 5: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	B.2.1. Appendix D	Acceptable. The company searched a combination of bibliographic databases, conference websites, clinical trials registries, websites of relevant organisations, google scholar, and review of reference lists of relevant studies. The strategy used appeared appropriate, although the terms used to conduct supplementary searches were not reported in the CS. At clarification (question A1), the company submitted the terms used to search one such resource, which were appropriate and provided reassurance that other sources were appropriately searched.
Inclusion criteria	B.2.1	Excellent. A comprehensive SLR was conducted to identify evidence for the CS.
Screening	Appendix D	Excellent. Double screening with involvement of a third reviewer was used to select relevant publications at all screening levels.
Data extraction	Appendix D	Acceptable. A single reviewer conducted data extraction with review by a senior reviewer and involvement of a third reviewer where required.
Tool for quality assessment of included study or studies	Appendix D	Poor. The NICE checklist for comparative trials was used for the Marigold double-blind phase, which was acceptable. However, only the minimum criteria were evaluated, and no account was made of variation in bias across outcomes (for example, where outcomes showed differences at baseline or were susceptible to measurement issues). The same checklist was used for the Marigold OLE and Phase IIa trial, which was not appropriate. This approach does not consider the risks relevant to trials without a control group and where group allocation is not random.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Evidence synthesis	NA	No evidence synthesis was conducted by the company, which was considered appropriate.

Abbreviations: CS, Company submission; EAG, External Assessment Group; OLE, open-label extension; SLR, systematic literature review.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS described two studies (shown in Table 6), including one double-blind randomised-controlled trial (RCT; Marigold) with an open label single arm extension (Marigold OLE), and a small phase IIa single-arm study with an extension for those who showed a response to treatment (Study 1042-0900). The latter study was small (n=7 and n=4 in the extension period) and was used by the company as supporting evidence for the RCT only.

The EAG identified a further double-blind, placebo-controlled trial to evaluate GNX for treating seizures in infants with CDD (aged 6-months to 2 years), though this trial had yet to begin recruiting (final data cut estimated December 2024; NCT05249556) and was not considered further in the appraisal.

Table 6: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
Marigold (1042-CDD-3001) [14,15] NCT03572933	Double-blind RCT with 17-weeks follow-up	People aged 2 – 19 years with CDD and ≥16 major motor seizures per 28 days (N=101)	GNX + ECM. Titration period = 4 weeks, full dose = 13 weeks	ECM	Clinical efficacy and safety
Marigold OLE NCT03572933	Single-arm extension to Marigold with further follow-up available in the CS (February 2021) and in the company's clarification response (June 2021). Study ongoing and expected to complete data collection in December 2022, with data available in Q1/2023	All those completing Marigold and still meeting eligibility criteria	GNX + ECM. Titration period for people receiving placebo during Marigold = 4 weeks	NA	Long-term clinical effectiveness and safety
Phase IIa study (1042-0900) NCT02358538	Open-label, single arm proof-of-concept study with 26-weeks follow-up	People with rare genetic epilepsies, including PCDH19 (n=11), LGS (n=7), continuous spikes in slow wave (n=2), and CDD (n=7)	GNX + ECM.	NA	Clinical effectiveness and safety
Phase IIa study extension (1042-0900) NCT02358538	Extension period with 52-weeks follow-up	Participants in the initial Phase IIa follow-up who attended all study visits and showed a ≥35% improvement in mean seizure	GNX + ECM.	NA	Clinical effectiveness and safety

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
		frequency. Participants with CDD n=4.			

Abbreviations: CDD, CDKL5 deficiency disorder; ECM, established clinical management; GNX, ganaxolone; LGS, lennox-gastaut syndrome; NA, not applicable; OLE, open-label extension; PCDH19, Protocadherin 19; RCT, randomised controlled trial

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The pivotal study for GNX in this indication was the Marigold RCT and its OLE. The availability of a high-quality RCT in such a rare disease area was notable, and the EAG considered that the follow-up (17-weeks plus data of at least 1 year in the latest data cut of the OLE) would be sufficient to determine whether treatment with GNX was effective for reducing seizures as compared to existing treatments, which typically lose their effect after 3-months. The latest available data cut for the Marigold OLE provided in the CS was 24th February 2021, though at clarification the company provided evidence for a subsequent data cut-off of [redacted]. Only a subset of outcomes were presented at this later data cut-off and, given the timeline, the EAG was unclear why these were not provided with the original CS. At clarification (QA10), the company stated that data for a cut-off in [redacted] would be available by [redacted].

An overview of the Marigold trial design was shown in Figure 6 in the CS (p.38). An 8-week period was used to collect data on seizure frequency used to determine participant eligibility for the trial (see Section 3.2.2.2), after which the double-blind phase began with a 6-week 'baseline' period for the collection of seizure frequency data to be used as baseline measures. Following the baseline phase, participants allocated to GNX entered a 4-week period in which GNX was titrated to reach the target dose that they received for a further 13-weeks. Primary analyses for Marigold were based on the full 17-week period incorporating both the titration and target dose trial periods, though sensitivity analyses were also conducted restricted to the period when participants were receiving the full target dose. In the OLE, participants allocated to placebo in Marigold were unblinded and switched to GNX. As with the original Marigold trial, GNX was titrated to the full target dose over a 4-week period.

The EAG considered the initial phase of the Phase IIa as supporting evidence for Marigold, though due to the small sample size, it agreed with the company that the data was limited for the purposes of decision-making. The EAG considered that the extension period of the Phase IIa study was not suitable for evaluating the clinical effectiveness and safety of GNX, due to the risk that the eligibility criteria excluded those with poor efficacy or safety data, and that this would have a notable effect amongst a small sample.

3.2.2.2. Population

Study eligibility criteria

Eligibility criteria for the Marigold trial were provided in Table 9 of the CS (page 42).

Inclusion criteria for the trial included those aged 2 – 21 years. The lower age limit was considered appropriate and was in line with the NICE scope, though the EAG considered the upper age limit to be restrictive given that the NICE scope and company decision problem included people with CDD with no upper age limit. There is a great deal of uncertainty about the typical survival of people with CDD, owing to a lack of long-term data, though in the company's survival estimations, 65% of patients may survive to reach ~53 years old. The EAG considered it plausible that the effects of CDD on a person's life may worsen over time, as health may be impacted by the cumulative effect of neurodevelopmental impairment. Overall, despite the uncertainty surrounding survival, the EAG considered that the lack of data in those aged over 21 years presents uncertainty for the long-term outcomes of treatment.

The trial was restricted to people with CDD for whom ≥2 previous anti-seizure medications (ASMs) had failed to control their seizures, and thus GNX was evaluated as a third-plus line therapy. The anticipated marketing authorisation for GNX [redacted]. Clinical advice to the EAG was that those in the trial may have received ASMs both prior to and following a diagnosis of CDD. In practice, broad-spectrum ASMs are commonly used to treat seizures while awaiting a diagnosis of CDD, which may take several months. Following diagnosis, alternative ASMs would be used. If GNX became available in practice, the EAG was uncertain whether this would be used first line following a diagnosis of CDD, or whether people would only receive GNX following a failure to respond to other ASMs (as in the trial). The EAG understood that few people with CDD may achieve a satisfactory response to other ASMs, and therefore the trial population may nevertheless be comparable with a first line population in practice.

The inclusion criteria permitted participants to be receiving a stable regimen of up to four ASMs at baseline, not including non-pharmacological treatments. Polypharmacy for seizures in practice was common, and evidence suggests that people will CDD receive a lifetime average of six ASMs (range 0-18).[11] Clinical advice to the EAG was that people with CDD often receive between 2 – 4 ASMs concurrently, which was consistent with the trial participants. With regard

to seizures, participants were required to be experiencing ≥ 16 major motor seizures per 28-day period, as assessed over an 8-week period prior to the trial. The EAG were uncertain how representative this was of seizure frequency in the target population, though noted evidence that some people may experience fewer seizures that this. [6] In Key Issue 1, the EAG considered the possibility that the trials included people who were experiencing a temporary exacerbation in seizures, necessitating consideration of ASM. This issue is discussed further in Section 3.2.2.5.

The inclusion criteria for the phase IIa trial were not reported in the CS but were available to the EAG from the CSR[14] provided by the company. Compared to Marigold, the criteria required a [redacted] seizure frequency [redacted] trial CSR, p. 18). At clarification, the EAG requested a rationale for the change, but the company stated that they did not have access to this information. The company suggested that more restrictive criteria may have been used for a smaller trial that was to be used as exploratory and a proof-of-concept evaluation, which the EAG agreed was plausible despite the broader uncertainty.

Baseline characteristics

Participants in Marigold were most frequently from the United States (US; 41.6%), followed by Italy (14.9%) and Russia (13.9). Seven participants (6.9%) were from the UK. Overall, trial arms appeared comparable. The EAG identified baseline quality of life scores for Marigold from the trial CSR appendices (ref) provided by the company at clarification. These were comparable between arms and were also comparable to total scores reported in a published study using the same scale with a sample of people with CDD. [16] The EAG noted there to be a difference in the median percentage of seizure-free days (SFD) between trial arms, though no further differences in seizure-free outcomes were noted and as quality of life was also comparable, the EAG did not consider this to be a major concern. However, this was noted when considering findings for this outcome.

Baseline characteristics were considered to be representative of the likely population of people with CDD in the UK who would be eligible for GNX, though as discussed above, the EAG noted that no participants were treatment naïve.

Table 7: Baseline characteristics of participants in the included trials

	Marigold		Phase II
	Ganaxolone (N=50)	**Placebo (N=51)**	**Ganaxolone (N=7)**
Demographics			
Age, mean (SD)	6.8 (4.7)	7.7 (4.4)	[redacted]
Female sex, n (%)	39 (78%)	41 (80.4%)	6 (85.7%)
Weight, mean (SD)	[redacted]	[redacted]	-
Age at diagnosis	-	-	-
CDD recorded in participants' medical history at baseline, n (%)	[redacted]	[redacted]	-
Confirmed pathogenic CDKL5 variants identified at baseline, n (%)	[redacted]	[redacted]	-
Age at first seizure, median (range)	[redacted]	[redacted]	-
Measurements during the baseline period			
Total number of seizures per 28 days, median (range)	-	-	[redacted]
Number of bilateral tonic seizures per 28 days, median (range)	[redacted]	[redacted]	-
Number of people who exhibited bilateral tonic seizures, n (%)	[redacted]	[redacted]	-
Number of major motor seizures per 28 days, median (range)	54.0 [redacted]	49.2 [redacted]	-
Number of seizure-free days per 28 days, median (range)	[redacted]	[redacted]	[redacted]
Treatment history			
Use of ASMs at start of trial, n (%)	49 (98.0%)	48 (94.1%)	[redacted]

	Marigold		**Phase II**
	Ganaxolone (N=50)	**Placebo (N=51)**	**Ganaxolone (N=7)**
Use of non-pharmacological treatment for seizures at start of trial, n (%)	29 (58.0%)	26 (51.0%)	-
Number of previous ASMs, median (range)	7 (2 – 16)	7 (1 – 14)	-
Number of concurrent ASMs, mean (SD)	2.6 (1.39)	2.2 (1.14)	-

3.2.2.3. Intervention

The intervention for the included trials was GNX in combination with established clinical management (ECM), including adjunctive treatment with up to four ASMs.

In the Marigold trial, participants were treated with GNX as an oral suspension in accordance with the licensed dose in the US: 50mg/mL taken three times daily. [17] A weight-based method was used to titrate the dose in children weighing under 28kg, and a standard titration schedule was used for other participants. No information was provided in the CS about the tapering of treatment in the event of discontinuation, which was notable given that a steady reduction in ASM is needed to reduce the risk of a rebound in seizures following withdrawal. [17]

The majority of participants achieved the maximum dosage of GNX, though dose reductions due to adverse events (AEs) were needed in 22% (11/50) of those in the GNX arm and 23.5% (12/51) in the placebo arm. Participants in the GNX arm in the double-blind phase continued on their final dose throughout the OLE.

Mean (SD) treatment exposure length was 113.0 (23.32) days in the double-blind trial, and [redacted] days in the OLE (data cut-off February 2021). Adherence to the medication was moderately high: [redacted]% of participants in the GNX arm received treatment on 90% of the days in the double-blind phase.

The company prohibited the use of cannabidiol as an adjunctive treatment in the double-blind phase of Marigold unless participants had a stable, pre-existing prescription of epidiolex. Conversely, use of cannabidiol was permitted as an adjunct to GNX during the OLE. The EAG understood that the use of cannabidiol to control seizures was common for people with CDD, and that the exclusion of this as an option during the double-blind phase of the trial was excluding an established method of managing seizures. The EAG also considered that the variation in approach between the double-blind and OLE phases of Marigold was not substantiated. However, given the unregulated nature of cannabidiol that was not provided on prescription, the EAG did not consider it unreasonable to exclude this from the double-blind phase of the trial.

The CS also described that a small number of participants (10.9%) were following a ketogenic diet during the double-blind phase of Marigold to manage seizures. More than half of participants (58.0%) were also receiving other non-pharmacological therapies, such as physiotherapy, speech rehabilitation and occupational therapy.

3.2.2.4. Comparator

Only the Marigold double-blind phase involved a comparator to GNX, which was a placebo administered in addition to ECM including use of up to four concurrent ASMs. The placebo method used was also an oral suspension administered to the same schedule. A similar number of participants were following a ketogenic diet during the double-blind phase (13.7%) and were receiving non-pharmacological therapies (51.0%).

3.2.2.5. Outcomes

The outcomes reported in the included trials of GNX are summarised in Table 8, and the EAG provides an appraisal of the specific outcomes measured in the sections below. As discussed in Section 2.4, the EAG considered that the outcomes reported were consistent with the scope for this appraisal.

Outcomes measured included consideration of the impact of GNX on seizure outcomes and safety, as well as broader functional and HRQoL outcomes. With some exceptions, overall the EAG considered that detail about some clinical outcomes were limited both within the CS and the main report documents for the trial CSRs, so the EAG requested appendices to the trial CSRs during clarification (QC4), as these contained full data tables for measured outcomes. The company provided these for the Marigold trial but not the Phase IIa trial, and no trial CSR was provided for the Marigold OLE, which at clarification the company confirmed was because no such document exists. The CSR appendices for Marigold were provided later than the clarification response deadline, meaning that the EAG were unable to explore these in full detail, meaning that further relevant outcome data may have been measured.

Outcome reporting was most comprehensive for the Marigold double-blind phase. Very few outcomes were reported in the CS for the Phase IIa study, which the company explained was due to the small sample size of this trial and its lesser importance for informing the CS and economic model. Some outcomes were also not reported for the Marigold OLE. In the CS, data for the Marigold OLE was limited to the February 2021 data cut, though at clarification (QA12), the company provided additional data for a subset of clinical outcomes from the [redacted] data cut.

It was unclear whether the Marigold trial included sufficient follow-up to evaluate the full way in which treatment would be used in practice. The company did not specify the likely duration of treatment with GNX in clinical practice and no stopping rule was considered within the

company's economic model (Section 4.2.6.1). Clinical advice to the EAG was that people with CDD may be treated for a minimum of 6-months, at which point those not exhibiting a response would discontinue treatment. GNX may then be used up to a maximum of 2-years, at which point people may be discontinued to consider whether there was ongoing benefit. While the Marigold OLE provided some longer-term data that may be used to inform the use of a 2-year treatment period, the EAG identified concerns about the quality of these data for decision-making (see Key Issue 1, and Sections 3.2.2.5 and 3.2.2.6).

Table 8: Outcomes reported in the included trials

Outcome	Marigold	Marigold OLE	Phase IIa study	Phase IIa extension
Seizure outcomes				
Number of major motor seizures per 28 days	✓	✓	✓ (CSR)	✓ (CSR)
Number of other/all seizure types	✓	×	✓	✓
% of participants who experienced a response in major motor seizures	✓	✓	×	×
% of participants who experienced a response in all seizure types	✓	×	✓ (CSR)	✓ (CSR)
Number of seizure-free days	✓	✓	✓	✓
Duration of time seizure-free	✓ (CSR)	×	✓ (CSR)	✓ (CSR)
Proportion of people seizure-free	×	×	×	×
CGI-I parent report	✓	✓	✓	✓
CGI-I clinician report	✓	✓	✓	✓
CGI of change in seizure intensity, duration and severity (CGI-CSID)	✓	✓	×	×
Use of rescue medication	✓(CSR)	×	×	×
HRQoL and functioning				
QI-disability scale	✓	×	×	×
CGI of change in attention	✓	✓	×	×
Parenting stress	✓(CSR)	×	×	×
Children's sleep habit questionnaire (CSHQ)	✓(CSR)	×	×	×
Anxiety, depression and mood scales (ADAMS)	✓(CSR)	×	×	×
Safety				
Adverse events	✓	✓	✓ (CSR)	×

Seizure outcomes

Following infancy, people with CDD experience seizures that are both generalised (affecting both sides of the brain) and focal (affecting one side of the brain). People often experience a combination of difference seizure types, including generalised tonic, generalised clonic, absence, and drop seizures, and focal seizures that can cause a broad range of symptoms (depending on where in the brain the seizure occurs). It is typically challenging to measure the frequency and duration of seizures in everyday life as reliable, physiological measures of seizure activity can be invasive and/or are restricted to hospital settings. This would not be appropriate for trials of seizure treatments in CDD, where people typically experience seizures every day.

The EAG noted a number of concerns with the measurement of seizures within the trials of GNX. These issues were common across seizure research and did not represent a failing in the way that the trials were conducted or analysed. However, they nevertheless affected the reliability of the trial findings and their interpretation. A summary of the issues is shown in Table 9, with further discussion below.

Table 9: Measurement issues associated with seizure outcomes in the clinical trials

Measurement issue	EAG comment
Physiological measures that provide a more accurate method for assessing seizures would not have been appropriate for use in trials of GNX, and therefore seizure frequency was assessed using carer and clinician reported outcomes. The frequency of seizure outcomes and participants' use of rescue medication were assessed using daily electronic diary (e-diary) entries completed by caregivers	The EAG considered that these methods were the best available to the company for the trials, however there were several limitations to this approach: • These measures may be less reliable for certain types of seizures, e.g. absence, drop, and focal seizures may be less visible and/or noticeable to caregivers during their day-to-day activities. Measures of generalised clonic seizures may therefore be most reliably assessed using this method. • Self-report measures of count data can be burdensome for caregivers alongside their daily activities, which can sometimes lead to unreliable measurements if caregivers attempt to complete diary entries retrospectively. It is plausible that measurements become less accurate over time if caregivers struggle to manage the burden over the long-term. • Caregivers and clinicians may not be able to determine some changes in the effects of seizures, for example small changes in intensity or the presence of certain after-effects, particularly in context of the broader health issues experienced by people with CDD. • Subjective outcomes are vulnerable to bias within open-label designs, meaning that seizure outcomes during the Marigold OLE and the Phase IIa trial were more uncertain.
There were no definitive measures of seizure severity or duration. Carer and clinician perceptions of seizure intensity and duration were measured using the CGI-CSID	Clinical advice to the EAG was that severity includes consideration of the impact and duration of the seizure, as well as any after-effects (for example, fatigue over several days). The EAG considered that carer and clinician reports would not be able to accurately represent the full impacts of seizures on people with CDD, despite their knowledge and experience of participants. In particular, the EAG considered that small changes in severity may be challenging to detect against a complex condition with many impacts on people's health and function.
Some people may experience a sudden increase in seizures that occur very closely together, which is defined as a cluster. This is challenging to measure	Due to challenges in measuring cluster seizures, the company defined each cluster as one seizure. This was a simplistic approach that inevitably under-estimated seizure count.

Measurement issue	EAG comment
as there may be little break between individual seizures	
Some people with CDD may experience a steady rate of seizures, while in others, seizure frequency can vary naturally over time	There was limited evidence about the rate of change in seizure frequency over time and so the length of trial follow-up that would be needed to account for natural variation over time. The EAG was also aware of evidence that it is rare but possible for people with CDD to experience prolonged periods of time without seizures and that these may not be captured within the timeline of clinical trials.
People with CDD may receive new treatment for seizures following an increase in severity, which may also be true for the decision to enter a clinical trial. This means that seizure frequency in some people would be expected to regress naturally towards the mean over time.	There was limited information about the methods of recruitment used for the clinical trials, and whether longer treatment history was collected in addition to measuring seizure frequency during the 4-week baseline period. It is therefore unclear whether a proportion of the trial sample entered the trial during an exacerbation in seizures. The EAG were also unclear about the typical length of seizure exacerbations, and whether a regression to the mean would be discernible within the 17-week double-blind phase of Marigold. This issue is included in Key Issue 1.
People may experience exacerbations in seizure frequency following the withdrawal of a treatment, particularly if medications are withdrawn too quickly. [17]	There was limited information in the CS about the way GNX and other treatments were discontinued, and no outcome data were included for those who withdrew from treatment. If withdrawal from GNX was associated with an increase in seizure severity, this should be considered in clinical and cost effectiveness analyses.

The company took several steps to account for the subjective measurement of seizure frequency in the trials; for example, the first 17-week phase of Marigold was double-blind and in all studies they conducted quality checks on diary entries and removed data points that appeared erroneous. The company also conducted separate analyses according to different seizure types, including analyses limited to seizures they considered 'countable' (the latter were not reported in the CS, but were identified by the EAG from the trial CSR). While the EAG considered these steps to be appropriate, the EAG noted that these would not account for limitations in the measures. Firstly, blinding halted at the end of the double-blind phase of Marigold, at which point outcomes in the OLE would be subject to an increased risk of overestimating treatment effects (see Section 3.2.2.6). Secondly, quality checks on diary entry data are necessarily conservative (to avoid the deletion of valid data), and therefore do not resolve issues with the reliability of the data. Thirdly, while the exclusion of uncountable seizures increased the reliability of measurement, outcomes did not account for the full spectrum of seizures experienced by people with CDD. Finally, there were no steps open to the company to improve the accuracy and sensitivity of carer and clinician reported measures of seizure severity and duration, and changes in these outcomes may be undetected in the clinical trials.

The EAG identified the risk of a regression to the mean effect in the clinical trials as a key issue in this appraisal (Key Issue 1). Clinical advice to the EAG was that people with CDD may receive a new treatment for seizures following an increase in seizure severity, with one advisor describing seizures as being at a 'crest of a wave' at the start of clinical trials for ASMs in general. Inclusion criteria for the Marigold trial specified a requirement for >16 major motor seizures per 28 days in a historical period, though a longer treatment history for participants was not reported (and plausibly not measured). The EAG considered it to be plausible that some participants in the sample may experience improvements in SF due a regression towards the mean effect. During the double-blind phase of Marigold, any natural decline could be accounted for through relative comparisons between the two treatment arms (though absolute outcomes, including absolute thresholds for response, would incorporate any natural decline that occurred). However, once entering the OLE, there was no comparator arm, and therefore all outcomes may be affected by any regression to the mean effect. For this reason, the EAG was concerned about the validity of seizure frequency outcomes in the OLE and considered that this weakened the company's assertion of a sustained treatment effect for GNX. Finally, with regards the measurement of seizures, trials did not evaluate whether those withdrawn from

GNX experienced an exacerbation in seizure frequency, which is a common effect of withdrawal. The CS did not clearly describe the strategy used to withdraw GNX from participants who discontinued the trial (see Section 3.2.2.3), and therefore the EAG was unable to discuss with clinical advisors whether the approach was able to reduce the risk of exacerbation. The EAG considered it plausible that some participants may have experienced an exacerbation in SF following withdrawal, however without clinical data the EAG was unable to consider how this would affect the clinical and cost effectiveness of GNX.

The EAG identified two issues regarding the analysis of seizure outcomes in the Marigold OLE that affected the interpretation of the results. Firstly, the EAG were concerned with outcome data based on a pooled population of the two group (i.e. those on GNX throughout the double-blind and OLE phases [GNX/GNX] and those switched from placebo to GNX during the OLE [PBO/GNX], company to clarification question A12). The EAG viewed these data to be more uncertain that data presented separately for each group, given that variations in outcomes might be expected depending on whether GNX was received during the double-blind phase or the OLE. For example, changes in blinding, longer experience with outcome measures, different rules about permitted background care, and different rules concerning discontinuation from treatment may all influence treatment outcomes.

Secondly, a number of participants discontinued from Marigold either prior to or during the OLE. Of 101 patients randomised, 88 proceeded to the OLE, and 31 had discontinued at the data cut reported in the CS (doc B, Table 11). Of these 31, 12 (38.7%) withdrawals were reported as being due to ‘lack of efficacy', and the EAG considered it plausible that more ambiguous reasons for discontinuation (e.g. clinician judgement) may also have been informed by efficacy outcomes. The EAG therefore considered it plausible that participants who discontinued from the trial were experiencing higher SF, which lends further uncertainty to claims of a sustained treatment effect for GNX. The EAG considered it a major concern that the company did not conduct any analyses exploring the impact of missingness from OLE data. The EAG identified as a key issue for this appraisal (Key Issue 1).The EAG reviewed the analysis of seizure frequency conducted by the company, which calculated the percentage change in 28-day seizure frequency (PCSF) for an individual as (described in clarification question B2):

$$(f(t_1)_i - f(t_2)_i)/f(t_1)_i \times 100$$

where $f(t_1)_i$ was the 28-day seizure frequency for individual 'i' at baseline, and $f(t_2)_i$ was the same at the end of the 17 week double-blind period. The EAG noted that this approach can be seen as adjusting for baseline SF, which the EAG agreed was logical.

The company utilised the Hodges-Lehmann estimator of location shift in PCSF between the trial arms. This was a nonparametric estimator of the median difference robust to outliers, which the EAG believed was a judicious method considering the very wide variations in measured SF (see responses to clarification queries A8 and B8). However, as described in Section 4, issues arise when applying this estimate to model cost-effectiveness.

HRQoL and functioning

No HRQoL or functional outcomes were reported for the OLE of Marigold or the Phase IIa trial.

Participant quality of life was measured in Marigold using the QI-disability scale, which is a parent-completed measure of quality of life in children and adolescents with intellectual disability. The scale authors describe it as appropriate for use in both children and adults with CDD[18] and a published study has used QI-disability in a CDD population (ref). [16] The scale includes 32 questions across 6 domains: social interaction, physical health, independence, positive emotions, leisure and outdoors, and negative emotions. To the knowledge of the EAG, there was no validated threshold for a clinically meaningful change in QI-disability for people with CDD.

The company assessed several other measures in Marigold to explore whether treatment with GNX affected other outcomes important to the lives of people with CDD and their caregivers, including attention, sleep habits, mood and anxiety, and parenting stress. The EAG did not identify any additional outcomes that would have been relevant for inclusion.

Safety

The company assessed both drug-related and treatment-emergent adverse events in clinical trials of GNX. In response to a query from the EAG at clarification (QB27), the company stated that they considered the assessment for identifying drug-related AEs to be unreliable, due to the subjective assessment needed to determine if AEs were caused by the drug. To some extent the EAG agreed that there may not always be definitive evidence that AEs have been caused by the drug under evaluation, but noted that these judgements are made by experienced clinicians, and that this method is frequently used across clinical trials. The EAG considered that

inspection of both drug-related and treatment-emergent rates of AEs may be informative for evaluating the safety of treatments.

Overall, the EAG considered that measurement of AEs in clinical trials of GNX may be challenging due to the heterogenous nature and severity of the effects of CDD on the health and functioning of people with CDD. Moreover, GNX was delivered as an adjunctive to ECM, which included a range of permitted medications for seizures and other health concerns. In these circumstances, relative comparisons of AEs are the most reliable method for determining treatment safety. However, the EAG considered that the small sample size of the trials would increase uncertainty about these outcomes, particularly for AEs with low event rates.

3.2.2.6. Critical appraisal of the design of the studies

Critical appraisal checklists for Marigold, its OLE, and the Phase IIa trial were reported in the CS appendices (appendix D). The minimum criteria were evaluated within the checklists, and the company used only the checklist for randomised trials for all three assessments, rather than using a checklist for non-randomised/uncontrolled trials.

The EAG considered that the company's assessment of Marigold was acceptable, though it did not account for potential variation in bias across outcomes. Notably, the EAG considered that a difference in baseline in SFD between treatment arms would at minimum increase the risk of bias for this outcome. The company also did not comment on the potential risks of bias due to issues with outcome measurement (discussed in Section 3.2.2.5).

A similar number of participants in both arms opted to continue from the double-blind phase of Marigold into the OLE, though ≥10% of participants discontinued. Reasons for discontinuation were reported by the company in the CS and included reasons related to trial outcomes (i.e. safety and efficacy of treatment). This issue was not thoroughly assessed in the company's appraisal. Discontinuation during the OLE was assessed by the company as being non-problematic, even though further discontinuations were due to treatment outcomes, and declining sample size over time would have affected the robustness of data at follow-up. The EAG agreed with the company assessment that the lack of blinding in the OLE was a potential source of bias. All outcomes for this appraisal were subjective outcome measures, and therefore susceptible to bias in open-label designs. The EAG considered that pooling of data in the OLE of the GNX/GNX and PBO/GNX arms was particularly problematic, due to changes in the trial protocols between phases (e.g. on blinding, background treatment, and

discontinuation). The company stated that all outcomes measured in the trials were reported, though the EAG were not presented with some outcomes for the OLE that were measured, including quality of life and functional outcomes. Finally, the same measurement issues related to assessing seizures as apply to the double-blind phase of Marigold also applied to the OLE.

The Phase IIa trial was a very small, uncontrolled, open-label trial, which the EAG considered to be at a high risk of bias.

Overall, the EAG considered the double-blind phase of the Marigold trial to be the best quality evidence available for GNX in this indication. Risk of bias was generally considered to be low but the EAG considered that issues relevant to measuring seizure outcomes should be considered when interpreting outcomes. The EAG further considered there to be a number of quality issues with the Marigold OLE that should be considered when interpreting the results.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

Seizure outcomes

Double-blind phase (up to 17-weeks treatment)

During the double-blind phase of Marigold, there was a greater reduction in median major motor seizure frequency and all seizure frequency in the GNX arm compared to placebo (CS Doc B p. 56-57, 64). There were participants in both arms exhibiting reductions and increases in seizures over the course of the 17-weeks, though participants in the GNX arm were less likely to experience an increase and more likely to experience a decrease in seizures. Using the threshold of 50% reduction in seizures (a common threshold used to determine a meaningful change in seizures), 24.5% of people in the GNX arm experienced a reduction in major motor seizures compared to 9.8% in the placebo arm, and [redacted]% in the GNX arm experienced an increase in major motor seizures compared to [redacted]% in the placebo arm. Rates of response were generally similar for all seizure types (CS Doc B p.63), [redacted] (CSR appendices Table 14.2.5.6.1 and 14.2.5.6.2). The cumulative proportion of people in each arm showing reductions and increases in major motor seizure frequency is shown in Table 10; please note that these figures were estimated from graphs provided by the company (CS Doc B Fig 9, p.59, and clarification response QA5, Fig 1 p.4) and so may lack some accuracy. These data were not available for analyses of all seizure types.

Table 10: Response rate in Marigold DB phase

	Cumulative % change in major motor seizure frequency							
	-80%	-60%	-40%	-20%	+20%	+40%	+60%	+80%
Ganaxolone	7%	22%	32%	60%	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	5%	6%	16%	33%	[redacted]	[redacted]	[redacted]	[redacted]

Source: figures estimated from graphs provided by the company: CS Doc B Fig 9, p.60, and clarification response QA5, Fig A.

Results using the CGI-I showed that caregivers and clinicians were more likely to say that participants in the GNX arm had improved, though differences were marginal and not statistically significant (CD Doc B p.60). However, there was a greater difference in carer reported CGI-CSID, where caregivers were statistically more likely to say that those in the GNX arm showed improvements in seizure intensity/duration/severity (CS Doc B p.61). From the data

presented by the company, it was not possible to determine if carer responses were comparable for both severity and duration.

[redacted] CSR p.57).

There was a small increase in the median percentage of SFD reported by participants in the GNX arm (CS Doc B p.62), though there was no clear difference between arms. [redacted] (trial CSR appendices, Table 14.2.5.3.1 and 14.2.5.3.2).

OLE

Data from the latest data cut of the Marigold OLE ([redacted]) were presented by the company at clarification (QA12).

Reductions in median major motor seizure frequency were reported based on a combined population of those who started and were switched to GNX in Fig A (clarification response p.13) and separately between groups in Fig B (clarification response p.14). The company suggested that the data showed reductions in major motor seizure frequency shown in the double-blind phase [redacted] Response rates using a 50% threshold were higher in the OLE than in the DB phase ([redacted]% vs. [redacted]%, [redacted]%, [redacted]%, and [redacted]% at 1-3, 4-6, 7-9, and 10-12 months, respectively). [redacted] median reductions continued to increase, though the number of participants available for follow-up reduced due to the staggered entry of participants into the OLE.

A higher rate of SFD was shown in the OLE in the PBO/GNX arm than in the GNX arm (no statistical test performed; clarification response p.12).

Carer perceptions of severity and duration of seizure as assessed by the CGI-CSID were comparable between arms, with the PBO/GNX arm showing a rate of improvement comparable with the GNX arm during the double-blind phase.

HRQoL and functioning

There was no statistically significant difference in quality of life between the two arms of Marigold at the end of the double-blind phase. While four subscales (positive emotions, social interaction, leisure and outdoors, and independence) showed a numerical benefit for GNX, these differences were not statistically significant, and variance was high. Furthermore, there were no clear benefits of GNX over placebo for parenting stress; anxiety, depression and mood; attention; or children's sleep habits. Quality of life and functional outcomes were not reported separately for responders to treatment, and therefore the EAG considered is plausible that some benefits may be shown for those participants who experience a reduction in seizures with treatment. However, the EAG considered that the potential for treating seizures to produce meaningful change in quality of life and function in the context of such a severe disease to be unproven. Clinical experts to the EAG disagreed about whether reducing seizures early in life would lead to later benefits for functioning, with both acknowledging that such an effect was not yet supported by evidence.

Subgroup analyses

In the CSR appendices, seizure outcomes were reported separately for a subgroup of participants based in the UK, Australia, France, Israel and Italy (n=35). For this group, data showed that trial arms differed in baseline major motor seizure frequency, with a higher rate of seizures in the GNX arm (median [IQR]: [redacted] vs. [redacted]). While there was a greater overall reduction in major motor seizure frequency in the GNX arm, this was not statistically significant and a similar number of people in each arm showed a response (GNX [redacted]% and PBO [redacted]%) and were considered by caregivers to have improved (GNX [redacted]% and PBO [redacted]%).

In the trial CSR appendices, the company reported data separately for different types of seizures, including tonic, tonic-clonic, myoclonic, drop, absence, and motor seizures without altered awareness. The EAG noted that GNX was more likely to show an effect for seizures with a major motor feature. As discussed in Section 3.2.2.5, the EAG considered it likely that this may be due to difficulties in detecting an effect in seizures without major motor symptoms. However, the EAG also noted that it was plausible that GNX may have a differential effect across different types of seizures.

Safety

The company provided data for AEs reported in Marigold and its OLE in the CS (Document B, section B.2.10): Table 23 [Marigold] and Table 26 [Marigold OLE]. AE event data for the Phase IIa trial was reported in the trial CSR[19] provided by the company.

During the Marigold trial, rates of overall treatment-emergent adverse events (TEAEs) were comparable between arms, but there was [redacted] rate of treatment-related adverse events in the GNX arm (70.0%) compared to placebo (43.1%). Inspection of the drug-related AEs reported in the trial CSR appeared mild in nature, with no clear pattern of effect aside from an increased risk of somnolence in those receiving GNX.

The vast majority of participants in both arms of Marigold experienced at least one TEAE, though in general these were mild or moderate in nature. There was a trend for those in the GNX arm to experience more moderate than mild TEAEs, and the reverse in the placebo arm. Severe TEAEs were experienced by 2.0% (n=1) and 5.9% (n=3) of participants in the GNX and placebo arms, respectively. Comparison of specific AE types showed that somnolence and pyrexia were more common in the GNX arm than in the placebo arm. All other event rates were low in incidence and a clear pattern was not discernible. There was no clear difference in TEAEs that would be expected to lead to significant healthcare resource use, such as hospitalisation. There was also no clear evidence that GNX was more likely to cause TEAEs leading to permanent or temporary discontinuation, or to a dose reduction.

Rates of TEAEs reported by those who switched to GNX in the Marigold OLE were comparable to those reported for the GNX arm of the double-blind phase. In the CS, the company claimed that a lower rate of TEAEs between the GNX/GNX arm compared to the PBO/GNX arm (reported to the February 2021 cut-off) was suggestive that adverse events occurred early in the treatment and/or reduce over time. However, the EAG did not think there was sufficient evidence to support this claim, considering that there was only a small change in the number of participants receiving GNX in both trial phases who experienced TEAEs (86% in the double-blind phase and 76.7% in the OLE). The company also did not report TEAE data at later timepoints of the OLE, which may have demonstrated whether such a reduction in AEs occurred over time. Moreover, there was a higher rate of discontinuation in the OLE compared to the double-blind phase, meaning that rates of AE may appear artificially low in comparison.

There was one TEAE resulting in death in the OLE trial in the GNX/GNX arm. Though the company reported that the event was unlikely due to the study drug, the EAG highlighted that there was no explanation behind mortality cause in the CS, and there is no detail into how the company determined if the mortality was treatment-related.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken.

3.4. Additional work on clinical effectiveness undertaken by the EAG

All additional work has been reported throughout.

3.5. Conclusions of the clinical effectiveness section

- GNX was more likely than ECM to reduce seizure frequency for a minority of people with CDD as assessed during the 17-week DB phase of Marigold. The EAG was uncertain about absolute reductions in seizure frequency due to the risk of a regression to the mean effect during the trial (Key issue 1), and evidence was strongest for the impact of treatment on major motor seizures compared to other seizure types.
- All outcomes assessed in the OLE were at risk of this due to the lack of a comparator and the discontinuation of participants due to the treatment outcome (and the absence of a missing data analysis). Overall, the EAG therefore considered that the long-term data showed a promising prolongation of treatment effect for some participants, which may exceed the typical length of time that ASMs show effect for people with CDD. However, the magnitude of the effect and the number of people who may benefit were both considered uncertain, due to limitations in the OLE data.
- Caregivers reported that GNX may have a beneficial effect for seizure duration and/or severity (reported as a combined outcome), however there was no effect of GNX for HRQoL, functioning, or caregiver wellbeing as compared to ECM.
- The EAG considered that it was unclear reductions in seizure frequency shown in the trials would be meaningful to people with CDD and their caregiver and, if so, what impacts these would likely have. All participants in the trials continued to experience regular seizures, and the EAG therefore considered the potential benefit of GNX to be a reduction in the

frequency of these for some people. Clinical experts advised that there was no high-quality evidence to suggest that reducing seizures would have long-term benefits for functioning and wellbeing. One expert considered this to be unproven yet plausible, while another considered that the severe nature of the condition and its impacts on brain development may mean that reducing seizures may have little overall impact. The EAG considered that reducing seizure frequency may have benefits for carer burden, though these may be difficult to measure against the broader carer burden for the condition.

- Overall, the evidence suggested that GNX was a relatively safe treatment option for treating seizures in people with CDD and may therefore be considered as an option alongside existing ASMs and therapies. However, the EAG noted that many people may still not experience a response to treatment, and in the absence of evidence for population effect modifiers, treatment would likely follow a ‘trial and error’ method.

4. COST-EFFECTIVENESS

During the appraisal, the company submitted three versions of their economic model to evaluate the cost-effectiveness analysis: one in the original submission (Model 1; 27/10/2022) and two subsequent versions at clarification (Model 2; 30/11/2022) and following clarification (Model 3; 22/12/2022). Each model version included a distinct company base case. Table 11 provides a top-line summary of the changes to the company's base case over the three versions.

Table 11: Company revisions to their cost-effectiveness model

Model identifier used in subsequent sections	Key differences to previous	Company base-case ICER
Model 1 (27/10/2022)	NA	£20,860
Model 2 (30/11/2022)	• 50% higher mortality for ECM patients for entire time horizon (EAG not notified) • Maintenance efficacy of 29.31% applied (EAG not notified) • Correction of 0.02 patient disutility error (B16) • Correction of applying annual mortality every 28 days (B17) • Increase time horizon to 100 years (B17) • Correction of extrapolating general population mortality based on only males in a predominantly female population (B18) • Correction of incorrect dosing for GNX (B23) • Inclusion of rescue medication costs per arm (B25) • Correction of AE costs for entire follow up being applied every cycle (B26) • Other minor changes	£19,419
Model 3 (22/12/2022)	• Reversion of 50% mortality increase for ECM patients • Reversion from maintenance period HL shift of 29.31% to full Marigold HL shift of 27.08%	£22,200

Abbreviations: AE, adverse event; EAG, External Assessment Group; ECM, established clinical management; GNX, ganaxolone; ICER, incremental cost-effectiveness ratio; OLE, open-label extension.

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted a single review to identify all relevant evidence for this submission, including evidence for the clinical effectiveness, cost-effectiveness, health-related quality of life (HRQoL), and cost and resource use. A summary of the EAG's critique of the company's approach to identifying these types of evidence is provided in Table 12.

Ultimately, the company did not identify any cost-effectiveness evaluations of therapies for people with CDD; though it is unclear from the CS whether any relevant studies were identified for other genetic epilepsy populations captured within the inclusion criteria of the searches. Similarly, the company's SLR did not yield any HRQoL or cost and resource use studies in a CDD population specifically, though studies from other populations were considered to serve as a proxy for CDD (for the purpose of informing the company's cost-effectiveness model).

Table 12. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D, Section D.1.1	The company searched a combination of bibliographic databases, conference websites, clinical trials registries, websites of relevant organisations, google scholar, and reference lists of relevant studies. The strategy used appeared appropriate, although at clarification (question A2) the EAG questioned the search terms used for alternative patient populations. In response, the company re-ran the search using alternative terms to confirm that no studies had been missed. At clarification (question A1), the EAG also requested further details about the strategy used for supplementary searches. In response, the company submitted the terms used to search one such resource, which were appropriate and provided reassurance that other sources were appropriately searched.
Inclusion criteria	Appendix D, Section D.1	Inclusion criteria were not formally defined with respect to cost-effectiveness evidence. However, criteria appeared broad (including non-CDD populations and a range of burden-of-illness studies) and therefore were likely to have captured available evidence if it existed.
Screening	Appendix D, Section D.1.3.1	Dual screening was used at all levels of evidence, with involvement of a third reviewer as needed.
Data extraction	Appendix D, Section D.1.3.1	A DET was discussed but not explicitly presented. A single reviewer extracted data with quality assurance by a second reviewer.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
QA of included studies	Appendix G, Section G.1	There was no apparent QA of cost effectiveness studies in other populations, though their inclusion in the review was unclear. No QA was conducted for HRQoL or cost and resource studies.

Abbreviations: CDD, CDKL5 deficiency disorder; CS, Company Submission; DET, data extraction template; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment.

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 13: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, caregivers	× Perspective of model captured health effects on both patients and caregivers, but was not exhaustive and was subject to a number of limitations
Perspective on costs	NHS and PSS	✓ All costs included related to patients – no costs included for caregivers
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	✓ Single comparison (GNX + ECM versus ECM alone) presented
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓ Lifetime horizon of up to a maximum of 100 years, set to 75 years in original base-case analysis and updated to 100 years following clarification
Synthesis of evidence on health effects	Based on systematic review	✓ Relevant studies identified from systematic review (with scope extended to include proxy conditions given anticipated low number of hits in a CDD-specific population)
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	✓ Health effects expressed as QALYs, though EQ-5D not used for estimation of all included utility values
Source of data for measurement of health-related quality of life	Reported directly by patients and/or caregivers	× Seizure-related utility based on a vignette study
Source of preference data for valuation of changes in	Representative sample of the UK population	× Vignette study by Lo *et al.*, (2022) used general population valuation, though as 200 participants

Attribute	Reference case	EAG comment on company's submission
health-related quality of life		were included the representativeness of this sample is unclear
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**?** Severity weighting of 1.7 applied to QALYs gained by both patients and caregivers
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✓ Majority of costs sourced from standard NHS and PSS reference material. Some costs were assumed, but these only influenced incremental results when a survival benefit was modelled
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓ Costs and QALYs discounted at 3.5% per annum

Key: CDD, Cyclin-depended Kinase-like 5 [CDKL5] Deficiency Disorder; ECM, established clinical management; EQ-5D, EuroQol 5 dimension; GNX, ganaxolone; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

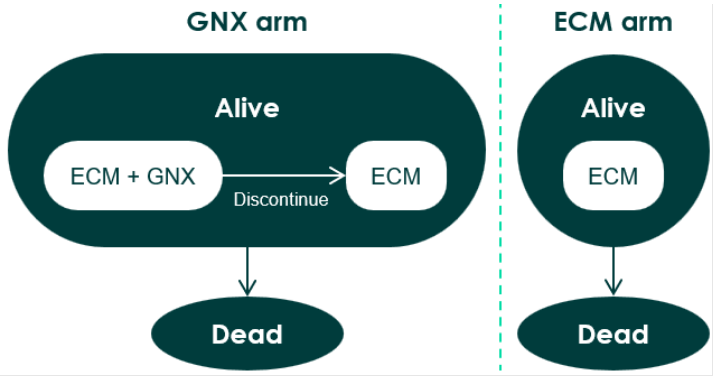
4.2.2. Model structure

The company presented a simple Markov state-transition model with two primary health states (alive and dead). In each 28-day (28d) cycle, patients transitioned from the alive state to the dead state in accordance with an overall survival extrapolation. This extrapolation was derived using a standardised mortality ratio (SMR) applied to general population survival, which asserted several assumptions that are discussed in Section 4.2.6. Patients in the GNX arm could also be on or off GNX treatment, with patients that were alive and on GNX discontinuing GNX at a rate of [redacted]% per 28d estimated based on data from the Marigold study (see Section 4.2.6). This effectively added a health state for the GNX arm for patients that were receiving GNX treatment, and so the EAG provided a revised model schematic to illustrate this (see Figure 1).

Patients treated with GNX were assumed to instantaneously receive the full treatment effect calculated using data from baseline and week 17 in the double-blind phase of the Marigold trial. Mechanically, the distribution of seizure frequency (SF) amongst a cohort treated with GNX was assumed to immediately change from that of the ECM population at baseline in the Marigold trial to a "shifted" distribution using the GNX treatment effect estimate using a Hodges-Lehmann estimation of location shift (hereafter referred to as HL for brevity). [20]

Upon discontinuation of GNX, the treatment effect was assumed to be immediately lost and the distribution of SF for discontinued patients became that of the ECM arm. No change of treatment effect over time was modelled, meaning that the company's model assumed that the 27.08% reduction in SF associated with GNX remains irrespective of the amount of time a patient has been treated with GNX.

Figure 1: Company model structure



Key: ECM, established clinical management; GNX, ganaxolone.
Note: Discontinuation of GNX at a rate of [redacted]% per cycle.

The model structure illustrated in Figure 1 may be considered atypical for NICE technology appraisals of genetic epileptic syndromes like DS or LGS. Previous NICE TAs have included Markov models with discrete SF-based health states (e.g., TA614 in DS) and patient-level microsimulations (e.g., TA808, also in DS). The EAG expected that these structures could potentially have been more appropriate in the case of this decision problem due to a number of potential advantages in this disease area. For instance, the SF-state based Markov model approach was non-parametric and considered changes in the distributional shape of SF in the population over time in both treatment arms. It would have also been possible to calculate the transition probabilities between health states to align with the health state definitions implied by the two available utility studies (see Section 4.2.7 for further details on utility values). The microsimulation approach would have allowed for nuances like seizure-free days (SFD) or repeated GNX treatment periods (see Section 4.2.6.2) to be modelled alongside SF, possibly taking correlation structures and non-linear associations into account. It may have also been possible in a patient-level simulation to simulate the process of response assessment and discontinuation of treatment. Within the timeframe of the appraisal, the EAG was unable to fully investigate whether there would be barriers to using these methods for this appraisal, though it

did not consider that the company had provided sufficient justification for using its chosen structure.

Overall, the EAG believed that a Markov approach in this context was reasonable in principle. However, while the EAG accepted that CDD was a rare condition and data was scarce, it considered that the company's implementation of the approach was heavily simplified. Limitations of this include that the analysis may have failed to consider the full effect of the treatment on this population and may therefore offer either an optimistic or a conservative estimate of the treatment effect and modelled outcomes.

4.2.3. Population

The prevalent population of people with CDD varies in age, symptom burden, and both the frequency and severity of seizures. In practice, people are likely to be treated with several different combinations of concomitant treatment to control seizures and other symptoms of the disease. Seizures in patients with CDD are recognised to be difficult to treat, requiring constant care associated with serious disease burden on both patients and those that provide care to them.[21] As CDD is extremely rare, there are challenges in generating high quality data showing the natural history of the disease under current standards of care. Moreover, as CDD was established as a disease in its own right relatively recently, there is an inevitable absence of long-term data.

The EAG had concerns regarding the population considered in the cost-effectiveness analysis in terms of its representativeness of the expected population who would be treated with GNX in UK clinical practice for two main reasons: (i) the age at which treatment would be initiated in practice (described below), and (ii) how SF was captured by the model (including the baseline distribution and how this may change over time; described in Section 4.2.6.1).

In the company's model, GNX was assumed to be initiated at an average age of [redacted] old. This differed from the expected marketing authorisation of GNX, which was for patients aged two years and over. In the Marigold trial, a small minority of participants only were aged under three years (range 2-19 years, median 6, mean 7.26, IQR 3-10 years).

Pending the marketing authorisation, the EAG considered it likely that, upon introduction into UK clinical practice, GNX would likely be initiated in people younger than seven years of age due to increasing awareness of CDD and facilities for diagnosis. However, the EAG was unclear whether GNX would likely be introduced before or after people with CDD had been prescribed

other ASMs. Uncertainty surrounding the likely starting age of people who receive GNX was significant to the appraisal as dosing of GNX was weight-based and would therefore be affected by age. As no dose-response relationship was assumed in the model (i.e., the treatment effect remained the same regardless of weight/age/dose), a reduction in starting age reduced the ICER for GNX as patients achieved the same SF % reduction for a smaller amount of GNX and therefore cost.

To explore the uncertainty of this, the EAG conducted a scenario analysis setting the baseline age of the modelled population to match that of the Marigold study. This is discussed in Sections 4.2.8.1 and 6.2.

4.2.4. Interventions and comparators

4.2.4.1. Intervention

The intervention modelled by the company was GNX and ECM. GNX was administered via an oral delivery syringe. EAG discussions on dosing and implications for the cost-effectiveness analysis are provided in Section 4.2.8.1. GNX is intended to be used adjunctive to ECM, meaning that unless contra-indicated, alternative treatments for seizures used in people with CDD may continue following GNX initiation.

4.2.4.2. Comparator

The comparator to GNX was ECM without GNX. ECM included a wide variety of different treatment approaches to manage seizures, including ASMs and non-pharmacological therapies. Please see Section 3.2.2.4 for more detail concerning the specification of ECM in the Marigold trial.

The estimation of a treatment effect for ECM was modelled differently across the three versions of the model submitted by the company. In the final submitted model, the company assumed the SF distribution of ECM was time invariant and therefore ASMs on average maintain SF indefinitely (regardless of the likelihood that ineffective treatments will be withdrawn, and new treatments initiated). This is discussed further in Section 4.2.6.1.

For the purposes of cost-effectiveness modelling, only those elements likely to differ between treatment arms (i.e., GNX+ECM and ECM) necessitated inclusion in the model. Some elements of ECM may have theoretically been relevant to the decision problem through an efficacy modifying effect, or potentially through GNX reducing the need for some existing ASMs. For

example, if GNX were to reduce the need for people to receive multiple ASMs to treat seizures, this may have resulted in benefits through reduced negative effects of polypharmacy. The EAG noticed that cannabidiol use in the Marigold study was restricted, and clinical advice to the EAG was that use may be higher in practice. The EAG was unclear whether cannabidiol would be expected to interact with GNX or alter the ECM treatment effect, and this issue was therefore not explored further.

4.2.5. Perspective, time horizon and discounting

4.2.5.1. Time horizon and discounting

The company included a time horizon of 100 years in the company's final model, arguing that this was a lifetime horizon and included the period in which any feasible clinical benefit and cost associated with introducing GNX to the CDD treatment pathway in the UK would be relevant. In principle, the EAG agreed with the company, however, the company did not present any scenarios using alternative time horizons.

The company applied discounting per the NICE reference case, at a rate of 3.5% per annum. The EAG agreed that this was appropriate. However, like the base-case choice of time horizon, the company did not present any scenarios based on discount rates applied.

Due to the above, the EAG introduced several scenario analyses, based on time horizon and discount rates applied within the cost-effectiveness model (see Section 6.2), to further explore the sensitivity of cost-effectiveness results.

4.2.5.2. Perspective on outcomes

The perspective taken throughout the submission was that of patients and caregivers, and outcomes were presented in the form of QALYs. However, the company's model did not fully capture all relevant outcomes which may be affected by the introduction of GNX. This is discussed in Section 4.2.6.1.

4.2.5.3. Perspective on costs

The perspective of the company's cost-effectiveness analysis was NHS and Personal Social Services (PSS). The company sourced the cost inputs for the cost-effectiveness model from a combination of the National Schedule of NHS Costs 2020-2021, and Unit Costs of Health and Social Care 2021 from the Personal Social Services Research Unit (PSSRU). The company also cited UK sources for resource use where available.

4.2.6. Treatment effectiveness and extrapolation

In the company's model, GNX was modelled to impact the estimation of QALYs through (i) SF, (ii) treatment duration, and (iii) mortality. These aspects of the company's model are described in the sub-sections that follow.

4.2.6.1. Seizure frequency (SF)

The company modelled and extrapolated count data on SF per 28-days by applying the estimated treatment effect from Marigold (see Table 31 of the CS) directly to the parameters of a parametric (lognormal) fit to baseline SF pooled across Marigold treatment arms.

The treatment effect of GNX was applied as a percentage reduction directly to the [redacted]. As discussed later in this sub-section, this was a mathematical error due to it violating the [redacted] – i.e., that:

[redacted]

Also see Section 6.1.1 where the EAG corrected this application. However, irrespective of implementation errors, the treatment effect of GNX was to move the SF distribution to the left (i.e., to reduce population average SF) for those remaining on GNX.

The company assumed that patients transitioned from one distribution (the pooled baseline SF from Marigold) to the other (the same distribution with the treatment effect applied) instantaneously upon initiation of GNX, that the treatment effect did not change over time, and that the treatment effect was lost immediately upon discontinuation of GNX. In the cost-effectiveness model, this translated to a simple modelling framework which essentially provided a weighted average SF distribution for patients in the ECM and GNX arms, depending on the GNX treatment effect and the proportion of patients that remained alive and on treatment. Mean SF was not explicitly calculated in the model but was reflected in the proportion of patients that fell into the health-state utility values (HSUVs), which were linked to SF (see Section 4.2.6.3 for further discussion related to utilities).

The lognormal fit to the SF data was not extrapolated or investigated for changes in distributional shape at different time points using the Marigold data, and no alternative candidate distributions were included in the company's model. The EAG asked the company about alternative distributions at clarification stage (see question B9), and the company explained that [redacted]. The EAG did not see this as a

justification for exclusion but agreed that the lognormal distribution provided the best fit from the included distributions.

The company's overall approach to capturing SF incorporated a large number of assumptions which had a considerable impact on modelled patient outcomes and therefore cost-effectiveness results. Many of the assumptions were implemented in the absence of evidence for this condition. An overview of the company's model assumptions for modelling SF and the EAG view on these is provided in Table 14. The importance of each assumption was determined by the potential impact on the cost-effectiveness of GNX. Where necessary, more thorough discussion on each issue is provided in the sub-sections that follow.

Table 14: Summary of key assumptions made by the company on CDD seizure frequency

Assumption	Company evidence and/or justification	EAG position, comments, and importance
Treatment effect maintained provided patients still on treatment	None provided	**High importance:** Disagree based on clinician input • Clinical experts suggested that they would perform an assessment at 6 months from initiation and determine response/discontinuation at this point • In clinical practice, patients are likely to discontinue if they have not or are no longer responding to treatment. This would then mean that amongst those that stay on treatment, the proportion that are responders would increase over time (see e.g., Specchio 2020). A regression to the mean effect may also be expected in those people who initiate treatment following a surge in SF (Key Issue 1). Pending clarity on the way in which treatment with GNX would be initiated and discontinued, the EAG was unable to incorporate a scenario to test the effect of alterations on the cost-effectiveness of GNX. However, the EAG was confident that the cost-effectiveness of GNX would be considerably improved by the implementation of clinically based treatment discontinuation (rather than just based on adverse events).
Secondary and tertiary seizures omitted from model	Secondary/ tertiary seizures not primary endpoint of Marigold, less common, difficult to measure and less impactful	**High importance:** Disagree. True ICER may be between scenarios with "primary seizures only" and "all seizures" • Effect of GNX could potentially differ by seizure type, though this is difficult to establish from limited data and challenges with measurement • All seizures would have been more in keeping with the scope of the appraisal • Company's estimate of HL shift for "all seizures" scenario was likely to be conservative
Baseline SF distribution in Marigold representative of UK clinical practice	None provided	**High importance:** Inconclusive. Current data were extremely scarce. However, there was a published survey which could have provided an alternative scenario • Clinical experts explained that ASM trial inclusion criteria (including Marigold) restrict baseline populations to high SF, which for some participants may be *"at the crest of a wave"* of seizures • Marketing authorisation for GNX was pending and there was uncertainty surrounding the way GNX would be used in clinical practice and if this would be comparable to Marigold (i.e., minimum threshold SF and previous failed ASMs)
Distribution of SF will not change over time	Some limited evidence provided in clarification response	**High importance:** Inconclusive. There was a lack of evidence to show long-term trends in SF, but longer-term comparative follow-up data could have influenced the ICER substantially • The company provided some evidence at clarification (question A9) that supported stable SF over time, but this had limitations (only information on the 17-week double-blind period was supplied and it was understandably difficult to illustrate the data without some clutter in the graphs). The accumulation of events appeared linear but the response was not considered by the EAG to be definitive • The EAG also identified a published survey in people with CDD showing that SF may change over time. [22]

Assumption	Company evidence and/or justification	EAG position, comments, and importance
		• Model results were considered likely to be sensitive to the shape of SF distribution at baseline, so the representativeness of the Marigold SF distribution remained an area of uncertainty
Appropriate to apply HL shift directly to the distributional parameters	None provided	**High importance:** Agree, following the EAG correction (see Section 6.1.1) • The original application was incorrect, which the EAG investigated further through a simulation exercise (presented in Section 6.1.1) • The EAG method generated reductions in mean, median and standard deviation close to 27.08%, whilst the company's method led to approximately [redacted]% reductions. HL shift estimates should generate corresponding changes in mean, median, standard deviation (i.e. 27.08%)
No change in seizure type or severity following introduction of GNX	None provided	**Medium importance:** Unclear. Evidence to the contrary was provided in the Marigold CSR, [14] but there was an unclear impact on cost-effectiveness results • Evidence in the Marigold CSR suggested there could potentially be variation in effect across different types of seizures, suggesting seizure type distribution changed for GNX patients • The EAG considered it plausible that seizure types had distinct utility and resource use impacts, and that GNX patients will then have had different utility and resource use implications per seizure versus ECM
Instantaneous treatment effect	None provided	**Medium importance:** Disagree. Contrary evidence was provided in the Marigold CSR[14] and the CS • The Marigold CSR reported a smaller HL shift estimate for GNX vs PBO during the titration weeks 0-4 vs. weeks 0-17 and 4-17 (-18.70%, -27.08% and -29.31%) • The EAG linearly interpolated the treatment effect between weeks 0, 4, and 16 in their base case (due to impossibility of 17 weeks within model structure, see following sections), which increased the ICER. Scenarios are presented without interpolation for comparison.
SF distribution best modelled with a lognormal distribution	Statistical fit of the distributions included in comparison to Marigold data at baseline (pooled across arms)	**Low importance:** Agree with choice of distribution, but some limitations. • The EAG expanded testing to include count-data distributions (Poisson, binomial, and negative binomial). Lognormal remained statistically best fitting • Lognormal distribution [redacted] • Alternative yet plausible distributions important to consider where possible
SF immediately reverts to baseline distribution after discontinuation of GNX	No evidence provided, but justified as being conservative	**Low importance:** Disagree due to down-titration of GNX per SmPC • SmPC for GNX stated that patients were to be down titrated upon discontinuation, as sudden discontinuation could cause an increase in the frequency of seizures • Clinical experts consulted by the EAG suggested that the down-titration phase of many ASMs would be long, ranging from 2 weeks to several months, depending on context • Discontinued patients would mostly consist of non-responders causing attrition effects, leading to GNX SF reduction moving upwards over time

Assumption	Company evidence and/or justification	EAG position, comments, and importance
		• Cost and efficacy implications of the down-titration period were unclear as there was no evidence, so the EAG were not able to include a scenario to test cost-effectiveness impacts

Key: ASM, anti-seizure medication; CSR, clinical study report; EAG, External Assessment Group; ECM, established clinical management; GNX, ganaxolone; HL, Hodges–Lehmann; ICER, incremental cost-effectiveness ratio; SF, seizure frequency; SmPC, summary of product characteristics.

Types of seizures to include in the cost-effectiveness model

The company elected to include “primary seizures” only within its model (see Section 3.2.2.5 and the Marigold CSR[14] for definitions) using the following justification:

1. Primary (major-motor) seizures were the primary endpoint of the Marigold trial
2. Secondary and tertiary seizures are less frequent and can be difficult to measure
3. Primary seizures tend to be the most impactful on patients and caregivers

The EAG discusses each of these points below.

The restriction of the model to primary seizures only was inconsistent with the scope for this appraisal (Section 2.4), regardless that it was the primary endpoint in the clinical trial evidence. As other seizure types were evaluated in the available clinical trial evidence, the EAG considered that these may have been considered within the company’s model.

The EAG noted that the number of observed secondary and tertiary seizures were lower than the number of primary seizures (see Marigold CSR Section 11.1.1.3.4), and agreed that these may be more challenging to measure (see Section 3.2.2 and Document B Section B.3.3.1). Data points for secondary and tertiary seizures provided in the trial CSR appendices had a high level of variance, though suggested the possibility of numerical differences in treatment effect between primary and secondary seizures type. While the EAG considered the data to be uncertain, it considered that the company had not been able to demonstrate that the treatment effect for GNX would be consistent across seizure types. This was, in the EAG’s opinion, a source of uncertainty surrounding the treatment effect of GNX which warranted consideration.

The total number of seizures in the analysis was based on a larger sample when including more types of seizures, so the company's argument of smaller N for secondary and tertiary seizures held only when analysing secondary and tertiary seizures separately from primary seizures. To clarify, the EAG did not advocate isolating secondary and tertiary seizures but considered that these could be combined within an “all seizures” analysis. However, as the estimated treatment effect of GNX may differ by seizure type, the primary SF distribution and the GNX impact on primary SF was unlikely to be a good proxy for secondary and tertiary SF distributions and the respective effects of GNX. This was complicated further when considering that the proportion of seizures by type may have been impacted following the introduction of GNX, which was not captured by the company’s model.

It was the EAG's view that all direct health effects associated with the introduction of GNX for people with CDD in the NHS were directly relevant to the decision problem at hand, per the final scope issued by NICE. The clinical experts consulted by the EAG both indicated that any seizure (irrespective of type) over five minutes in duration was an emergency, requiring both rescue medication and hospitalisation, and having considerable impact on patients and their caregivers. As people with CDD experience a broad range of seizure types, and the trial evidence for GNX suggested that the treatment effect may vary across types, it did not follow that secondary and tertiary seizures could be considered irrelevant to the NICE decision problem, even if they were expected to be less common and less impactful.

In the EAG's opinion the exclusion of secondary and tertiary seizures from the cost-effectiveness model introduced decision uncertainty and potential bias. Ideally secondary and tertiary seizures should have been incorporated into the model to take into consideration the potentially differential treatment effect. Yet, due to issues with the data on SF for secondary and tertiary seizures, there was inherent uncertainty linked with introducing these additional seizure types within the model.

The EAG expected the most accurate ICER to lie between the two approaches (i.e., only primary seizures vs. all seizures). However, the EAG expected the ICER was likely to be closer to the "primary seizures" scenario ICER, due to the lower incidence of secondary and tertiary seizures, so the EAG continued to use primary seizures within its base case. However, in the EAG's opinion the all-seizures scenario analyses presented contributed considerably to the overall uncertainty surrounding GNX cost-effectiveness.

Baseline SF distribution

Overall, the EAG considered that many of the eligible criteria for the Marigold trial may align with the target population in clinical practice (see Section 3.2.2.2). However, the EAG were uncertain whether the frequency of seizures experienced by trial participants was representative of the whole CDD population. For instance, a published survey of (non-UK) caregivers for people with CDD by Leonard *et al.* reported distributions of SF at two time points ("baseline" and "follow up") [22] which differed from the Marigold sample, as shown in Table 15.

Table 15: CDD seizure frequency from Leonard *et al.*, (2022)

Seizure frequency	Baseline (n, %)	Follow-up (n, %)
None	12 (8.4)	17 (11.9)

Seizure frequency	Baseline (n, %)	Follow-up (n, %)
≤4 per month	14 (9.8)	15 (10.5)
1-6 per week	28 (19.6)	21 (14.7)
1-4 per day	59 (41.3)	38 (26.6)
≥5 per day	30 (21.0)	52 (36.4)

Notably, these data suggested that a considerable proportion of people with CDD may experience periods without seizures. The EAG assumed that some of these patients would not be eligible for GNX and were therefore not relevant to the appraisal. However, it also considered it plausible that some people with CDD may experience periods of time without seizures. A different shaped SF distribution may therefore be applicable to people with CDD in real-world practice versus the Marigold trial.

The company elected to represent the SF distribution at baseline in the Marigold trial via a lognormal distribution. Goodness of fit tests were performed on each candidate distribution explored by the company. The results of this process were reported in Table 30 of the CS, which included Akaike and Bayesian Information Criteria (AIC and BIC, respectively) and "GOF test p-value". These "GOF tests" were different for each distribution, which was not explained in the CS. At clarification stage, the company explained: [redacted] (company's response to question B7). Unfortunately, the EAG was unable to fully interpret the rightmost column in CS Table 30. However, the AIC and BIC values for the lognormal distribution were the smallest by a considerable margin, perhaps indicating superior distributional fit.

Overall, the EAG acknowledged that data on the distribution of SF in CDD populations was limited. However, it was the EAG's opinion that how well the SF distribution in the cost-effectiveness model characterised the SF of patients likely to receive GNX in clinical practice was critical to accurately capturing cost-effectiveness. In addition, while the lognormal distribution appeared to provide a reasonable fit to the Marigold data, this did not necessarily mean that this distribution provided a good fit to the real-world SF distribution.

Application of the treatment effect

The company presented an analysis of the change in SF over time to provide evidence for the efficacy of GNX in CDD. However, the distributional shape of SF was positively skewed, with

more patients having fewer seizures per four-week period (though some patients were shown to have hundreds of seizures). Consequently, the mean became less useful for characterising impacts on patients. Furthermore, SF was considered likely to non-linearly impact patient HRQoL. For example, the impact of one additional seizure for patients experiencing an average of 0 seizures per month was likely to be greater than the impact for patients already experiencing a large number of seizures per month (e.g., 100 increasing to 101 seizures per month). Consequently, simple characterisation of efficacy using the effect of GNX on mean SF was likely to provide biased cost-effectiveness analysis results.

The Marigold statistical analysis investigated changes in SF using individual patient data, including the arithmetic and proportional (percentage) change in SF at baseline and week 17. The arithmetic and percentage changes in SF were calculated as below for individual i:

$$\delta SF_i = SF_{w17,i} - SF_{bl,i}$$

$$\delta SF\%_i = \frac{SF_{w17,i} - SF_{bl,i}}{SF_{bl,i}} \times 100$$

Where SF is seizure frequency, δ is change, $w17$ is week 17, and bl is baseline.

The mean of δSF_i was then the mean of the individual changes in SF in the baseline cohort. In other words, this was one way of characterising the average change in SF or treatment effect. The same would have been true of the median, which may also be more appropriate in non-normally distributed contexts.

The company did not report the distribution of δSF_i or $\delta SF\%_i$, and therefore no evidence that these were non-normal in shape was provided. As δSF_i and $\delta SF\%_i$ were based on differences in SF over time rather than a cross-sectional or time-average estimate of SF itself, it does not follow that δSF_i and $\delta SF\%_i$ must have the same distributional characteristics as SF_i. Consequently, it was not possible for the EAG to examine whether the HL estimate of shift was the most appropriate means to incorporate the effect of GNX on individual patient changes in SF over time into a cost-effectiveness model. It may have been the case that mean difference or some simple mixed-effects regression analysis of SF, δSF_i or $\delta SF\%_i$ was a more appropriate approach for extrapolating SF and the efficacy of GNX long-term in a cost-effectiveness modelling setting.

Generally, the application of HL shift estimates to distributions of SF to estimate the distributional shape of SF for treated patients could have been a reasonable approach to capturing the value of a treatment that reduces seizures. However, applying it in this way assumed that the treatment effect did not include changing the *shape* of the distribution and therefore the effect was not itself in some way dependent on the number of seizures a patient was having at baseline (for instance, exponentially more beneficial for patients with higher initial SF). This application of the treatment effect assumed that all patients were affected in the same way, with the same percentage reduction of their SF.

The company assumed that the full treatment effect at 17 weeks in the Marigold trial applied to patients immediately from week 0. This implied that the first titration dose received by patients was just as effective as the full dose, and that patients immediately experienced the full reduction in SF. Both were optimistic assumptions that likely biased the cost-effectiveness analysis in favour of GNX. Clinical advice suggested that the effect would take time to manifest.

The CS detailed the treatment effect identified at the end of the titration period (4 weeks from baseline). This reported an HL shift estimate that was considerably smaller than the treatment effect at 17 weeks (-18.70% and -27.08%). This evidence directly contradicted the assumption that the treatment effect was instantaneously at its week-17 level. Therefore, the EAG amended this in its base-case cost-effectiveness analysis (see Section 6.3). The EAG interpolated the distributional parameters for modelled primary SF each 4 weeks linearly, using an initial value of 0, a 4-week value matching that of the Marigold trial, and a 16-week value equal to the 17-week value of Marigold. The treatment effect values were half-cycle corrected for fairness. This was slightly optimistic as it assumed the treatment effect reached maturity at week 16 rather than 17. However, due to the confines of the company's model structure, the EAG considered this sufficient to account for the evidence that SF gradually fell in a cohort treated with GNX.

Treatment waning and prolonged efficacy

The company assumed that the treatment effect never waned, meaning a patient was assumed to derive the same benefit from GNX for as long as they continued to receive treatment. Upon questioning about the clinical plausibility of this assumption, the clinical experts consulted by the EAG could not provide a definitive opinion due to a lack of long-term follow up data. Other ASMs typically only provide short-term benefits for SF, and so it is plausible that GNX may also offer only temporary relief. The EAG's opinion was therefore that this may have been an optimistic assumption which could have overestimated the long-term effectiveness of GNX (if,

for example, the effect of GNX reduces over time). However, a clinical expert suggested to the EAG that GNX would be withdrawn in practice from people who had not responded or had lost a response. If this was true, then SF only for those remaining GNX would improve when 'removing' non-responders from the sample until a point of stability (until any treatment effect waning occurred, at which point the on-treatment SF distribution would worsen). This effect is present in the poster by Specchio *et al.* reporting interim results from the Marigold OLE, and showing diminishing N but apparent continued improvement in SF amongst GNX/GNX patients. [23]

While the assumption of permanent treatment efficacy was potentially optimistic, the effect of attrition on the SF of those remaining on treatment was not accounted for within the model. On balance, the EAG expected that the combination of no treatment effect waning but no attrition-driven continued improvement in SF in those continuing to receive GNX to be a preferred approach that was a conservative-yet-uncertain assumption.

Upon discontinuation, the company assumed that the treatment effect was immediately lost. On the surface this seemed a conservative assumption. However, the SmPC for GNX revealed that patients must be down-titrated upon discontinuation from GNX to avoid the risk of an increase in SF. The EAG therefore assumed that in practice patients would continue to receive diminishing doses of GNX beyond discontinuation. This was not represented in the model, but as the EAG did not have any data on which to base a tapering off of the treatment effect and cost upon treatment discontinuation, it was not able to develop a scenario for this. The EAG expected that accounting for this would increase the ICER for GNX (though it was uncertain due to the uncertainty around down-titration duration and lingering treatment effect).

Overall, the application of the treatment effect in the company's base-case model via a HL shift estimate applied to a fitted distribution was heavily simplified, and this led to a mix of optimism and conservatism, the net effect of which was unclear. Where possible the EAG made adjustments and introduced scenarios to correct what it considered to be errors (see Section 6.1) and tested the sensitivity of the model result (see Section 6.2).

4.2.6.2. Duration of treatment

The company used data from the Marigold trial to estimate a discontinuation rate for GNX (see Document B Section B.3.3.1.3). This used what the EAG believed to be the number of discontinuations between the baseline and the end of the OLE (n=[redacted]), the number of patients

that continued to the end of the OLE (n=[redacted]), and the duration from baseline to the end of the OLE (2 years, or 104 weeks in the cost-effectiveness model). The company incorporated the following calculation to obtain the discontinuation rate used in the cost-effectiveness model:

[redacted]

For completeness, the model assumed that once patients discontinue treatment with GNX they will never reinitiate treatment with GNX (i.e., discontinuation was assumed to be permanent).

The EAG considered two important aspects of the company's approach to be important assumptions that required further consideration. These were: (i) that patients were assumed to discontinue GNX at a constant rate over time, and (ii) that patients could receive GNX only once over their lifetime. For brevity, the EAG's agreement or disagreement along with explanation for each of these two important assumptions are summarised in Table 16. Where necessary, more thorough discussion on each issue is provided in the sub-sections that follow.

Table 16: Summary of key assumptions about duration of ganaxolone treatment made by the company

Assumption	Company evidence and/or justification	EAG position, comments, and importance
Patients discontinue GNX at a fixed rate	Based on analysis of discontinuation for any reason in the Marigold study	**High importance:** Disagree based on clinical advice received • Estimation of the discontinuation rate was flawed as it was not based on exposure time • One clinical expert consulted by the EAG suggested that patients would be assessed at 6-months and those that have not experienced sufficient clinical benefit from the treatment would be discontinued from GNX • The EAG agreed that the model should reflect clinical advice and should incorporate clinical assessments for response if this was expected in practice
Patients can only receive GNX once in their lifetime	None provided	**Medium importance:** Disagree based on clinical advice received • One clinical expert consulted by the EAG suggested that patients could be initiated and discontinued from GNX multiple times in their lifetime, as a response to their SF increasing • The EAG considered that accounting for multiple uses of GNX could have influenced the cost-effectiveness of GNX in either direction. However, no evidence was available on repeated provision of GNX to CDD patients, so the EAG could not comment further on the likely impact.

Key: CDD, CDKL5 deficiency disorder; EAG, External Assessment Group; GNX, ganaxolone; SF, seizure frequency.

Constant discontinuation rate

The formula used by the company to estimate the discontinuation rate assumed that [redacted] patients were at risk of discontinuation throughout the DB and OLE phases of Marigold, and that discontinuations happened at a continuous rate (i.e., an exponential model would best characterise time on treatment). This calculation was incorrect, leading to a substantial overestimation of the discontinuation rate for GNX, which then led to an underestimate of GNX treatment cost, biasing the ICER downwards.

In the absence of a robust analysis of time on treatment, the EAG considered this an area of uncertainty which had a considerable impact on the ICER. To capture the GNX discontinuation rate more accurately using the data available to the EAG (i.e., summary-level data from the Marigold trial), the EAG estimated the total person time at risk of discontinuation in the Marigold DB phase (i.e., GNX dosed days) in units of 28 days to match the company's model, using Table 12 in the Marigold CSR.[14] The resulting rate (converted to a probability) was [redacted] per 28 days. This is detailed in Section 6.2.1. The EAG used this discontinuation rate in its base case.

The company model applied discontinuation randomly within the sample, rather than this being based on response to GNX, which the EAG considered implausible. A clinical expert informed the EAG that an assessment at 6 months from baseline would be conducted, at which time a patient would be considered for continuation or discontinuation of treatment. There was no consensus on the threshold of SF reduction which should be used to make this decision, and at clarification the company confirmed that they have not defined specific discontinuation criteria for GNX, and so the EAG was unable to consider this further. However, the EAG considered it plausible that an informal stopping rule would be adopted in practice, which would be associated with considerable improvement to the cost-effectiveness of GNX.

One course of GNX treatment possible during patient lifetime

A clinical expert informed the EAG that people would likely not receive GNX permanently but would stop and re-initiate treatment over their lifetimes. The plausibility of this would be evident with experience of its use in clinical practice, however benefits of this approach would include reduced polypharmacy, which is a major concern for people with CDD. If this occurred, eventually there would be a stable proportion of people being retreated with GNX. On the individual level for cost-effectiveness modelling, this was more complicated and required data

that was not available (i.e., time to event data on time to retreatment with GNX given number of previous rounds of GNX treatment). As these data did not exist, the EAG was unable to factor this into the cost-effectiveness modelling. This therefore remained an area of uncertainty.

4.2.6.3. Mortality

The company modelled the mortality of people with CDD based on a standardised mortality ratio (SMR), which was based on values provided by Chin *et al*'s study on LGS mortality and HCRU.[24] The SMR calculated by the company was 8.33, based on the ratio 5/0.6 deaths per 1,000 person-years. The value of 5 was taken as the midpoint from the statement: *"Results from the present study, using ONS linked data, demonstrate patients with LGS have a crude mortality rate of 4–6 per 1000 person-years"*. This rate was applied to the company's extrapolation of general population overall survival. The result was reported in CS Figure 17.

The key mortality assumptions made by the company, along with a summary of the EAG critique is summarised in Table 17 with further details provided in the subsections below.

Table 17: Summary of key assumptions about mortality made by the company

Assumption	Company evidence and/or justification	EAG position, comments, and importance
No explicit relationship between SF and mortality	None provided	**Medium importance:** Inconclusive. There were several publications linking SF to ORs for SUDEP, but not in a CDD population • SUDEP was a known issue in epileptic conditions and increased SF was highlighted as a risk factor, implying a relationship between SF and mortality • There was some evidence suggesting generalised seizures and ASM use were both associated with increased SUDEP risk in epilepsy[25] • Incorporating this into the model would decrease the ICER for GNX
Unclear derivation of mortality estimate	Limited explanation of source material provided	**Low importance:** EAG agreed with the overall approach taken to base mortality on proxy diseases given lack of data for CDD, but the derivation of the SMR is unclear • Mortality had a small impact on results if no difference is assumed between arms • However, mortality ultimately drove how long carer benefits were modelled, so it was necessary to ensure the approach taken was plausible

Key: ASM, anti-seizure medication; CDD, CDKL5 deficiency disorder; EAG, External Assessment Group; GNX, ganaxolone; ICER, incremental cost-effectiveness ratio; OR, odds ratio; SF, seizure frequency; SMR, standardised mortality ratio; SUDEP, sudden unexpected death in epilepsy.

No explicit link between SF and mortality

The company did not link mortality to SF, a factor which may have led to a slightly conservative analysis. There was a known relationship between seizures and sudden unexpected death in epilepsy (SUDEP), with some papers publishing odds ratios by level of SF. For this reason, it may be the case that reducing SF in a population could be associated with a marginal survival benefit, though the magnitude of this is likely to be small considering the -27.08% HL shift between arms in Marigold.

Determination of mortality in CDD relative to general population

As there is a lack of long-term data for survival amongst people with CDD, mortality estimates used in the company model are highly uncertain. Clinical advisors to the EAG disagreed widely on estimations of survival, and whether estimates for LGS (which is a common diagnosis in people with CDD) may offer a reasonable proxy estimate. Chin *et al.* reported crude mortality rates of 6.12 and 4.17 for confirmed and probable LGS per 1000 person-years, respectively. [24] Therefore, in the absence of data in the target population, the EAG suggested that the average crude mortality rate of the confirmed and probable LGS values reported by Chin *et al* should be used. This was a small change, and the effect on the cost-effectiveness model results was negligible in the company's original base-case analysis

The EAG was unable to reconcile the 0.6 per 1000 person-year value with the citation provided in the company submission, or the corresponding citation from Chin *et al.* The document cited was Death registrations, Populations and Age Standardised Rates, England 1981 to 2018. [26] The reported statistics are per 100,000 population, not per 1000 person-years, and it was unclear to the EAG how these rates could be used to calculate rate of death per person-year without further (and therefore uncited) information.

4.2.7. Health-related quality of life

Within the company's base-case model, utility values for patients were estimated based on a published study by Lo *et al.*, (2022) which allowed for differences in utility to be estimated according to the frequency of seizures within a given model cycle (the company explained that this approach was validated by a Key Opinion Leader (KOL), with reference to a review of types of seizures, their impact, and general comparability to CDD). [27] These utility values were then adjusted according to general population norms to take into consideration the impact of aging. A sensitivity analysis was presented using data from a study by Auvin *et al.*, (2021). [28]

For caregivers, utility values were also taken from Lo *et al.*, (2022), and were based on the estimated frequency of seizures, with each patient having an assumed number of caregivers for whom utility was impacted while patients were still alive. [27] However, no age adjustment was applied for caregivers. In the sub-sections that follow, a critique of these approaches is provided.

4.2.7.1. Patient utility

Lo et al. (2022) was a vignette study that aimed to produce utility values for people with tuberous sclerosis complex (TSC), and their caregivers. From this study, the company extracted values shown in Table 18.

Table 18: Utility values taken from Lo *et al.*, (2022) – patient utility

Label in Lo *et al.*	Value: mean (SE)	Description in Lo *et al.*	Application in company's model
P1	0.7250 (0.0250)	0 GSD^{-1}; 0 FSD^{-1}	[redacted]
P2*	0.5040 (0.0370)	0 GSD^{-1}; 1-2 FSD^{-1}	[redacted]
P3*	0.2820 (0.0530)	0 GSD^{-1}; 3-4 FSD^{-1}	[redacted]
P4*	0.0740 (0.0550)	0 GSD^{-1}; 5-14 FSD^{-1}	[redacted]
P5	0.1830 (0.0570)	1 GSD^{-1}; 0 FSD^{-1}	[redacted]
P6	0.0890 (0.0540)	2 GSD^{-1}; 0 FSD^{-1}	[redacted]
P7	-0.1130 (0.0590)	3-4 GSD^{-1}; 0 FSD^{-1}	[redacted]
P8*	-0.2340 (0.0560)	3-4 GSD^{-1}; 5-14 FSD^{-1}	[redacted]

Key: FSC^{-1}, focal seizures [with impaired awareness] per 28-day model cycle; FSD^{-1}, focal seizures [with impaired awareness] per day; GSC^{-1}, generalised seizures per 28-day model cycle; GSD^{-1}, generalised seizures per day; SE, standard error.

Note(s): *These greyed-out values are not applied in the company's base-case analysis, since focal seizures were not modelled.

Source(s): Values taken from Lo *et al.*, (2022). [27] Company model description based on submitted model file.

An alternative utility source was provided by the company and used in a scenario analysis. This was a different vignette study of people (and caregivers) with LGS or DS by Auvin *et al.*, (2021). The company did not state whether KOL validation was performed on this study (as well as the study by Lo *et al.*) to assess its suitability for use in this modelling context, nor did it explicitly state why Lo *et al.* was chosen in favour of Auvin *et al.* to inform its base-case analysis. The Auvin *et al.* study reported utility values based on the number of seizures within a month versus the number of SFD. The utility values from this study that were applied in scenario analysis ranged from 0.83 (0 seizures per month) to 0.36 (130 seizures per month).

There were some important limitations with the company's approach using Lo *et al.*. First, from Table 18 it could be seen that patients experiencing 0-27 seizures per 28 days were assumed to have the utility of the health state in Lo *et al.* defined as having 0 seizures per day. This assumption was incompatible with the fact that 0% of patients on both treatment arms were modelled to have 0 seizures per 28-day model cycle as a direct consequence of using a lognormal distribution to describe SF (see Section 4.2.6 for further details concerning estimation of SF). No information was available from Lo *et al.* concerning the utility of patients experiencing between 1 and 27 seizures per 28 days (i.e., greater than 0 per day, but less than 1 per day on average). Therefore, the EAG considered that the application of the values from Lo *et al.* may lack accuracy in describing the impact of SF on patient utility, with the expectation that in general, patient utility may be overestimated (e.g., a patient with 0.9 seizures per day is modelled to have the utility of 0 seizures per day, rather than 1 per day or a value between these estimates).

The second limitation was that there was a misalignment of the descriptions of seizures by type used in the study by Lo *et al.* and the company's model. The company's model took data from Lo *et al.* regarding generalised seizures (in its base-case analysis) and assumed these could be used as a proxy to describe the impact on utility for patients that experience primary ("major motor") seizures, excluding the impact of any focal seizures. It was unclear to the EAG whether this meant the impact of seizures on utility is under- or over-estimated by the company's model, considering that Lo *et al.* demonstrated that the addition of focal seizures had a marked impact on utility (i.e., an increase in focal seizures on top of generalised seizures led to a further decline in utility). Furthermore, it was unclear precisely how much overlap there was (in terms of utility impact) for patients that experienced generalised versus primary ("major motor") seizures.

In addition to these limitations, there was additional uncertainty with using data generated from a vignette study in a different patient population to inform utility values within the company's model. The EAG considered the two populations from the vignette studies (TSC [Lo *et al.*] and LGS or DS [Auvin *et al.*]) to be potential proxies for CDD. However, the EAG undertook further exploratory analysis of the utility values used in the company's model to investigate how influential alternative values were on model results (see Section 6.2).

There was a small difference in the percentage of SFD between the PBO and GNX arms in Marigold, both at baseline and at the end of follow up. This difference may have resulted in differences in patient HRQoL in states of the world with and without GNX included in the

treatment pathway for CDD. Clinical experts supported the importance of SFD to patient and caregiver health-related quality of life, further illustrating the merit of Auvin *et al.* to inform utility values within the model.

The utility values estimated by Auvin *et al.* were generally higher than those in Lo *et al.,* but both studies showed that increased SF was associated with considerable disease burden. In Auvin *et al.,* the range in health states was 0.21-0.83 (1 SFD and 130 seizures per month vs seizure-free). However, caregiver utilities were provided in the supplementary materials to the article which were lower than those applied to people with LGS or DS, which the EAG considered to lack face validity (see Section 4.2.7.2).

Overall, the EAG considered Auvin *et al.* to be a more appropriate study to inform utility values and applied the reported outcomes within its preferred base-case analysis for the following reasons:

- Auvin *et al.* utilities are for the same disease as Chin *et al.* for HCRU and mortality[24,28]
- Auvin *et al.* utilities cover more granular health states for SF
- Auvin *et al.* utilities take into account the proportion of SFD patients have

4.2.7.2. Caregiver utility

As per patient utility in the company's base-case analysis, the utility impact for caregivers was based on data from the study by Lo *et al.* (2022).[27] A summary of the corresponding utility values from this study is provided in Table 19.

Table 19: Utility values taken from Lo *et al.*, (2022) – caregiver utility

Label in Lo *et al.*	Value: mean (SE)	Description in Lo *et al.*	Application in company's model
P1	0.9050 (0.0080)	0 GSD^{-1}; 0 FSD^{-1}	[redacted]
P2*	0.7910 (0.0170)	0 GSD^{-1}; 1-2 FSD^{-1}	[redacted]
P3*	0.6380 (0.0370)	0 GSD^{-1}; 3-4 FSD^{-1}	[redacted]
P4*	0.4310 (0.0490)	0 GSD^{-1}; 5-14 FSD^{-1}	[redacted]
P5	0.5460 (0.0390)	1 GSD^{-1}; 0 FSD^{-1}	[redacted]
P6	0.4760 (0.0450)	2 GSD^{-1}; 0 FSD^{-1}	[redacted]
P7	0.3190 (0.0480)	3-4 GSD^{-1}; 0 FSD^{-1}	[redacted]
P8*	0.2210 (0.0530)	3-4 GSD^{-1}; 5-14 FSD^{-1}	[redacted]

Key: FSC^{-1}, focal seizures [with impaired awareness] per 28-day model cycle; FSD^{-1}, focal seizures [with impaired awareness] per day; GSC^{-1}, generalised seizures per 28-day model cycle; GSD^{-1}, generalised seizures per day; SE, standard error.

Note(s): *These greyed-out values are not applied in the company's base-case analysis, since focal seizures were not modelled.

Source(s): Values taken from Lo *et al.*, (2022).[27] Company model description based on submitted model file.

Within the company's model, caregivers were modelled to be separate entities to patients. This assumption entailed caregiver utility falling out of the scope of the NHS and PSS perspective upon the death of the patient being cared for. In a model, this is mechanically identical (though philosophically different) to assuming that the caregiver dies along with their patient. An immediate consequence of how caregiver utility was modelled was that estimates of survival were important drivers of caregiver QALYs, since this drove how long a difference in utility was modelled between the treatment arms (unless there was no difference in modelled survival between arms, per models 1 and 3). This result was exaggerated when considering that patients could have multiple caregivers (in this case, 1.8 caregivers until the age of 18 years, and then 1 after this point in time). At clarification stage, the company explained that values of 1.8 and 1 were chosen "due to the contribution of parental care during childhood and reflecting the average number of parents would be less than 2; after which the average reduces at age 18 due to patients reaching adulthood." (Company's response to clarification question B13). While based on assumption, the EAG considered it plausible that people with CDD under the age of 18 may have multiple caregivers versus adult patients.

In past NICE appraisals of ASMs for Dravet Syndrome (such as TA808 and TA614), the committee's preference was to take a "decrements only" approach to incorporating carer utility within a cost-effectiveness model. For example, the final guidance from TA808 contains a section titled: *"Incorporating carers' quality of life in the model is appropriate but this should be done by applying a carer disutility"* (TA808 technology appraisal guidance, p.23).[29] More specifically, the committee commented that incorporating carer utility – whereby caregivers were modelled to die at the same time as the patient – was unusual and would result in biased results. In the context of the current appraisal, the EAG concurred in principle with the preference of the committee for TA808 and agreed that carer utilities should only be considered in terms of disease burden additive to that of the patient being cared for. However, there are other limitations with using a "decrements only" approach, especially when the disease burden is extremely high as in CDD, due to the perverse incentives the approach may provide. In this appraisal, the EAG did not consider the use of a "decrements only" approach to caregiver

utilities to avoid negative utilities and difficulty with interpretation of results, and thus retained the utility approach used by the company. However, the EAG acknowledged the limitations of this approach, and that this was inconsistent with previous NICE committee preferences.

While not highlighted within the CS or implemented in the cost-effectiveness model, the study by Auvin *et al.*, (2021) also provided utility values for caregivers. These were reported in the supplementary appendix to the main text of this study. Values included:

- 0.38 (130 seizures and 3 SFD in an average month)
- 0.52 (80 seizures and 15 SFD in an average month)
- 0.78 (0 seizures, and 30 SFD in an average month)

The EAG was unclear on why these values were not incorporated into the scenario analysis which makes use of the Auvin *et al.* utility values for patients, and instead the company used values from Lo *et al* to inform the Auvin scenario. Furthermore, the EAG noticed that the company's implementation of Auvin *et al.* calculated the utilities of the states relative to the best state (seizure-free), rather than applying the utility values reported as they are reported. As no justification for or mention of this was provided by the company in its submission, the EAG implemented Auvin *et al.* as (absolute) utility values for both caregivers and patients in its base-case, per NICE methods guidance.

4.2.7.3. General population adjustment

The company applied the study by Ara & Brazier 2010, [30] which was used in previous NICE technology appraisals. However, this publication did not include the variance-covariance matrix required to apply a multivariate normal distribution to simulate the correlation structure between the parameters. Consequently, varying the parameters of the equation published in the article led to an unknown bias in the probabilistic results.

In 2022, the NICE decision support unit (DSU) published updated general population norms, which then updated the preferred source for NICE. [31] This source also provided a variance-covariance matrix which allowed the utilities to be varied according to their correlation structure. However, within the timeframe of the appraisal, the EAG chose not to apply this in the model as it was anticipated that it would have a small impact on model results.

4.2.8. Resources and costs

The company's model included costs that could broadly be considered to fall into one of three categories: (i) drug acquisition and treatment administration, (ii) health-state and resource use, and (iii) resolution and management of adverse reactions. These are discussed in the sub-sections that follow.

4.2.8.1. Drug acquisition and administration

GNX was administered orally three times daily with food, based on the following weight-based dosages:

- For patients weighing 28 kg or less:
  - Maximum dose 63 mg/kg per day (see CS Section B.3.5.4.1)
  - Average dose of [redacted] mg/kg per day (see CS Table 37)
- For patients weighing more than 28 kg:
  - Maximum dose 1,800 mg per day (see CS Section B.3.5.4.1)
  - Average dose of [redacted] mg/kg per day (see CS Table 37)

Initiation of GNX was based on a titration schedule for the first three weeks of treatment, again based on patient body weight (schedule taken from the FDA prescribing information)[32]:

- For patients weighing 28 kg or less:
  - Days 1 to 7: 18 mg/kg per day
  - Days 8 to 14: 33 mg/kg per day
  - Days 15 to 21: 48 mg/kg per day
- For patients weighing more than 28 kg:
  - Days 1 to 7: 450 mg per day
  - Days 8 to 14: 900 mg per day
  - Days 15 to 21: 1,350 per day

In addition to GNX, the company's model included two other types of drug acquisition costs: ECM and rescue medication. ECM was costed at £15 per day, irrespective of SF or treatment assignment. Rescue medication costs were omitted from the company's Model 1, as a cost of £0 per day was attributed to rescue medication. Both costs were applied as a daily cost, and the CS stated that in the Marigold study, *"… patients could receive a broad range of medications and other treatments concomitantly; received by both patients on ECM alone and ECM + GNX"*

and that *"no difference between arms"* was observed (CS Section B.3.5.4.1, Table 37). At Model 2 onwards, the company incorporated these based on a previous NICE TA (see Table 11). However, the implementation was incorrect (See Section 6.1.7).

The company model did not include any administration costs for GNX or other treatments given to patients as part of ECM across both arms.

In the company's model, the titration schedule for GNX was not explicitly modelled (nor was it defined within the CS). While the EAG would have preferred for the titration schedule to be explicitly modelled for accuracy of costings, it did not consider the omission of this likely to have a large impact on the overall acquisition costs of GNX.

Patients were assumed to enter the company's model aged [redacted], with a mean body weight of [redacted] kg (based on data collected in the Marigold trial). Over the course of the model's time horizon, the average weight of the cohort increased as patients aged, and the required dose was adjusted accordingly.

The company's model assumed no wastage in the acquisition cost of GNX. It was the EAG's understanding that GNX would be available in 110 mL (50 mg/mL) bottles, containing a total dose of 5,500 mg. Taking the maximum daily dose of 1,800 mg as an example, this meant that one bottle would provide at least three days treatment with some remaining (3 x 1,800 mg = 5,400 mg, with 100 mg remaining). The EAG considered it plausible that some wastage would occur both while administering a dose to a patient and in the changeover between bottles. Clinical advice suggested that around 10% of each bottle may be wasted in real-world practice.

The EAG considered the inclusion of ECM at a simple cost of £15 per day to be reasonable though arguably unnecessary given that no difference to ECM was expected across arms, and that this cost therefore had no impact on incremental costs in the model unless there is a difference in overall survival between arms.

Several errors with the company's implementation of rescue medication costs were identified by the EAG. These are addressed in Section 6.1.7. As noted above, at Model 2 onwards (see Table 11), the company incorporated rescue medication, based on NICE TA614 (mislabelled as ID1211 in the "CostParams" sheet). The EAG presumed that the values entered into the cost-effectiveness model were based on the values presented in Tables 29 and 30 of the CS in the TA614 committee papers. [33] Yet the implementation in the cost-effectiveness model does not match the align with the values those tables.

The company's model did not include any administration costs for GNX. Given that GNX was anticipated to be administered three times daily in the community setting, and that there was no difference in modelled ECM costs, the EAG considered the omission of an administration cost to be appropriate.

The impact of addressing the discordance in the anticipated dosing regimen for GNX versus the application in the company's model is explored further in Section 6 of the EAG's report, and a revised application was incorporated within the EAG's preferred base-case analysis (see Section 6.3). In addition, an alternative approach to account for potential wastage was also considered in Section 6 of the EAG's report.

4.2.8.2. Health-state and resource use

In the company's base-case analysis, health-state and resource use costs were included on the basis of a study by Chin *et al.*, (2021).[24] This was a retrospective linkage cohort study using data from the UK Clinical Practice Research Datalink (CPRD) GOLD database of patients with LGS. This study reported estimated frequencies of specific resource use items per patient year, stratified by whether patients were aged <12 or ≥12 years of age. In its model, the company applied the estimated frequencies for patients aged <12 years of age with 'confirmed' LGS (excluding those with 'probable' LGS). No explanation was provided in the CS concerning the restriction to patients aged <12 years of age or those with confirmed LGS.

The following costs were captured within the model: General practitioner (GP) consultation, GP home visit, GP phone call, nurse consultation, nurse home visit, nurse phone call, hospital outpatient visits, hospital inpatient admissions (all cause), hospital inpatient admissions (epilepsy related), and accident and emergency (A&E) visits. However, the latter two of these (i.e., epilepsy related inpatient admission and A&E visits) were assumed to differ between treatment arms – all other items were assumed to have the same frequency for both treatment arms for the full model time horizon.

The company acknowledged that use of inputs from Chin *et al.*, (2021) represented a non-CDD population, and as such inputs from other proxy conditions could have also reasonably been included. Therefore, the company provided an alternative option using inputs from a study by Lagae *et al.*, (2019).[34] This study comprised a survey of mostly European patients with DS and their caregivers, with total costs reported in USD, but results were presented on a subgroup analysis of UK patients only. While not explicitly stated in the CS, costs appeared to have been

converted from 2016 USD into 2021 GBP using a ratio of approximately 0.811. The specific categories included are presented in Table 40 of the CS (Section B.3.5.5.2, p.110).

The CS stated that in using this alternative approach, it was assumed that *"… there was no difference in the healthcare resource use between GNX as adjunctive therapy and ECM alone arms"* (CS, Section B.3.5.5.2, p.110). However, this was incorrect as similar to the base-case approach, GNX was assumed to lead to a 27.08% reduction in emergency visits and ambulance calls.

Overall, this alternative approach led to a smaller difference in the per-cycle resource use costs across both arms, as illustrated in Table 20.

Table 20: Comparison of resource use costs per 28 days

Arm	Chin *et al.* (2021) cost per 28 days	Lagae *et al.*, (2019) cost per 28 days
ECM alone	[redacted]	[redacted]
GNX + ECM	[redacted]	[redacted]
Difference	[redacted]	[redacted]

Abbreviations: ECM, established clinical management; GNX, ganaxolone.

Owing to a lack of data to the contrary, the EAG tentatively accepted the company's base-case approach to use the study by Chin *et al.* to inform resource use estimates that did not vary by treatment arm, with the understanding that there may have been differences in real-world practice (possibly in favour of GNX, if resource use was related to SF). Instead, the EAG focused its critique on the two items that were assumed to differ between treatment arms and therefore impact the model results.

In Chin *et al.*, (2021), 1.50 admissions associated with epilepsy were estimated per patient year (<12 years of age with confirmed LGS), whereas for GNX patients a 27.08% reduction in hospital admissions was assumed (using the point estimate of reduction in SF, discussed further in Section 4.2.6.1 of the EAG's report), resulting in 1.09 admissions per patient year. The same approach to capture the difference between arms was used to adjust the number of A&E admissions in the company's model: 0.85 for ECM, reducing to 0.62 for GNX (i.e., a reduction of 27.08%). The CS stated that this assumption *"was validated by the clinical KOL consulted"* (Section B.3.5.5.1).

The main assumption inherent in this approach was that a reduction in SF was perfectly positively correlated with the number of epilepsy-related hospital admissions and A&E visits. No empirical evidence was presented in support of this assumption, though the EAG acknowledged that limited data were expected to be available within the context of a CDD population. While this assumption was potentially plausible, the EAG highlighted that not all seizures would result in hospitalisation or an A&E visit. As such, a better proxy for the difference in resource use could potentially have been based on only including severe seizures (or at least specific types of seizures known to be linked with hospitalisation). The potential impact of this on the model results remained unclear and could have plausibly led to a lesser or greater reduction in resource use costs associated with GNX.

The unit cost used for an epilepsy-related hospital admission was £6,545.75, based on NHS reference costs 2020/21. A weighted average by the recorded number of Finished Consultant Episodes (FCEs) for the codes PRO2A, PRO2B, and PRO2C (paediatric epilepsy syndrome), as a non-elective long-stay admission. The EAG noted that the assumption of a long-stay admission was somewhat at odds with the Chin *et al.*, (2021) study which reported an average length of stay for an epilepsy-related hospital admission of 2.48 days (<12 years of age with confirmed LGS). However, the CS cited a study by Mangatt *et al.*, (2016) to support the assumption of a long-stay admission in a CDD population, citing an average length of stay of 27.4 days. [35] The exact quote from Mangatt *et al.*, (2016) was: *"For the children of the 69/91 families with seizure-related admissions who provided sufficient detail on these, the mean number of days in hospital due to seizure-related events was 27.4 (median 19 days, range 1 day to 4.9 months)"*. [35] The EAG highlighted that it was unclear from this whether the value of 27.4 days referred to an average length of stay per admission, or an overall average length of stay in hospital over an extended period of time potentially covering multiple admissions. As such, the EAG explored an alternative analysis wherein a non-elective short-stay admission was used in place of a long-stay cost (reducing the cost from £6,545.75 to £1,036.71). This cost was used in the EAG's base-case analysis.

4.2.8.3. Resolution and management of adverse events

The company's model also included costs associated with the resolution/ management of AEs. The approach used to capture these costs was relatively simple. The proportion of patients across both arms in the Marigold trial that experienced any AE requiring or prolonging

hospitalisation ([redacted] out of 101, [redacted]%) were assigned the cost of an inpatient stay (£1,182) at each model cycle for the full model time horizon.

The EAG highlighted two potential issues with the approach taken to capture costs associated with AEs. First, the EAG considered it inappropriate to apply this proportion at each model cycle across the full model time horizon (i.e., that it was unlikely that [redacted]% of patients would require an inpatient stay every 28 days). In Section 6 of the EAG's report, a revised approach was proposed to incorporate this adjusting for the duration of the Marigold trial (see Section 6.3). However, this change had no impact on the model results since no difference in the occurrence of AEs by treatment arm was modelled.

Second, the risk of AEs was assumed to be symmetrical in the GNX and ECM arms, which the EAG considered to lack face validity. While GNX was not associated with a major increase in AEs within the Marigold trial, some differences in AEs were noted by the EAG (see Section 3.2.3.1). Due to uncertainty about the generalisability of rates of AEs in the trial (caused by the small sample size and low event rate of AEs), and the expectation that AE costs would have little impact on model results, the EAG elected not to change this assumption in the model, despite its limitations.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

The results reported by the company are shown in Table 21 (based on Model 3, see Table 11). The deterministic and probabilistic results were associated with ICERs of £22,200 and £23,139 per QALY gained, respectively. However, the EAG identified errors in the company base-case analysis, and the corrected company base case results are presented in Section 6.1. Of note, the EAG highlighted that a severity modifier of 1.7 was applied both to patient and caregiver incremental QALYs. The severity modifier is discussed further in Section 7.

Table 21: Company base case results (model 3)

	Discounted costs	Discounted QALYs*	Incremental discounted costs	Incremental discounted QALYs*	Cost per QALY gained
Company deterministic base case					
ECM	[redacted]	[redacted]	-	-	-
GNX + ECM	[redacted]	[redacted]	[redacted]	[redacted]	£22,200
Company probabilistic base case					
ECM	[redacted]	[redacted]	-	-	-
GNX + ECM	[redacted]	[redacted]	[redacted]	[redacted]	£23,139

Abbreviations: ECM, established clinical management; GNX, ganaxolone; QALYs, quality adjusted life years;.

Note: *QALYs presented are adjusted to account for a severity modifier of 1.7, which is applied to the QALYs gained by both patients and their caregivers. Numerical results differ to those contained within the original company submission owing to edits made post-submission (see Table 11).

5.2. Company's sensitivity analyses

5.2.1. One-way sensitivity analysis

To explore the impact of changing key model parameters on the ICER, the company undertook a deterministic one-way sensitivity analysis (OWSA). The results of this analysis are provided in Figure 2 in the form of a tornado plot. The main parameters shown to influence the ICER were related to the dosing of GNX, utility values (including the number of caregivers), medical resource use, and the average age of patients entering the model.

Figure 2: Company's one-way sensitivity analysis tornado plot (model 3)

Abbreviations: FS, focal seizures; GS, generalized seizures; ICER, incremental cost-effectiveness ratio.

The EAG noted that all parameters were varied based on taking values equivalent to plus or minus 20% of the base-case value, regardless of any available information concerning parameter uncertainty (e.g., standard error [SE]) or skew within the distribution for each parameter. This also meant that the uncertainty expressed within the OWSA was misaligned with the uncertainty feeding into the probabilistic sensitivity analysis (PSA).

To illustrate this issue with an example, the primary measure of treatment effect took a base-case value of 27.08% and was varied at bounds of 21.66% and 32.50% in the OWSA. However, this parameter was sampled according to a Beta distribution within the PSA, using a SE of approximately 0.0969. If 2.5th and 97.5th percentiles were drawn from a Beta distribution using this information, the equivalent bounds would be 10.55% and 47.92%. This would be more closely aligned with the original 95% CI reported in the CS of 9.95% to 47.92% (CS, Section B.3.3.1.2, Table 31). Taking these values of the HL location shift, the ICER range was estimated to be [redacted] (lower bound) and [redacted] (upper bound). Therefore, it was the EAG's view that the OWSA did not adequately reflect the 'true' parameter uncertainty inherent within the company's model, and did not provide a reliable basis on which to determine which parameters appear to have the greatest influence on results, or the magnitude of impact on results.

5.2.2. Probabilistic sensitivity analysis

In addition to the OWSA, the company also undertook a probabilistic sensitivity analysis (PSA) to further explore parameter uncertainty. To do this, 1,000 iterations of the model results were produced informed by sampled parameters. The results of this analysis are provided in [redacted]

in the form of a scatterplot, demonstrating the incremental costs and QALYs for the comparison of GNX + ECM versus ECM alone. Per the company's base-case analysis, the probability that GNX + ECM was cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained (taking into consideration severity weighting*) is [redacted] and [redacted], respectively.

[redacted]

Abbreviations: ECM, established clinical management; GNX, ganaxolone; QALY, quality-adjusted life year.

Note: Scatterplot re-formatted for ease of interpretation by presenting incremental scatterplot, changing colours, adding reference lines for willingness-to-pay thresholds, average results, and adjusting dimensions of plot for clarity of presentation within this report. Numerical results are unchanged from company's model re-submitted in response to clarification questions. Numerical results differ to those contained within the original company submission owing to edits made post-submission.

The EAG noted with respect to [redacted] that there was a large spread in the results outputted by the PSA, with incremental QALYs ranging from [redacted] to [redacted], and incremental costs ranging from [redacted] to [redacted] (the deterministic and mean probabilistic results were also similar).

In its submission, the company speculated that the average probabilistic ICER was slightly higher than the deterministic ICER due to *"a 'floor effect' introduced by attempts to*

* Severity weighting applied per company's base-case approach.

conservatively model the left-skewed [SF] *data from the Marigold study"* (CS, Section B.3.10.1.3, p.120). However, the EAG noted that the average ICER presented in the CS was taken as the average across each iteration, rather than basing this on the ratio of the average incremental costs and QALYs in each instance. When re-calculating the mean probabilistic ICER (and taking into consideration the edits made by the company following clarification questions), the results were broadly aligned (see Table 21). The EAG therefore did not consider the company's comment regarding a 'floor effect' to be of material impact to decision making. Overall, the EAG did not identify any major concerns with the PSA undertaken by the company. However, owing to the number of assumptions made to inform the model, the EAG noted that the results of the PSA may underestimate the true uncertainty associated with the model results.

5.2.3. Scenario analyses

In its original submission (i.e., using model 1), the company presented several deterministic scenario analyses to further test model settings and assumptions.

Scenario analyses were not updated following submission of model 2 or 3. For completeness, the EAG attempted to re-produce all the scenarios using model 3, and available results are shown in Table 22. The EAG was unable to re-produce the results of scenarios B and C provided in the CS as changing the related settings in the model did not replicate the results presented by the company, and so Table 22 includes the ICERs the EAG calculated when changing the relevant model settings.

Overall, the EAG highlighted that the range of scenarios presented by the company was limited in number. Other scenarios of potential interest included exploration of alternative discontinuation rates, inclusion/exclusion of rescue medication costs, and alternative assumptions related to mortality. Where feasible within the timeframe available to the EAG to conduct its review, further analyses were undertaken and are reported in Section 6.2 of this report.

Table 22: Summary of company scenario analyses

Scenario*	CS ICER	EAG comment	EAG calculated ICER post-CQs†
Base case	[redacted]	-	[redacted]

Scenario*	CS ICER	EAG comment	EAG calculated ICER post-CQs†
A	[redacted]	Switch included within the company's model, which functions as intended.	[redacted]
B	[redacted]	No switches provided but could re-produce manually and in automated scenario analysis incorporated by the EAG. Results do not match CS as base-case has changed at Models 2 and 3 (Table 11), and the company have not provided any results errata or addenda.	[redacted]
C	[redacted]		[redacted]
D	[redacted]		[redacted]
E	[redacted]		[redacted]
F	[redacted]		[redacted]

Abbreviations: CQs, clarification questions; CS, company submission; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio.

Note: *For scenario labels, please refer to CS Table 50; †ICERs presented here are aligned with the company's base-case results provided at clarification stage. **Note that this matches the ICER of Model 3 sent to the EAG, see Table 11.

5.3. Model validation and face validity check

The company did not present any information concerning model validation. While the company stated that no published economic evaluations of treatments for CDD were identified in the SLR (CS, Section B.3.13.1, p.123), the EAG did not consider this to be sufficient justification in accordance with NICE methods. [36] The CS stated that steps were taken to test the proposed data and conditions used as proxies via validation with a clinical KOL, but no further details were provided. As such, the EAG was unable to critique the company's approach taken to model validation and assessing the face validity of results.

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified a number of limitations within the company's base case and explored the impact of parameter values and assumptions that the EAG believes are more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the company model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis.

In Section 6.3, the EAG base-case is presented based on a combination of the exploratory analyses presented in Section 6.2, and taking into consideration the corrections made in Section 6.1.

6.1. EAG corrections and adjustments to the company's base case model

The EAG identified errors in the original model submitted by the company (model 1). In its response to clarification (questions B16, B17, B23, B26, C1, C2), the company resolved several of these, which were then considered to be resolved and not discussed further in this section. However, a number of errors were remaining in model 3. These are summarised in Table 23, and where necessary, more detail is then provided in the sections that follow.

Table 23: Errors found in Company's cost-effectiveness model

Error found and section (if necessary)	Importance and explanation	EAG solution
Error 1: The application of the HL shift estimate to the distribution of SF was mathematically incorrect ([redacted]), considerably overestimating the treatment effect. Section 6.1.1	**High**. The ICER was sensitive to SF and the error results in a modelled ~67.5% reduction in mean, median and SD SF, not 27.08% or 29.31% as per HL estimates	The EAG followed [redacted] correct the error. This resulted in reductions in mean, median and standard deviation in line with the HL estimates reported (via simulation).
Error 2: Caregivers were simulated to be ageless and their utilities were not age-adjusted	**High**. Caregiver utility was implemented as constant, leading to an overestimate of caregiver QALYs	The EAG used ONS data[37,38] on the distribution of age at parenthood and the baseline age of CDD patients in Marigold to estimate the age of caregivers at baseline, then used this to age-adjust their utility values using Ara & Brazier 2010

Error found and section (if necessary)	Importance and explanation	EAG solution
Error 3: The company omitted the caregiver utility values reported in the supplementary materials of Auvin *et al.* 2021 from the model. Instead, the company linked to the caregiver utilities from Lo *et al.* 2021. Section 4.2.7.2	**High** when Auvin et al. was used as utility source (no effect on company base-case, but considerable effect on EAG base-case)	The EAG incorporated the omitted caregiver utilities from Auvin *et al.*
Error 4: The implementation of rescue medication was incorrect, overestimating the cost and therefore the cost reduction of GNX. Section 6.1.7	**High** cost of rescue medication was considerably overestimated, which disproportionately benefitted GNX	The EAG corrected the error by calculating the proportion of patients in each state at each timepoint and calculating a weighted average cost using the correctly inflated rescue medication cost value
Error 5: The parameters were not varied correctly in the one-way sensitivity analysis. Section 5.2	**High**. The company's tornado plot was misleading and does not appropriately reflect the true sensitivity of the ICER to changes in model parameters	This issue increased uncertainty in model results
Error 6: Absolute utility values estimated via Ara & Brazier 2010 were applied to patient utilities as multipliers.	**Moderate**. This should be relative to general population age- and sex- adjusted utility at baseline	The EAG calculated age-adjusted utilities relative to their value at baseline
Error 7: The maximum SF per 28 days included in the model was 400, meaning the total density in each distribution was not the same and the area under the curve did not approach 1. Section 6.1.4	**Moderate**. The 400 limit underestimated QALY benefit of GNX	The EAG expanded SF to 1000/28d to ensure that >99% of the density was included for both treatment arms and the distributions could be more consistently compared
Error 8: The values from Lo et al were not applied correctly due to a small overlap in days (28 days). Section 6.1.2	**Low**. ICER effect was small	The EAG fixed this error and included this in its automated scenario analysis
Error 9: The SMR based on Chin *et al.* was incorrectly based on rounded values. Section 6.1.5	**Low**. ICER effect was small	The values 6.12 and 4.17 from Chin *et al.,* are used by the EAG instead of 6 and 4.
Error 10: The scenario analyses presented in the CS could not be replicated accurately by the EAG due to model version changes and lack of automation. Section 5.2	**Unclear**.	The EAG have built automated scenario analysis into the cost-effectiveness model to ensure consistency. The EAG uses their own scenario results for inference

Error found and section (if necessary)	Importance and explanation	EAG solution
Error 11: The probabilistic ICER was calculated incorrectly as the mean of the probabilistic ICERs, rather than the mean of incremental costs divided by the mean of incremental QALYs	**Low**. Affects uncertainty estimations	The EAG included a single cell in the PSAcalcs sheet which calculated the correct probabilistic ICER

Abbreviations: EAG, external assessment group; CDD, CDKL5 deficiency disorder; DS, Dravet's syndrome; HL, Hodges–Lehmann; ICER, incremental cost-effectiveness ratio; LGS, Lennox-Gastaut Syndrome; ONS, Office for National Statistics; QALY, quality-adjusted life year; SF, seizure frequency; SMR, standardised mortality ratio.

Note: *For scenario labels, please refer to CS Table 50; †ICERs presented here are aligned with the company's base-case results provided at clarification stage.

6.1.1. The treatment effect was applied incorrectly

The company argued for a lognormal distribution to characterise the distribution of SF in CDD patients. The EAG expanded testing of potential distributions, and agreed with the company that lognormal was likely the most appropriate distribution (see Section 4.2.6.1).

The EAG investigated the application of treatment effect in the model. A full discussion is provided in Appendix A. To summarise, the company implementation was incorrect and resulted in a large overestimate of the impact of the estimated HL shift associated with GNX treatment on a lognormal distribution. This was investigated further by the EAG via a simulation study, which showed that the company's implementation resulted in an effect of around 67%, whilst the EAG-corrected implementation results in an effect of approximately the HL shift observed in the Marigold study.

6.1.2. Lo et al. implementation error

In Cells Q87:R88 in "ClinicalParams", the days included in the two rows both include 28. This was a simple implementation error, which the EAG corrected. The EAG implemented the switch "EAG_corr_loTopRow" so that the company can easily toggle the fix.

6.1.3. Age adjustment for caregivers

The company did not implement age adjustment for caregivers, assuming them to be ageless which was incorrect. The EAG considered this to be an implementation error biasing the ICER in favour of GNX due to the overestimate of incremental caregiver QALYs that resulted from not adjusting for the age caregivers over time.

To correct this, an estimated age of caregiver at baseline was calculated by the EAG using data from ONS[37,38] and the Marigold study. ONS data on the frequency of maternity by age was used to calculate a weighted average age at birth of child (calculations were provided in the "Settings" sheet of the EAG's modified company cost-effectiveness model). This resulted in a value of 30.41 years. The model then simply added age at baseline from the cost-effectiveness model (assumed [redacted] in the company's base-case) to this to provide expected age of parent at the time of GNX initiation. This age value was then applied to the equation in Ara & Brazier to produce a utility for age and sex matched general population utility corresponding to caregiver characteristics at baseline.

The EAG implemented age adjustment for caregivers to align with the age adjustment applied for patients. See Section 6.1.6 for the discussion on implementation.

6.1.4. SF distribution is truncated at 400 seizures / 28-days

In the 'seizure model' sheet within the cost-effectiveness model, the company presented a table providing the density associated with each SF value from 0 to 400. The lognormal distribution does not have an upper bound and therefore it was impossible to have an integral of 1 without an upper bound of infinity. The usual course of action would be to select an upper bound which covered at least 99% of the distribution in both arms to reduce bias and ensure a reasonably accurate estimate of the mean value. However, the company did not do this, which resulted in the total density of the ECM arm summing to 96.06% whilst the total density of the GNX arm summed to 99.83%. This introduced bias into the cost-effectiveness model. For instance, the mean estimated in the ECM arm in the company base-case was [redacted], which was considerably less than the [redacted] estimated when setting the upper bound to 5000, or the true mean of [redacted]. Consequently, expected SF in the ECM arm was underestimated by a larger percentage than in the GNX arm. This error biased the model *against* GNX through underestimating incremental QALYs.

To correct this error, the EAG made the following changes:

1) The EAG increased the upper limit of SF to 1000 to include more of the density
2) The EAG designed a VBA function to approximately calculate area under the curve between two integer bounds (default 0 and 1000), allowing either expected value or proportion to be produced (provided in the cost-effectiveness model)

3) The EAG incorporated this function into the Excel model, allowing both interpolation of the treatment effect over time and efficiently increasing a larger upper bound to SF

6.1.5. Chin *et al.* LGS mortality rate incorrectly calculated

As discussed in Section 4.2.6.3, the company used values from Chin *et al.* to provide an estimated SMR to apply to general population mortality. This was based on the values 4 and 6, which were rounded. Elsewhere in the article, Chin *et al.* reported slightly different values (6.12 and 4.17). Therefore, the EAG took the average of those (5.145), instead of 5 per the company's original base-case.

6.1.6. Age adjustment for patients

The EAG implemented a revised approach to age-adjusted utility values for patients, via a multiplicative approach rather than an additive approach. Two absolute utility values cannot be multiplied as the resulting value has no basis, whereas an absolute utility value and a relative utility can be multiplied, with the result having a basis in the absolute value. The company's original implementation of age adjustment was to calculate what they refer to as a "base utility" value for the age- and sex-matched general population. This base value was an absolute utility value of the age- and sex-matched general population. This value was then multiplied by the health state utility value for CDD given SF per either Lo *et al.* or Auvin *et al.* This was incorrect as the result of multiplying two absolute utility values had no meaning.

To amend this, the EAG calculated general population utility relatively to its value at baseline, and then applied this relative utility to the absolute utility of CDD given SF. This method was used by default for age adjustment of caregiver utility (See Section 6.1.3).

6.1.7. Correction to the implementation of rescue medication costs

As discussed in Section 4.2.8.1, at Model 2 (see Table 11), the company incorporated rescue medication costs into the cost-effectiveness model. These were based on NICE TA614. However, the EAG identified several errors with this implementation and have corrected them.

The company multiplied the proportion of patients with SF 0-28 per 28-days by £204 and those 28+ per 28 days by £408 using the proportions fitting into the Lo et al health states for reasons the EAG did not understand. This was incorrect for several reasons:

- The underlying cost value had not been inflated from 2018 values to the most recent available using the PSSRU[39]

- The calculation should be based on the states in Table 29 of the TA614 committee papers (i.e., $SF \leq 8$, $8 < SF \leq 25$ and $SF > 25$ with SF monthly). However, only under- and over-28 were used by the company, and the wrong values were used for this (e.g., 24 uses per year * £34 per use = £816 per year for those between 8 and 25 seizures per month, but only £204 and £408 used by company without any explanation in the report or response to clarification)

- Months were not translated into 28-day cycles, so the time unit was mismatched between the source material and cost-effectiveness model

- The rates reported in Table 30 of the committee papers were uses of rescue medication per year (the table in the TA614 committee papers is titled “annual rates”). Yet, the company used costs calculated based on these annual rates at every 28 days (See “Trace Gan” and “Trace SoC” sheets column AP). This led to an estimated lifetime rescue medication cost of around £266,000 for ECM patients, which translated to 7824 uses of rescue medication for the average patient lifetime, or 137.52 times per year of life (i.e., 10.6 times per 28-day cycle, around 2-3 times per week).

The EAG incorporated a correction (controlled in the cost-effectiveness model using the toggle “EAG_corr_rescueMed”), which used the VB function described in Section 6.1.4 to estimate the proportion of patients in each of the states corresponding to TA614 at each time point in the model (See Sheet “EAG_util_and_RM”). These proportions were used to calculate a weighted average cost of rescue medication for patients on ECM+GNX and ECM (over time when the treatment effect is interpolated). For instance, the estimated rescue medication cost per cycle for ECM patients was £112.20, which corresponded to a per cycle use of rescue medication of 3.14/28d. This was on the high end for the TA614 health states, as the worst state is 25+ seizures per month which corresponded to 75.05% of patients at baseline in Marigold (for the lognormal fit).

6.1.8. EAG-corrected company base-case analysis

To summarise, the corrections made to the company’s cost-effectiveness model were:

- Correction 1 (Error 1): The mathematically incorrect treatment effect application

- Correction 2 (Error 8): Minor error in implementation of Lo *et al.* utilities
- Correction 3 (Error 2): Age adjustment applied to caregivers
- Correction 4 (Error 9): Correction of the SMR calculated using Chin *et al.*
- Correction 5 (Error 7): Function for area under lognormal and increase upper bound to 1000
- Correction 6 (Error 6): Correction of age adjustment for patients
- Correction 7 (Error 4): Errors in the implementation of rescue medication costs
- Other corrections (Errors 3, 5): Inclusion of Auvin *et al.* caregiver utilities, use of absolute utilities reported from Auvin *et al.*

Note, errors 10 & 11 related to issues with the sensitivity analyses and did not affect the company deterministic base-case.

Table 24 reports the individual and cumulative impacts of these corrections on the estimated ICER. Notably, the correction with the largest impact was the application of the HL shift estimate to the lognormal distributional fit to the Marigold baseline SF data discussed in Section 6.1.1. This considerably increased the ICER because the company's incorrect implementation substantially over-applied the treatment effect, leading to the GNX cohort experiencing approximately a 67% reduction in SF rather than the company's intended base-case reduction of 27.08%.

Aside from the correction to the application of the treatment effect, the other corrections were less impactful. Corrections 5 and 6 reduced the ICER, corrections 2, 3, and 7 increased the ICER, and correction 4 had a negligible effect due to the lack of any mortality benefit for GNX in the company's base-case. The net impact of the other changes to the model was to reduce the ICER slightly from that with only correction 1. This was because the ICER-reducing impact of corrections 5 and 6 were larger than the combined increasing effects of corrections 2, 3, 4, and 7. Note that correction 7 was made following Model 2, which reintroduced rescue medication following clarification questions.

Table 24: Individual and cumulative impact of corrections made to errors in the Company's model

Preferred assumption	Section in EAG report	Incremental costs	Incremental QALYs	ICER £/QALY	+/- company base case
Company base-case	5	[redacted]	[redacted]	[redacted]	
Impact of individual EAG corrections					
Correction 1: Incorrectly implemented treatment effect	6.1.1	[redacted]	[redacted]	[redacted]	[redacted]
Correction 2: Implementation of Lo *et al.* utilities	6.1.2	[redacted]	[redacted]	[redacted]	[redacted]
Correction 3: Age adjustment for caregivers	6.1.3	[redacted]	[redacted]	[redacted]	[redacted]
Correction 4: SMR based on wrong values from Chin et al	6.1.5	[redacted]	[redacted]	[redacted]	[redacted]
Correction 5: Using EAG AUC function and increasing SF upper limit to 1000	6.1.4	[redacted]	[redacted]	[redacted]	[redacted]
Correction 6: Age adjust patients	6.1.6	[redacted]	[redacted]	[redacted]	[redacted]
Correction 7: Rescue medication	6.1.7	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of EAG corrections					
Correction 1+2		[redacted]	[redacted]	[redacted]	[redacted]
Correction 1+2+3		[redacted]	[redacted]	[redacted]	[redacted]
Correction 1+2+3+4		[redacted]	[redacted]	[redacted]	[redacted]
Correction 1+2+3+4+5		[redacted]	[redacted]	[redacted]	[redacted]
Correction 1+2+3+4+5+6		[redacted]	[redacted]	[redacted]	[redacted]
Correction 1+2+3+4+5+6+7		[redacted]	[redacted]	[redacted]	[redacted]

Note: In the corrections, the severity modifier used was calculated to be 1.7x for caregivers and patients throughout. This was primarily due to the use of the Lo *et al.* SF-based utility values. See Section 7 for discussion.

Table 25 provides the EAG's corrected version of the company's base-case analysis results. Two base-cases are presented to show the results both with and without the severity modifier for caregiver utilities.

Table 25: EAG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case (**With** severity modifier* for caregivers)					

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
ECM	[redacted]	[redacted]	-	-	-
GNX+ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company deterministic base case (**Without** severity modifier* for caregivers)					
ECM	[redacted]	[redacted]	-	-	-
GNX+ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company probabilistic base case (**With** severity modifier* for caregivers)					
ECM	[redacted]	[redacted]	-	-	-
GNX+ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company probabilistic base case (**Without** severity modifier* for caregivers)					
ECM	[redacted]	[redacted]	-	-	-
GNX+ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years

Note: In the EAG-corrected company base-case, the severity modifier used was calculated as 1.7x. See Section 7.

Figure 3 provides an updated cost-effectiveness plane incorporating the severity modifier for patients and caregivers, showing that only a small minority of probabilistic iterations were cost effective at a willingness to pay threshold of £30,000 ([redacted]%). When not applying the severity modifier to caregivers this probability fell to [redacted]% (Figure 4).

Figure 3: Cost-effectiveness plane for corrected company base-case with 1.7x severity modifier applied to incremental caregiver QALYs

Note: The severity modifier used was calculated to be 1.7x. See Section 7 for discussion.

Figure 4: Cost-effectiveness plane for corrected company base-case with 1x severity modifier applied to incremental caregiver QALYs

Note: See Section 7 for discussion around severity modifiers.

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The scenario analyses presented in this section focus on the following issues and uncertainties:

- Changes made and included within the EAG's preferred base-case:
  - Discontinuation rates
  - Use of Marigold OLE efficacy estimate (for GNX/GNX cohort)
  - Removal of mortality benefit (not required upon receipt of Model 3, see Table 11)
  - Utility sources, and use of absolute utility values rather than relative to best state
  - Dynamics of the treatment effect
  - Inclusion of wastage
  - Adjustment of hospitalisation cost
  - The applicability of disease severity modification to caregivers
- 'Standard' scenarios requested in NICE methods guidance but not presented by the company:
  - Discounting scenarios
  - Time horizon scenarios
- EAG exploratory/robustness scenarios:
  - Seizure types to consider
  - Analysis time points to consider
  - Patient age at baseline
  - Number of caregivers
  - Caregivers for adult patients

6.2.1. Discontinuation rates

The company applied a value of [redacted]% per 28-days, which was calculated using discontinuations divided by patients at the end of follow up. In the Marigold trial, there were [redacted] GNX discontinuations (CSR section 10.1), and baseline GNX population at risk was [redacted] patients. The median exposure time was [redacted] treated days (CSR Table 12). An estimated total would be [redacted] days at risk of GNX discontinuation. Converting to 28-day cycles gave [redacted] 28-day cycles at risk of discontinuation from GNX. [redacted] produces a *rate*, r, of [redacted] GNX discontinuations per 28-day cycle at risk of discontinuation (i.e., on GNX treatment). Using $P = 1 - e^{-rt}$ to assume a continuous exposure (i.e., exponential), the resulting 28-day cycle probability of discontinuation from GNX was [redacted]%. This was applied in the EAG's preferred base-case analysis.

6.2.2. Efficacy data used

At Model 2 (see Table 11), the company changed its base-case to use the Marigold maintenance period HL shift estimate to power the model (29.31%). At Model 3, this was reverted to the estimate for the whole DB period (27.08%) without any explanation from the company.

In principle, the EAG agreed with Model 3 – that in the case that the treatment effect was applied from baseline, the efficacy for the DB period should be used. However, owing to the EAG's stance on the dynamics of the treatment effect (see Section 6.2.5) the EAG considered it more appropriate to apply the maintenance period reduction in SF from Marigold when interpolating the treatment effect over time. This then considered the difference between the treatment effect before and after titration of GNX. Consequently, in its base-case the EAG preferred to use the HL shift estimate from the maintenance period (29.31%).

6.2.3. Mortality assumptions

In Model 2, the company introduced the assumption that ECM patients were exposed to 50% more mortality than GNX patients, irrespective of whether they were on or off GNX at the time. The company labelled this as 'hypothetical' in the model file, though it featured within its revised base-case analysis. In Model 3 (see Table 11), this assumption was revoked. The EAG agreed with the removal of this assumption from the base case.

6.2.4. Utility assumptions

6.2.4.1. Auvin *et al.* 2021 utilities

In its model, the company included two different utility sources – both of which were vignette studies of potential proxy diseases to CDD in terms of disease burden. The EAG preferred Auvin *et al.* over Lo *et al.* for the following reasons (discussed in more detail in Sections 4.2.7.1 and 4.2.7.2):

- The intersection between LGS and CDD
- Granularity of SF health states
- Factoring in of SFD
- Consistency with basis of other modelling areas (i.e., LGS as a proxy disease for CDD)
  - Mortality data on LGS patients reported by Chin *et al.*
  - HCRU data on LGS patients reported by Chin *et al.*

The company implementation of Auvin *et al.* omitted the caregiver utilities that were reported in the supplementary materials (Appendix A; see Sections 4.2.7.1 and 4.2.7.2). Furthermore, supplementary data file 1 contained a full report of the caregiver vignette study, with a more detailed breakdown of the mapping exercises. The EAG considered this to be an error by omission, as no justification was provided for linking to the caregiver utilities in Lo *et al.* instead of simply using the caregiver utilities reported in Auvin *et al.* As the company did not use Auvin *et al.* in its base case, this did not affect the company corrected base-case ICER but did influence the results when using Auvin *et al.* as a utility source.

The company implemented the utilities from Auvin *et al.* as relative utilities (relative to utility in the seizure-free health state). This set patient utility in the seizure-free health state to 1, which the EAG saw as unrealistic considering patients would still be affected by the broader impacts of CDD. Therefore, the EAG preferred to apply the utilities from Auvin *et al.* as absolute values.

The EAG made the following adjustments to the cost-effectiveness model for its base case:

1) Use of Auvin *et al.* over Lo *et al.*, as discussed in Sections 4.2.7.1 and 4.2.7.2
2) Inclusion of caregiver utilities reported in Auvin *et al.*, as discussed in Section 4.2.7.2
3) Calculation of Auvin *et al.* utilities as absolute rather than relative values

6.2.4.2. Application of disease severity modifiers to caregivers

The relevant wording in the NICE methods guide on QALY shortfall and severity modifiers (methods guide section 6.2.12) is as follows:

> *"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 (including use of other available treatments, diagnostics, or best supportive care). The extent of unmet health need is reflected within the severity definition"*

The EAG considered this to apply to those who have the condition, and not those taking care of those with the condition. However, as the term "living with the condition" was used, the EAG considered that this could feasibly be interpreted to be ambiguous towards patients and their caregivers (who the EAG see as 'living with those that are living with the condition'). The EAG contacted NICE for clarification on whether the application of a severity modifier for caregivers would be considered to be consistent with the guidance, and at the time of submission of this report, the issue was under discussion within the NICE team.

To allow for a pending decision on the use of a severity modifier for carers, the EAG presents two separate base-case ICERs – one with caregiver severity modification and one without. This, and the applicability of the modifier are discussed in more depth in Section 7.

6.2.5. Treatment efficacy interpolation

As discussed throughout Section 4.2.6, the company presented three different HL shift estimates for primary seizures at three different time points. These were:

- -18.70% at 4 weeks from baseline in Marigold (titration period)
- -27.08% at 17 weeks from baseline in Marigold (DB period)
- -29.31% weeks 4-17 in Marigold (maintenance period)

The EAG considered this evidence that the treatment effect of GNX was not instantaneously the -29.31% effect estimated by the company for the maintenance period within Marigold or the -27.08% effect for the double-blind period. This suggested that it was potentially optimistic to assume the full effect immediately from baseline. To resolve this, the EAG linearly interpolated the treatment effect of GNX (see Section 6.2.5). This then ensured that the cost-effectiveness

model followed the clinical evidence on SF distributional change in a GNX treated cohort (as would be expected of a Markov model).

On the other hand, in other decision modelling settings, such as oncology, a treatment effect (e.g., a time-invariant hazard ratio) may be calculated using the full follow-up data and then applied from baseline for those on treatment. The company approach of applying an instantaneous treatment effect followed this convention as all patients instantaneously have their SF reduced by 27.08% conditional on GNX treatment (analogously to hazard being reduced according to a hazard ratio whilst on a treatment). Overall, the EAG preferred to reflect the dynamics of the treatment effect at different times reported according to the clinical data reported in Marigold and the OLE. Yet, to reflect the convention of instantaneous rather than cumulating treatment effect the EAG also presents scenarios reflecting the EAG's base case *without* interpolation of the treatment effect (Table 27).

The function was used to estimate the proportion of patients in the Lo *et al.* and Auvin *et al.* health states over time up until [redacted] weeks (the extent of the follow up in the OLE).

6.2.6. Drug wastage

Two clinicians consulted by the EAG indicated that it may be likely that some GNX product would be wasted in practice. One expert suggested that drug wastage of approximately 10% may be expected and would seem a reasonable estimate to inform the model. This was incorporated into the model as a simple 10% increase to the cost of GNX per cycle. While the value of 10% was palpably uncertain, the EAG highlighted that the assumption of zero wastage was misaligned with the clinical advice received by the EAG, and so this estimate was preferred over the company's base-case analysis which included no wastage.

6.2.7. Resource use costs

As discussed in Section 4.2.8.2, the company implemented a long-stay cost when the data on LGS patients from Chin *et al.* suggested that hospital stays tended to be short. [24] Therefore, the EAG preferred to use a short-stay cost in its base-case.

6.2.8. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in the sub-sections above. Each change was made individually and was combined within the EAG's preferred base-case analysis (see Section 6.3).

The results of the EAG's exploratory analyses are provided in Table 26. All scenarios presented in the table are based on the EAG corrected company base-case. The individual changes are ordered descending in terms of impact on the corrected company base-case ICER.

Table 26: EAG's exploratory analyses

Scenario / change to cost-effectiveness model	Section in EAG report	Incremental costs	Incremental QALYs	ICER £/QALY	+/- corrected company base case
Impact of individual changes					
EAG corrected company base-case*	6.1	[redacted]	[redacted]	[redacted]	[redacted]
Use of Auvin *et al.* (with absolute values and caregiver utilities)*, ***	4.2.7 6.2.4.1	[redacted]	[redacted]	[redacted]	[redacted]
Age 7.26 years at baseline (Marigold age)	4.2.3	[redacted]	[redacted]	[redacted]	[redacted]
1 caregiver	4.2.7.2	[redacted]	[redacted]	[redacted]	[redacted]
No severity modifier for caregivers**	6.2.4.2	[redacted]	[redacted]	[redacted]	[redacted]
Interpolation of the treatment effect*	4.2.6.1 6.2.5	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation short stay based on Chin *et al.**	4.2.8.2 6.2.7	[redacted]	[redacted]	[redacted]	[redacted]
Including 10% wastage*	4.2.8.1 6.2.6	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate based on exposure time*	4.2.6.2 6.2.1	[redacted]	[redacted]	[redacted]	[redacted]
No caregivers 18+	4.2.7.2	[redacted]	[redacted]	[redacted]	[redacted]
Use of the maintenance HL*	6.2.2	[redacted]	[redacted]	[redacted]	[redacted]
"Standard" scenarios					
No discounting	Standard	[redacted]	[redacted]	[redacted]	[redacted]
No discounting - costs	Standard	[redacted]	[redacted]	[redacted]	[redacted]
No discounting - QALYs	Standard	[redacted]	[redacted]	[redacted]	[redacted]
TH 10 years	Standard	[redacted]	[redacted]	[redacted]	[redacted]
TH 20 years	Standard	[redacted]	[redacted]	[redacted]	[redacted]
TH 50 years	Standard	[redacted]	[redacted]	[redacted]	[redacted]
Selected combined scenarios					

Scenario / change to cost-effectiveness model	Section in EAG report	Incremental costs	Incremental QALYs	ICER £/QALY	+/- corrected company base case
Marigold age, primary seizures, caregiver severity 1x	Exploratory	[redacted]	[redacted]	[redacted]	[redacted]
Marigold age, primary seizures, caregiver severity 1x, all seizures	Exploratory	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TH, time horizon

Notes: *Used in the EAG base-cases, ** Included/excluded in the EAG base-cases, ***1.2x severity modifier calculated using the ECM arm patient flow sheet in the company cost-effectiveness model

The most impactful individual changes were those affecting the cost of GNX (e.g., baseline age) and those affecting patient utility (e.g., use of Auvin *et al.*). Other notably impactful scenarios include interpolation of the treatment effect, which then interacted with those scenarios affecting patient HRQoL given SF.

Overall, none of these scenarios suggested that GNX had an ICER at or below £30,000/QALY gained, even when accounting for disease severity and applying a severity modifier to caregivers.

6.3. EAG's preferred assumptions

The EAG preferred base case ICERs were £868,980 without the severity modifier for caregivers and £783,900 with a (1.2x) modifier for caregivers. Table 27 shows the individual and cumulative impact of the changes selected by the EAG.

In preparation of the final preferred EAG base case, the EAG opted not to include scenarios shown in the top section of Table 26 that were considered conservative. The EAG therefore consider the final reported ICERs to be a balanced estimate of the cost effectiveness of introducing GNX into clinical practice. The results of relevant scenarios are presented in Table 28 for completeness.

Table 27: EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Company base-case	5	[redacted]
EAG corrected company base-case	6.1	[redacted]

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
EAG 1: Discontinuation rate based on exposure time	4.2.6.2 6.2.1	[redacted]
EAG 2: Use of the Marigold maintenance HL	6.2.2	[redacted]
EAG 3: Use of Auvin et al (with absolute values and caregiver utilities) (Note: affects severity modifier)*	4.2.7 6.2.4.1	[redacted]
EAG 4: Interpolation of the treatment effect	4.2.6.1 6.2.5	[redacted]
EAG 5: Including 10% wastage	4.2.8.1 6.2.6	[redacted]
EAG 6: Hospitalisation short stay cost	4.2.8.2 6.2.7	[redacted]
EAG 7: Severity modifier applied to patients only	6.2.4.2	[redacted]
EAG 1 + 2	4.2.6.2 6.2.1 6.2.2	[redacted]
EAG 1 + 2 + 3*	4.2.7 6.2.4.1	[redacted]
EAG 1 + 2 + 3 + 4*	4.2.6.1 6.2.5	[redacted]
EAG 1 + 2 + 3 + 4 + 5*	4.2.8.1 6.2.6	[redacted]
EAG 1 + 2 + 3 + 5 + 6*	6.2.5	[redacted]
EAG 1 + 2 + 3 + 6*	6.2.6	[redacted]
EAG base-case (EAG 1 + 2 + 3 + 4 + 5 + 6)*: applying caregiver severity modifier	6.3	[redacted]
EAG base-case (EAG 1 + 2 + 3 + 4 + 5 + 6 + 7)*: Not applying caregiver severity modifier	6.3	£868,980

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Note: *1.2x severity modifier calculated using the ECM arm patient flow sheet in the company cost-effectiveness model, and applied to incremental QALYs between GNX and ECM arms.

Table 28: Additional exploratory scenarios not included in the EAG base-case (based on the EAG's base-case)

Scenario / change to cost-effectiveness model	Section in EAG report	Incremental costs	Incremental QALYs	ICER £/QALY	+/- corrected company base case
Marigold age, primary seizures, applying caregiver severity modifier, maintenance efficacy	Exploratory	[redacted]	[redacted]	[redacted]	[redacted]
Marigold age, primary seizures, not applying caregiver severity modifier, maintenance efficacy	Exploratory	[redacted]	[redacted]	[redacted]	[redacted]
Marigold age, all seizures, applying caregiver severity	Exploratory	[redacted]	[redacted]	[redacted]	[redacted]

Scenario / change to cost-effectiveness model	Section in EAG report	Incremental costs	Incremental QALYs	ICER £/QALY	+/- corrected company base case
modifier, maintenance efficacy					
Marigold age, all seizures, not applying caregiver severity modifier, maintenance efficacy	Exploratory	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Note: *1.2x severity modifier calculated using the ECM arm patient flow sheet in the company cost-effectiveness model, and applied to incremental QALYs between GNX and ECM arms.

6.4. Conclusions of the cost-effectiveness section

- The company's model adopted a simple structure, revolving around health states of 'alive' and 'dead'. The EAG considered that this structure constituted an over-simplification of a complex disease, and in turn meant that interpretation of the cost-effectiveness results for GNX based on the model were subject to substantial uncertainty. In addition, a number of miscellaneous model errors and unsubstantiated assumptions were identified as part of the EAG's review, further adding to the uncertainty associated with the results generated from the model.

- While the Marigold trial suggested that GNX may reduce SF for some people with CDD compared to ECM, the long-term treatment effect of GNX was highly uncertain and this also impacted the results of the cost-effectiveness model. The application of the reduction in SF within the company's model was flawed from multiple perspectives, and so the EAG addressed this as far as was possible with the available data within its preferred analysis.

- Capturing the association between SF and HRQoL was challenging, especially considering that no utility values could be generated from the Marigold trial. In lieu of this, the company sought data from vignette studies, each of which were associated with notable uncertainty. The choice of study to populate the model had a large impact on cost-effectiveness results, impacting both patients and their caregivers.

- There were a number of outstanding issues associated with the cost-effectiveness modelling that the EAG was unable to address within the scope of its appraisal. These

included the potential for re-treatment with GNX over a lifetime horizon, the possibility of a different model structure better reflecting the impact of GNX on patient outcomes, and a lack of data available for a CDD-specific population to populate a number of model parameters (i.e., mortality, resource use, and quality of life).

- Overall, after correcting for errors in the modelling, the ICER for GNX appeared to be in excess of the range of £20,000 and £30,000 per QALY gained. This finding was based on what the EAG considered to be a highly optimistic corrected company base-case. When making what the EAG considered to be reasonable changes to the company's base-case analysis, the ICER increased substantially beyond the NICE willingness to pay threshold.

7. SEVERITY MODIFIER

The company applied a disease severity modifier to both CDD patients *and* their caregivers of 1.7x the incremental QALYs between the GNX and ECM arms. The company did not include any scenarios exploring different modifiers, or the applicability of those modifiers to caregivers and/or patients.

Using the mortality data provided by Chin *et al.* on patients with LGS, [24] and the utility estimates from Lo *et al.*, [27] the company calculated the expected lifetime discounted QALYs for a patient with CDD treated with ECM from aged [redacted] to be [redacted]. This compared to an age- and sex-matched general population discounted QALY estimate of [redacted] QALYs. As the absolute discounted QALY shortfall was more than 18, the corresponding severity modifier was 1.7x. In the EAG base-case, the expected lifetime discounted absolute QALYs for ECM patients was [redacted], leading to an absolute shortfall of 15.51 discounted QALYs, hence a severity weighting of 1.2x.

As discussed in Section 6.2.4.2, the EAG considered the guidance for the applicability of severity modification to caregivers as ambiguous. Further, the EAG considered that if the severity modifier were to be applicable to caregivers, then the determination of the severity modifier applied should be based on their distinct shortfall. That is, the amount of QALYs caregivers would be expected to accrue during their time (relevant to the NICE decision problem) compared to the equivalent period if they were not caring for a person living with the condition. Within the context of this decision problem, this would be when imposing the overall survival of CDD patients (estimated to be [redacted] years in the cost-effectiveness model) to general population HRQoL and comparing this to the equivalent for those caregivers in the ECM arm. From this, absolute and proportionate shortfalls could be calculated.

When this exercise was conducted, the absolute and relative QALY shortfalls based on discounted QALYs in the EAG corrected company base case were [redacted] QALYs and [redacted]% respectively ([redacted] QALYs and [redacted]% respectively in the EAG's base case). These were insufficient to meet either the 1.2x or 1.7x severity modification thresholds. Therefore, if caregivers were considered for disease severity modifiers based on their shortfall (i.e., treated as separate entities), the severity modification would not apply to them in this case as they would not meet the criteria. However, as it remained unclear whether the severity modification

based on patients should be used for caregiver utilities, the EAG presented results both including and excluding the modifier.

The QALY gain in the company's original (uncorrected) deterministic analysis reduced from [redacted] to [redacted] if the severity modifier was applied only to patients (i.e., removed for caregivers), which reduced further to [redacted] if the severity modifier was removed altogether (i.e., removed for both patients and caregivers). The corresponding (deterministic) ICERs for these scenarios were £[redacted] (severity modifier for patients and caregivers), £[redacted] (severity modifier for patients only), and £[redacted] (no severity modifier) in the original un-corrected company base-case. In the EAG corrected company base case the difference grew larger, and then larger again in the EAG base-case. The other scenarios are presented throughout Sections 5 and 6 and inclusion/exclusion of the severity modifier to caregivers had a similar effect of substantially affecting the ICER for GNX+ECM versus ECM.

References

1. Jakimiec M, Paprocka J, Śmigiel R. CDKL5 Deficiency Disorder—A Complex Epileptic Encephalopathy. Brain Sciences. 2020;10(2):107.

2. Kothur k, Holman K, Farnsworth E, et al. Diagnostic yield of targeted massively parallel sequencing in children with epileptic encephalopathy. Seizure. 2018;59:132-40.

3. Liang J-S, Huang H, Wang J-S, Lu JF. Phenotypic manifestations between male and female children with CDKL5 mutations. Brain and Development. 2019;41(9):783-9.

4. Kalscheuer VM, Tao J, Donnelly A, et al. Disruption of the Serine/Threonine Kinase 9 Gene Causes Severe X-Linked Infantile Spasms and Mental Retardation. American Journal of Human Genetics. 2003;72(6):1401-11.

5. Lyst MJ, Bird A. Rett syndrome: a complex disorder with simple roots. Nature Reviews Genetics. 2015;16:261-75.

6. Fehr S, Wong K, Chin R, et al. Seizure variables and their relationship to genotype and functional abilities in the CDKL5 disorder. Neurology. 2016;87(21).

7. Fehr S, Downs J, Ho G. Functional abilities in children and adults with the CDKL5 disorder. American Journal of Medical Genetics. 2016;170(11):2860-9.

8. Leonard H, Downs J, Benke TA, et al. CDKL5 deficiency disorder: clinical features, diagnosis, and management. The Lancet Neurology. 2022;21(6):563-76.

9. Mori Y, Downs J, Wong K, Heyworth J, Leonard H. Comparing Parental Well-Being and Its Determinants Across Three Different Genetic Disorders Causing Intellectual Disability. Journal of Autism and Developmental Disorders. 2018;48(5):1651-65.

10. Porter RJ, Meldrum BS. Antiseizure Drugs. In: Katzung BG, Masters SB, Trevor AJ, editors. Basic & Clinical Pharmacology (12th Edition). USA: McGraw-Hill; 2012.

11. Olson HE, Daniels CI, Haviland I, et al. Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder. Journal of Neurodevelopmental Disorders. 2021;13(40).

12. Dale T, Downs J, Wong K, Leonard H. The perceived effects of cannabis products in the management of seizures in CDKL5 Deficiency Disorder. Epilepsy & Behavior. 2021;122(108152).

13. Lim Z, Wong K, Downs J, et al. Vagus nerve stimulation for the treatment of refractory epilepsy in the CDKL5 Deficiency Disorder. Epilepsy Research. 2018;146:36-40.

14. Marinus Pharmaceuticals. Clinical Study Report for 1042-CDD-3001. A double-blind, randomized, placebo-controlled trial of adjunctive Ganaxolone treatment in children and young adults with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) followed by long-

term open-label treatment. Document date: Version 1.0: 12 Jan 2021. Version 2.0: 28 May 2021. 2021.

15. Pestana-Knight EM, Amin S, Bahi-Buisson N, et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. The Lancet Neurology. 2022;21(5):417-27.

16. Leonard H, Junaid M, Wong K, Demarest s, Downs J. Exploring quality of life in individuals with a severe developmental and epileptic encephalopathy, CDKL5 Deficiency Disorder. Epilepsy Research. 2021;169(106521).

17. Lamb YN. Ganaxolone: First Approval. Drugs. 2022;82:933-40.

18. Telethon Kids Institute. QI-Disability. Available at: https://www.telethonkids.org.au/our-research/brain-and-behaviour/disability/child-disability/qi-disability/ (last accessed 13 January 2023) 2023.

19. Marinus Pharmaceuticals. Clinical Study Report for 1042-0900. A multicenter, 26 week open-label proof-of-concept trial of Ganaxolone in children with PCDH19 female pediatric epilepsy and other rare genetic epilepsies followed by 52 week open-label treatment. 2019.

20. Hodges Jr JL, Lehmann EL. Estimates of Location Based on Rank Tests. The Annals of Mathematical Statistics. 1963;34(2):598-611.

21. Grabenstatter H, Leonard H, Kiriakopoulos E. CDKL5 Deficiency Disorder. Published 24 June 2022. Available at: https://www.epilepsy.com/causes/genetic/cdkl5-disorder#:~:text=Seizures%20in%20CDKL5%20deficiency%20disorder,received%20FDA%20approval%20for%20CDD (last accessed: 5 Jan 2023) 2022.

22. Leonard H, Junaid M, Wong K, et al. Influences on the trajectory and subsequent outcomes in CDKL5 deficiency disorder. Epilepsia. 2022;63(2):352-63.

23. Specchio N, Amin S, Aimetti A, Hulihan J. Extended Duration Safety and Efficacy of Ganaxolone for the Treatment of CDKL5 Deficiency Disorder: Preliminary Open-Label Extension Analysis (Marigold Study). Poster. American Epilepsy Socity, Virtual; 4-8 December.2020.

24. Chin RFM, Pickrell WO, Guelfucci F, Martin M, Holland R. Prevalence, healthcare resource utilization and mortality of Lennox-Gastaut syndrome: retrospective linkage cohort study. Seizure. 2021;91:159-66.

25. Hesdorffer DC, Tomson T, Benn E, et al. Do antiepileptic drugs or generalized tonic–clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia. 2011;53(2):249-52.

26. Office for National Statistics. Death registrations, Populations and Age Standardised Rates, England 1981 to 2018. Release date: 23 January 2020. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adho

cs/11168deathregistrationspopulationsandagestandardisedratesengland1981to2018 (last accessed 5 Jan 2023). . 2020.

27. Lo SH, Marshall J, Skrobanski H, Lloyd A. Patient and Caregiver Health State Utilities in Tuberous Sclerosis Complex. PharmacoEconomics Open. 2022;6(1):105-21.

28. Auvin S, Damera V, Martin M, et al. The impact of seizure frequency on quality of life in patients with Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy & Behavior. 2021;123: 108239.

29. National Institute for Health and Care Excellence (NICE). TA808: Fenfluramine for treating seizures associated with Dravet syndrome. Published 8 July 2022. Available at: https://www.nice.org.uk/guidance/ta808 (last accessed 5 Jan 2023). 2022.

30. Ara R, Brazier JE. Populating an Economic Model with Health State UtilityValues: Moving toward Better Practice. Value in Health. 2010;13(5):509-18.

31. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. Published on 12 January 2022. Available at: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d (last accessed 5 Jan 2023). NICE Decision Support Unit. University of Sheffield; 2022.

32. U.S. Food and Drug Administration (FDA). FDA prescribing information for ZTALMY (ganaxolone) . Issued 3/2022. Reference ID: 4955025. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215904s000lbl.pdf (last accessed 6 Jan 2023).

33. National Institute for Health and Care Excellence (NICE). TA614: Cannabidiol with clobazam for treating seizures associated with Dravet syndrome. Committee papers. Published 11 November 2019. Available at: https://www.nice.org.uk/guidance/ta614/documents/committee-papers (last accessed 6 Jan 2023). 2019.

34. Lagae L, Irwin J, Gibson E, Battersby A. Caregiver impact and health service use in high and low severity Dravet syndrome: A multinational cohort study. Seizure. 2019;65:72-9.

35. Mangatt M, Wong K, Anderson B, et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. Orphanet Journal of Rare Diseases. 2016;11:39.

36. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Published 31 January 2022. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (last accessed 5 Jan 2023). 2022.

37. Office for National Statistics. Birth characteristics in England and Wales: 2017. Release date: 10 January 2019. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bul

letins/birthcharacteristicsinenglandandwales/2017#average-ages-of-mothers-and-fathers-of-all-babies-have-continued-to-rise (last accessed 6 Jan 2023). 2019.

38. Office for National Statistics. Dataset Births by parents' characteristics. Release date: 13 January 2022. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthsbyparentscharacteristics (last accessed 6 Jan 2023). 2022.

39. Jones K, Burns A. Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/ (last accessed 6 Jan 2023). 2021.

40. R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: https://www.r-project.org/ (last accessed: 6 Jan 2023).

Appendix A: Detailed summary of HL shift implementation error

In Microsoft Excel, the function [redacted] was used by the company to simulate the distribution of SF for ECM patients (by pooling across arms at baseline, see Section 4.2.6.1). The [redacted] function in excel takes arguments for the desired value, [redacted]. The company entered these parameters into the function in a table ranging from 0 to 400 seizures (see Section 6.1.4 for the EAG's amendments to this).

To then simulate the distribution of SF in the GNX-treated cohort, the company [redacted]. However, applying the HL shift as a multiplier directly to [redacted] was not the same as applying it [redacted]. The HL estimate was based on [redacted], and so did not apply in this manner. The % HL estimate can, however, be applied correctly to lognormal distributional parameters using the [redacted]:

[redacted]

The HL shift estimate represents a 'shift' or compression/expansion of the SF distribution in the horizontal direction [redacted] and should therefore be associated with that same change in mean, median and standard deviation. That is, the mean, median and standard deviation of a lognormal distribution should all be reduced by approximately 27.08% using the marigold 17-week HL, or 29.31% using the Marigold maintenance period HL. In simple terms and functional form, the GNX distribution should simply be based on SF values with the % reduction applied:

$$f(SF_{ECM}) = f(SF)$$
$$f(SF_{GNX}) = f\big(SF * (1 - HL)\big)$$

So, for a lognormal distribution, it follows that:

[redacted]

Simulations were performed in the statistical software *R*, [40] using one million iterations of a lognormal distribution with the parameters provided by the company. An HL value of 27.08% (per the company's original base case analysis) was used and compared the SF distribution:

- For the ECM arm
- With the company's application of the 27.08% HL
- With the EAG corrected application of the 27.08% HL

The distributional characteristics of the simulation results were then compared to the Marigold baseline data and the results of the HL shift estimate. Note that no upper limit was placed on SF in these draws from the distribution. To align values with those in the company submitted cost-effectiveness model, the resulting draws could be filtered down to only those of 400 or under and the process repeated (to truncate the distribution as it has been truncated by the company, see Section 6.1.4). A simulation exercise conducted by the EAG demonstrated that the company's implementation led to an unambiguous overestimated treatment effect.

Box 1: Simulation exercise proving applicability of product rule to lognormal distribution

```
# simulate the distribution of SF per ECM with 10^6 iterations [redacted]
its         <- 1E6
ecm_meanlog <- [redacted]
ecm_sdlog   <- [redacted]
hl          <- [redacted]
set.seed(987321)

# ecm distribution and characteristics:
ecm_sim    <- [redacted]
ecm_mean   <- mean(ecm_sim  ) # [redacted]
ecm_sd     <- sd(ecm_sim  )   # [redacted]
ecm_median <- median(ecm_sim) # [redacted]

# apply treatment effect per company:
gnx_sim_company    <- [redacted]
gnx_company_mean   <- mean(gnx_sim_company  ) # [redacted]
gnx_company_sd     <- sd(gnx_sim_company  )   # [redacted]
gnx_company_median <- median(gnx_sim_company) # [redacted]

# apply treatment effect per EAG (i.e. product rule):
gnx_sim_eag    <- [redacted]
gnx_eag_mean   <- mean(gnx_sim_eag  ) # [redacted]
gnx_eag_sd     <- sd(gnx_sim_eag  )   # [redacted]
gnx_eag_median <- median(gnx_sim_eag) # [redacted]

# Calculate percentage changes to demonstrate alignment with HL shift estimate.
# Simple function to report tidy % change results to desired decimal places:
f_pr_chng <- function(new, orig, dp=2) {
  change <- new - orig
  return(paste0(round((change / orig) * 100,dp),"%"))
}

# company implementation of treatment effect. Highly optimistic:
f_pr_chng(gnx_company_mean  , ecm_mean)   # [redacted]% change in mean SF
f_pr_chng(gnx_company_sd    , ecm_sd)     # [redacted]% change in s.d. SF
f_pr_chng(gnx_company_median, ecm_median) # [redacted]% change in median SF

# EAG corrected implementation of treatment effect. Slightly optimistic:
f_pr_chng(gnx_eag_mean  , ecm_mean)   # [redacted]% change in mean SF
f_pr_chng(gnx_eag_sd    , ecm_sd)     # [redacted]% change in s.d. SF
f_pr_chng(gnx_eag_median, ecm_median) # [redacted]% change in median SF

# The EAG corrected method is therefore within 1% of HL estimate on all measures,
# whilst the company implementation more than doubles the treatment effect.
```

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Insert deadline for response** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Key Issue 1: Uncertainty surrounding clinical effects in the Marigold OLE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14 of the EAG report states: "Approximately 40% of participants receiving GNX withdrew from the trial before the **final follow-up** of the OLE, some of whom withdrew due to a lack of efficacy and some who withdrew for ambiguous reasons that the EAG considered could have been influenced by treatment efficacy (e.g. 'clinician decision')."	Please, amend to: "Approximately 40% of participants receiving GNX withdrew from the trial by the latest data cut-off of the OLE, where all patients had been followed up for at least 12 months. Some withdrew due to a lack of efficacy and some withdrew for ambiguous reasons that the EAG considered could have been influenced by treatment efficacy (e.g. 'clinician decision').	The OLE trial was still ongoing at the time of the data cut off, thus it was not the final "follow-up ".	Thank you for noting this, we agree and have corrected the text.

Issue 2 Description and critique of the design of the studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 31 of the EAG report states:	Please replace "plus data up to" with "plus data consisting of at least 1 year follow-up"	Follow-up time clarified, please also see comments to Issue 1.	Thank you for noting this, we have updated the text accordingly.

“The availability of a high-quality RCT in such a rare disease area was notable, and the EAG considered that the follow-up (17-weeks plus data up to 1 year in the latest data cut of the OLE) would be sufficient to determine whether treatment with GNX was effective for reducing seizures as compared to existing treatments, which typically lose their effect after 3-months.”			
Page 33 of the EAG report states: “The EAG noted there to be a difference in the median number of seizure-free days (SFD) between trial arms, though no further differences in seizure-free outcomes were noted and as quality of life was also comparable, the EAG did	Please, amend to: “The EAG noted there to be a difference in the median percentage of seizure-free days (SFD) between trial arms, though no further differences in seizure-free outcomes were noted and as quality of life was also comparable, the EAG did not consider this to be a major concern”	Outcome reported in Marigold CSR as median percentage of seizure-free days (Table 10, page 48).	The EAG did not consider this a factual inaccuracy, however the EAG has edited the text as suggested.

not consider this to be a major concern”			
Page 43 of the EAG report states: “The EAG these data to be more uncertain that data presented separately for each group, given that variations in outcomes might be expected depending on whether GNX was received during the double-blind phase or the OLE.”	Please amend to: The EAG viewed these data to be more uncertain that data presented separately for each group, given than variations in outcomes might be expected depending on whether GNX was received during the double-blind phase or the OLE.	Suspected missing word added, typo corrected. No impact.	Thank you for highlighting this, which we have now corrected
Page 48 of the EAG report states: “There was a small increase in the median number of SFD reported by participants in the GNX arm (CS Doc B p.62), though there was no clear difference between arms.”	Please, amend to: “There was a small increase in the median percentage of SFD reported by participants in the GNX arm (CS Doc B p.62), though there was no clear difference between arms”	Outcome reported in Marigold CSR as median percentage of seizure-free days (Table 10, page 48). No impact	The EAG did not consider this to be a factual inaccuracy however has edited the text as requested.

Issue 3 Description and critique of the results of the studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50 of the EAG report states: "Comparison of specific AE types showed that somnolence was more common in the GNX arm and pyrexia more common in the placebo arm."	Please, amend to: "Comparison of specific AE types showed that somnolence and pyrexia were more common in the GNX arm than in the placebo arm."	AE not correctly reported in the EAG report (CS, doc B, page 77). No impact.	Thank you for highlighting this, which we have corrected.

Issue 4 Typographic errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22 of the EAG report states: "A recent longitudinal study showed that around a quarter (82/213, 26%) of people with CDD reported cannabinoid use to aid seizure control, with around two-thirds reporting improvements in seizure control"	Please, amend to: "A recent longitudinal study showed that around a quarter (82/312, 26%) of people with CDD reported cannabinoid use to aid seizure control, with around two-thirds reporting improvements in seizure control"	Typographic error, no impact	Thank you for highlighting this, we have corrected this.

Page 36 of the EAG report states: "More than half of participants (58.0%) were also receiving other non-pharmacological therapies, such as physiotherapy, speech rehabilitation and occupational therapy"	The 58.0% refers to GNX arm only; please, amend to: "More than half of participants (54.5%) were also receiving other non-pharmacological therapies, such as physiotherapy, speech rehabilitation and occupational therapy"	Typographic error in % mentioned, no impact	This is not a factual inaccuracy as this section of the report is specific to the intervention received by those in the GNX arm of the clinical trials. No correction made.
Page 47 of the EAG report states: "During the double-blind phase of Marigold, there was a greater reduction in median major motor seizure frequency and all seizure frequency in the GNX arm compared to placebo (CS Doc B p. 57-58, 65)."	Please, amend to: "During the double-blind phase of Marigold, there was a greater reduction in median major motor seizure frequency and all seizure frequency in the GNX arm compared to placebo (CS Doc B p. 56-57, 64)"	Typographic error in page numbers, no impact	The page numbers in the EAG report were correct for the original CS submitted for this appraisal, but the suggested amendment is consistent with the final version submitted by the company on 22nd December 2022. The EAG has therefore corrected this in line with the latest version.

Page 47 of the EAG report states: "Rates of response were generally similar for all seizure types (CS Doc B p.64), [redacted] (CSR appendices Table 14.2.5.6.1 and 14.2.5.6.2)."	Please, amend to: "Rates of response were generally similar for all seizure types (CS Doc B p.63), [redacted] (CSR appendices Table 14.2.5.6.1 and 14.2.5.6.2)."	Typographic error in page number mentioned, no impact	As above, this has been changed to align with the latest version of the CS.
Page 47 of the EAG report states: "The cumulative proportion of people in each arm showing reductions and increases in major motor seizure frequency is shown in **Error! Reference source not found.**; please note that these figures were estimated from graphs provided by the company (CS Doc B Fig 9, p.60, and clarification response QA5, Fig A p.4) and so may lack some accuracy."	Please, amend to: "The cumulative proportion of people in each arm showing reductions and increases in major motor seizure frequency is shown in **Error! Reference source not found.**; please note that these figures were estimated from graphs provided by the company (CS Doc B Fig 9, p.59, and clarification response QA5, Fig 1 p.4) and so may lack some accuracy."	Typographic errors in page and Figure numbers mentioned, no impact	As above, the page number has been changed to align with the latest version of the CS, and we have corrected the figure label.
Page 47 of the EAG report states:	Please, amend to: "Results using the CGI-I showed that caregivers and clinicians were more likely	Typographic error in page number mentioned, no impact	As above, this has been changed to align

“Results using the CGI-I showed that caregivers and clinicians were more likely to say that participants in the GNX arm had improved, though differences were marginal and not statistically significant (CD Doc B p.61).”	to say that participants in the GNX arm had improved, though differences were marginal and not statistically significant (CS Doc B p.60).”		with the latest version of the CS.
Page 47–48 of the EAG report states: “However, there was a greater difference in carer reported CGI-CSID, where caregivers were statistically more likely to say that those in the GNX arm showed improvements in seizure intensity/duration/severity (CS Doc B p.62).”	Please, amend to: “However, there was a greater difference in carer reported CGI-CSID, where caregivers were statistically more likely to say that those in the GNX arm showed improvements in seizure intensity/duration/severity (CS Doc B p.61).”	Typographic error in page cited, no impact	As above, this has been changed to align with the latest version of the CS.
Page 48 of the EAG report states: “[redacted] CSR p.57).”	Please, amend to: “[redacted] CSR p.57).””	Typographic error corrected (last IQR upper limit should be 79). No impact.	Thank you, we have corrected this.
Page 49 of the EAG report states:	Please, amend to:	Typographic error in last IQR, no impact.	Thank you, we have corrected this.

[redacted]	“[redacted]		

Issue 5 Critique of economic model/cost-effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue for checking in model - application of [redacted] distribution capping	Confirm application of expansion to 1,000 seizure frequency is applying correctly especially with regard to utility; if needed expand the data range used to show the seizure chart by expanding the data ranges and chart series to 1,000 seizures or more.	The EAG has expanded the upper limit on seizures to 1,000 which has an effect on the columns on the ‘Seizure model’ sheet; however it is not clear if the increased patients captured (previously missed from the distribution’ are captured (e.g. in the Lo et al utilities); physically expanding the data ranges in the table and chart series to 1,000 seizures appears to lower the ICER.	The EAG considers this request as a clarification, rather than a factual inaccuracy. Accordingly, a response is included below for context, but as this does not constitute a factual inaccuracy, no change has been made to the EAR. The introduction of this function with truncation at 1,000 seizures does, *ceteris paribus*, lead to a reduction in the ICER compared to truncating at 400 seizures. The EAG scenario introduces a function which increases the truncation limit from 400 to 1,000, which can be explored further using the settings tab in the EAG’s edited version of the company’s model. This change was introduced because the average utility in the ECM arm was overestimated to a greater extent when truncating at SF of 400 rather than 1,000. When amending this aspect of the model, there is a greater potential HRQoL gain associated with the same % SF reduction. The result of this change in isolation of all other edits is an increase to the expected QALY gain associated with the intervention, lowering the ICER.

			Calculations demonstrating this are provided in the EAG modified model (see sheet 'SeizureModel'). The EAG also laid out a separate sheet (see sheet 'EAG_util_and_RM') which shows the state residency over time for both Auvin *et al.* and Lo *et al.,* by point in time. Note that the EAG have also built in the ability to extrapolate the state residency up to 104 weeks to accommodate the incorporation of the extension study HL shift results (and potentially this could be expanded for any longer-term data which could become available in the future). The EAG hopes this additional explanation helps with understanding the edit made to the company's model with respect to the upper limit for SF. Fundamentally, the EAG's edit to SF means that the upper limit is changed from 400 to 1,000 but this is done using different functionality to the original implementation by the company (i.e., via a custom function).
Page 53, Table 11, row 3, column 2, bullet 2 states: OLE efficacy of 29.13% applied (EAG not notified) states	Remove entire bullet point.	There are a few inaccuracies: 1. This appears the double blind period maintenance efficacy not OLE efficacy which was not used in any version	1. The EAG thanks the company for identifying this. The EAG has amended the text, but as the revised text is factually accurate, the EAG has not removed the point in its entirety. 2. The EAG thanks the company for identifying this typographical error. The EAG has amended the text, but as above, the bullet point is not removed in its entirety as it remains factually accurate after addressing the typographical error.

		2. The DB maintenance efficacy is 29.31% (not 29.13%) 3. The statement that this was applied and the EAG was not notified is not accurate; the base case in this version did not change from the full DB rate, and the maintenance period efficacy was added as a scenario (not base case) later; which was logged in the list of changes	3. 'Model 2' was set to a different scenario than the original model submitted to NICE, even after taking the initial error corrections into account and Table 11 of the EAR included all of the changes in the second model submitted compared to the model originally submitted by the company. The change log provided by the company in the Excel model was misaligned with the live settings for Model 2 at the time it was provided to the EAG (even if it was capable of generating different results). Therefore, this is not a factual inaccuracy and the EAG will not remove the bullet point.
Page 53, Table 11, row 4, column 2, bullet 2 states: Reversion from maintenance period HL shift of 29.31% to full	Remove entire bullet point	As noted and linked to the issues above, the baseline DB efficacy was intended as the base case, so there was no reversion from 29.31% at this stage.	Per the EAG's response above, Model 2 provided to NICE following error corrections during clarification used the maintenance efficacy, amongst the other changes pointed out by the EAG in Table 11. Model 3 changed multiple settings back to their original values per Table 11 in the EAR. Therefore, it is the EAG's view that this is not a factual inaccuracy as it remains an accurate account of the three models submitted.

Marigold HL shift of 27.08%			
Page 109, Table 26, row 9, column 1 states: Hospitalisation short stay based on Marigold data*	Clarify what has been used under this scenario and rename as appropriate	Unclear what data have been used; in any case, there are no hospital length of stay data in Marigold, so this must either be different data or a different source.	Thank you for highlighting this. The company is correct – this scenario is mistakenly labelled as an edit to the length of stay used in the model costs based on data from the Marigold study. This is incorrect – the length of stay was edited based on the study by Chin *et al.* Further information about this edit to the model is provided in Section 6.2.7 of the EAR. For completeness, the EAG has edited the description of this scenario where referred to within the EAR, affecting Table 26 (as noted) as well as Table 3 (see Section 1.7 of the EAR).

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Give full details of inaccurate marking - document title and page number **All rows relate to**	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.	

the document "ID3988 Ganaxolone for CDD_EAG report FINAL -230123 ACIC "			
p. 8	Original severity modifier value in the title of Figure 4 should be marked as confidential, CIC	Figure 4: Cost-effectiveness plane for corrected company base-case with [redacted] severity modifier applied to incremental caregiver QALY	We have added this.
p 12, table 1, last row	Original severity modifier value should be marked CIC	The company base case included a severity multiplier of [redacted]	We have added this.
p.14; Section 1.4 Key issues 1 (Table, last row)	OLE data cut timings should be marked as confidential, CIC	(latest data cut to inform the CS was [redacted]).	We have added this.
p. 18-19, Table 3 first row	In the first table, on first row of the table the value of the severity modifier should be marked as CIC as was in the CS	"The company applied a severity multiplier of [redacted] for ….	We have added this.

Page 18- Table 3 Right most column	All ICER values in Table 3 should be marked as CIC	Entire right-most column contents to be marked CIC ("ICER (change from company base case)")	We have marked up the majority of ICERs in this table, however we have not marked up the original company base case ICER and the EAG preferred base case ICER without severity modifier.
p 36	exposure duration in OLE and adherence % should be marked as ACIC	Mean (SD) treatment exposure length was 113.0 (23.32) days in the double-blind trial, and [redacted] days in the OLE (data cut-off February 2021). Adherence to the medication was moderately high [redacted] of participants in the GNX arm received treatment on 90% of the days in the double-blind phase	We have added this.
p. 37- end of second last paragraph	Open label extension data cut dates should be marked confidential CIC	…at clarification (QA12), the company provided additional data for a subset of clinical outcomes from the [redacted] data cut.	We have added this.
p 47; 1st paragraph	% worsening 50% or more by treatment arm should be marked ACIC	…. 24.5% of people in the GNX arm experienced a reduction in major motor seizures compared to 9.8% in the placebo arm, and [redacted] in the GNX arm experienced an increase in major motor seizures compared to [redacted] in the placebo arm	We have added this.
p 47 Table 10	All figures in right side of the table indicating	[redacted]	We have added this.

	worsening should be marked as ACIC		
P 49 Paragraph Subgroup analysis	All details for country group sub-analyses are yet to be published, and should be marked ACIC	that trial arms differed in baseline major motor seizure frequency, with a higher rate of seizures in the GNX arm (median [IQR] [redacted] vs. [redacted]). While there was a greater overall reduction in major motor seizure frequency in the GNX arm, this was not statistically significant and a similar number of people in each arm showed a response (GNX [redacted] and PBO [redacted]) and were considered by caregivers to have improved (GNX [redacted] and PBO [redacted]).	We have added this.
p.50	Rate of TEAEs can be openly given; mentioned in the main trial publication	…rates of overall treatment-emergent adverse events (TEAEs) were comparable between arms, but there was a higher rate of treatment-related adverse events in the GNX arm (70.0%) compared to placebo (43.1%). I	We have removed this.
p 56 second row in the top table	Original value of severity modifier should be CIC	Severity weighting of [redacted] applied to QALYs gained by both patients and caregivers	We have added this.
p 58 second last paragraph	"two years and over" is stated openly in other documents as part of the intended indication. CIC mark can be removed.	This differed from the expected marketing authorisation of GNX, which was for patients aged two years and over.	We have removed this.

p 64 in table 14, second row on page	67% should be marked as CIC	The EAG method generated reductions in mean, median and standard deviation close to 27.08%, whilst the company's method led to approximately [redacted] reductions.	We have added this.
p. 71-72 Duration of treatment	Patient numbers and equation should be CIC	This used what the EAG believed to be the number of discontinuations between the baseline and the end of the OLE ([redacted] the number of patients that continued to the end of the OLE ([redacted]… [redacted]	We have added mark-up for the number of participants, though the equation was already marked in the EAG report.
p 78 Table 18	Right most column in the Table 18 – should be CIC	**Application in company's model** [redacted]	We have added this.
p 80 **Table 19**	Right most column in the Table 19 – should be CIC	**Application in company's model** [redacted]	We have added this.

<table>
<tr><td></td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>p 84 middle of the page</td><td>Also the weight should be marked as CIC</td><td>Patients were assumed to enter the company’s model aged [redacted], with a mean body weight of [redacted] kg…</td><td>We have added this.</td></tr>
<tr><td>p 86 Table 20</td><td>All values in Table 20 to be CIC</td><td><table><tr><th>Chin et al. (2021) cost per 28 days</th><th>Lagae et al., (2019) cost per 28 days</th></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>We have added this.</td></tr>
<tr><td>p. 89 last paragraph</td><td>factors most influential in sensitivity analysis, other than the utility values, should be marked CIC</td><td>The main parameters shown to influence the ICER were related to [redacted], utility values [redacted] entering the model.</td><td>This sentence does not include commercially sensitive data and we have not added this.</td></tr>
<tr><td>p 94 Table 23, middle column</td><td>effect size estimate of maintenance period can be provided openly: remove CIC from the “29.31%</td><td>not 27.08% or 29.31% as per HL estimates</td><td>We have removed this.</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><td>p 100 Table 24</td><td>All column contents in Table 24, all rows, including incremental QALYs to be CIC;</td><td><table><tr><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER £/QALY</th><th>+/- company base case</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td></tr><tr><td colspan="4">[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>We have added this.</td></tr>
<tr><td>p 102 below Table 25</td><td>Original severity modifier should be marked CIC</td><td>Note: In the EAG-corrected company base-case, the severity modifier used was calculated as [redacted]. See Section Error! Reference source not found..</td><td>We have added this</td></tr>
<tr><td>p 101-102 Table 25</td><td>All values in Table 25 to be CIC, including all QALys</td><td><table><tr><td>ECM</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td></tr><tr><td>GNX+ECM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>We have added this.</td></tr>
<tr><td>p 103 – Figure 4</td><td>Original severity modifier should be marked CIC both in Figure title, and the text below the Figure 4</td><td>In title …..[redacted] severity…

Note: The severity modifier used was calculated to be [redacted]. See Section Error! Reference source not found. for discussion.</td><td>We have added this.</td></tr>
<tr><td>p 102 and 103</td><td>Percentages in text and
actual Fig 4 as a total and
actual Fig 5 as a total</td><td>[redacted] provides an updated cost-effectiveness plane incorporating the severity modifier for patients and caregivers, showing that only a small minority of probabilistic iterations were cost effective at a willingness to pay threshold of £30,000</td><td>We have added this to the percentages noted</td></tr>
</table>

<table>
<tr><td></td><td>should also be redacted as CIC</td><td>[redacted] When not applying the severity modifier to caregivers this probability fell to [redacted] ([redacted]).</td><td></td></tr>
<tr><td>p 109 Table 26</td><td>Also all incremental QALYs (all rows) ahould be marked CIC</td><td>Incremental QALYs
[redacted]
[redacted]
[redacted]
[redacted]</td><td>We have added this.</td></tr>
<tr><td>p 110 first paragraph below table</td><td>these factors, other than the patient utility, should be marked as CIC</td><td>most impactful individual changes were those affecting [redacted] and those affecting patient utility (e.g., use of Auvin et al.). Other notably impactful scenarios include [redacted]</td><td>This sentence does not include commercially sensitive data and we have not added this.</td></tr>
<tr><td>p 110 Section 6.3 first paragraph</td><td>ICERs from text to be marked as CIC, in line with the tables below that</td><td>The EAG preferred base case ICERs were [redacted] without the severity modifier for caregivers and [redacted] with a ([redacted]) modifier for caregivers</td><td></td></tr>
<tr><td>p 111- 112, Table 28-
all rows</td><td>All values, including Incremental QALYs and the change to the base case ICER (right most column) should be marked CIC, so as not to enable</td><td><table><tr><th>Section in EAG report</th><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER £/QALY</th><th>+/- <u>corrected</u> company base case</th></tr><tr><td>Exploratory</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>We have added this.</td></tr>
</table>

	calculating the resulting ICERs		
p 114 -115 Severity modifier details	In all paragraphs ALL the numerical details should be CIC, including QALY shortfall calculation details and original severity modifier values	The company applied a disease severity modifier to both CDD patients *and* their caregivers of [redacted]… the company calculated the expected lifetime discounted QALYs for a patient with CDD treated with ECM from aged [redacted] to be [redacted] This compared to an age- and sex-matched general population discounted QALY estimate of [redacted] QALYs. As the absolute discounted QALY shortfall was more than 18, the corresponding severity modifier was [redacted]. - discounted absolute QALYs for ECM patients was [redacted], leading to an absolute shortfall of [redacted] discounted QALYs, hence a severity weighting of [redacted] (estimated to be [redacted] years in the cost-effectiveness model .. EAG corrected company base case were [redacted] QALYs and [redacted] respectively ([redacted] QALYs and [redacted] respectively in the EAG's base case). [redacted]	We have added mark-up to the figures, but not for the final conclusion which (aside from the figures now marked up) does not contain confidential data.

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **19 April 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Dr. [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Orion Corporation, Orionintie 1A, 02200 Espoo, PO Box 65, FI-02101 Espoo, Finland
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosures

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding clinical effects in the Marigold open-label extension (OLE)	**Yes**	To alleviate the concern on the uncertainty of the long-term effect, as suggested by the EAG, further analyses on the most recent data cut available of the OLE (June 2022, complete 2-year OLE data) have been performed. This includes imputation of missing data for the full cohort and analysis of 28-day MMSF reduction only in responders. These demonstrate maintenance of the GNX effect over 2 years beyond the 4 months DB phase (**Attachment 1**). The model has been improved by assuming treatment discontinuation and full loss of effect from six months forward for all patients with less than 30% response in major motor seizure frequency. Treatment effect vs. regression to the mean The patients in Marigold have been recruited to both study treatment arms by the same criteria, thus, the difference in relative efficacy between the arms should not by default be driven by regression towards the mean, as any risk of such should be balanced across treatment arms. No further information on recruitment procedure is available to the company, however, “baseline seizure frequency” was based on 6-week period before treatment start, rather than the latest 28 days only, which mitigates the risk. Furthermore, the OLE data on the placebo patients who started GNX later, at week 17, demonstrate similar treatment effect to that of GNX in the DB phase, supporting that the patients have not been experiencing any peak exacerbation state prior to study recruitment.

		While longer term data from the MARIGOLD open-label extension suggest the effect of GNX appears to increase over time (beyond the study double-blind period), the model does not assume either increasing or decreasing effect beyond the initial 17-week double blind period in those remaining on medication, to avoid biasing in either direction.
Key issue 2: Model structure	**Yes**	The sample size of the Marigold study was, while large for an ultra-rare disease, too limited to reliably build a Markov model similar to those presented for the proxy conditions, in which prevalence is significantly higher, and consequently, also the clinical trials were 2-3 times larger than Marigold. For example, stratifying 49 ganaxolone patients (and even smaller subsets based on response) by their seizure reductions and/or other outcomes to generate data for a Markov state-transition or similar structure would be associated with high uncertainty (as the transition probabilities and other parameters would in many cases be calculated based on zero or very small numbers of patients as a percentage of an also limited total population). Given the lack of available data from either the Marigold study or literature surrounding CDD to inform the disease states within such a structure, it was determined as unfeasible to develop a model of this type specific to CDD. A Markov model based on the seizure frequency categories from other proxy conditions (e.g. TSC, LGS or DS) would have been challenging also because the types of seizures and/or seizure frequency distribution of CDD patients in the Marigold study did not correspond optimally with the seizure frequency categories which were used to define health states in models/utility studies for proxy conditions, especially those in DS/LGS (Auvin et al). A considerable proportion of CDD patients fell into the “floor" state (i.e. lowest seizure frequency category) and were thus already at baseline, with no scope to capture the impact of improvements on quality of life in patients despite experiencing seizure reductions (e.g. when using Lo *et al*). Even more impact could be seen at the upper end of the scale, where many patients are far above the lower cut-off interval of the highest seizure category

		within Auvin *et al*. in particular, leading to a similar issue, of not being able to gain QALYs. For example, patients with severe CDD and experiencing very frequent seizures would experience no change in utility despite clinically significant (30%, or even 50%) reductions in seizure frequency. This issue is particularly pronounced for caregivers when using the Auvin et al. study, as despite the intent to categorise health states based on a combination of seizure frequency and the incidence of seizure-free days, there are only three available states/utility values, of which one corresponds to no seizures/30 seizure-free days per cycle (which no patients in the MARIGOLD study in either arm would qualify for). In effect this leaves only two different utility values caregivers could experience across the entire spectrum of seizure frequency. However, we have revised the model with the following changes (for further details please see **Attachment 3**): 1. We have improved the model by assuming that patients not achieving at least 30% response will stop treatment and immediately lose the QALY gain from there on (see Key issue 1) 2. We have added accuracy to the baseline seizure-free-day (SFD) distribution, to match the Marigold patient level data (previously it was assumed patients are gathered around the mean within the same SFD class). 3. We have added an element to reflect the increase in SFDs with GNX over ECM, based on Marigold data in the DB period. This change was significant in GNX patients with ≥30% response in 28-day MMSF. In consideration of the EAG´s request we now also present the results from an alternative modelling approach based on microsimulation (bootstrapping) with individual patient data. However, of note even this approach is likely highly conservative for ganaxolone due to the high ceiling and floor effects mentioned above. QALY gains are minimal and in many cases state definitions preclude any QALY gains being demonstrated, even where clinically significant reduction in

		seizures was experienced. Despite this, the bootstrapping approach largely supports a lower, more narrow range of ICERs.
Key issue 3: Application of seizure frequency	**Yes**	We have submitted new OLE seizure data that extends to 2 years (Please see Key issue 1/ **Attachment 1** for the new Marigold OLE analysis). The availability of the longer follow-up period data gives increased confidence in the estimates used both for discontinuing treatment, as well as level of seizure reduction in the long term in those who stay on treatment. Based on the complete 2-year OLE data we have now also calculated the discontinuation rate as per time at risk of discontinuation (using exposure days), as suggested by the EAG. This makes the discontinuation rate by cycle [redacted] for the double-blind period. We also have now also introduced a 6-month stopping rule, whereby only the patients who achieve at least 30% seizure reduction at end of the DB phase are assumed to continue treatment at 6 months, which improves the ICER. The discontinuation rate for these “30%-responders” was [redacted]% in OLE, based on the same exposure days-based calculation as the pre-stopping rule discontinuation rate proposed using the double-blind exposure rates. These have now been used in the updated model. The EAG also suggests that interpolation of the effect should be applied. The company agrees with separating the titration period from the maintenance period. However, the company is of the opinion, that since the estimated 28-day seizure frequency reduction effect from the Marigold clinical trial represents an average of the entire dose maintenance period - weeks 5-17 – and not only the last 28 days before the end of the DB study, the full effect of 29.31% reported for the maintenance dose period should be applied from cycle 2, and not only from cycle 4. Please see the definition of how the DB 17-week seizure frequency is calculated, as per the statistical analysis plan: “Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with

		seizure data in the phase, multiplied by 28." A similar approach for calculating the 28-day seizure frequency applies to the maintenance dose phase. Thus, have now applied this in our base case.
Key issue 4: Utility values	**Yes**	The paucity of data specific to CDD necessitated the use of data relevant to conditions that could serve as a proxy to CDD. None of the diseases is fully optimal for modelling CDD. Furthermore, as we are using proxy data to represent CDD rather than attempting to model the specific proxy conditions, we feel it is not a priority to use the same condition for both costs and utility values, but rather to select the most appropriate source for each, based not only on the condition covered to serve as a proxy, but also on the way data are reported (e.g. the definition of health states, seizure types/outcomes considered), study design and so forth, with respect to how it will be used in the model. First, one should find a disease with similar seizure pattern considering both the type of seizures and their frequency. Analysing seizure types, Lo et al. (TSC) is the closest one to Marigold, including generalized (major motor) seizures as well as focal seizures (see **Attachment 2**). Auvin et al. have also reported **utilities** for convulsive seizures for Dravet, however, the maximum number of seizures (32/month) limits the applicability for CDD – in Marigold the median seizure frequency was over 50 and the mean over 100 seizures per 28 days, with frequencies ranging even beyond 1000. Auvin et al. have also reported utilities for LGS with somewhat wider spread of seizures (upper category 130 seizures/month); however, the utilities are for drop seizures only, while of the ganaxolone patients in the Marigold study, only 18% reported having experienced drop seizures (Table 1, Attachment 2). Furthermore, the **caregiver utilities** in Auvin et al. have been defined (based on LGS seizure distribution) only for two seizure states (80 seizures and 110 seizures/month) and a seizure free state. As many of the CDD patients fall out of these categories, it is quite likely that projecting the caregiver impact of CDD based on Auvin utilities would lead to highly underestimating the impact on

		caregivers. Lo et al. instead utilizes the full seizure distribution also for caregiver utilities. **Therefore, considering all the aspects, the company considers Lo et al. the most appropriate source of utilities for modelling CDD.** When considering costs, systematic literature review identified two studies. Chin et al. was the only study reporting resource use as well as the costs, including hospitalisation. Lagae et al. reported the costs for Dravet with clearly lower seizure burden – and did not include hospitalisation. Thus, Chin et al was perceived the only source with full range of costs. It is likely that both the utility and cost impact is somewhat conservatively modelled, given the higher number seizures in CDD (more severe nature of the disease) compared to the other diseases. The EAG has stated that the company implemented the utility values as relative to the seizure free state rather than absolute, which would have been per NICE methods guidance; **the company agrees in principle with using absolute values** considering Auvin et al, with the caveat that we consider Lo et al the most appropriate source of utility values.
Key issue 5: Miscellaneous model errors and unsubstantiated assumptions	No	The company agrees with the principle of **interpolation of effect** at start of treatment, however, a **modification to the approach** is proposed (please see Key issue 3 response), applying the full seizure reduction effect of 29.31% from already cycle 2 (start of the maintenance dose period), rather than from cycle 4 only. For the assumed **durability of treatment effect**, please see Key issue 1. The EAG has questioned the Company´s **assumption on waste**. The EAG propose a 10% estimate for wastage of medicine. Rather than a rational calculation or available data on the topic, the said estimate is based on one clinical

		opinion, that builds on the notion that *some children with CDD may have issues with spitting* out the medication. In the view of the company if any wastage were to occur, a more realistic estimate would be 0.47%, which equals 0.5mL per bottle. This assumes there is a 20% share of patients who miss a dose (average 8.4mL) once every week due to spitting, and, that in half of these cases a full replacement dose would be given as extra – a highly conservative assumption. However, the MA holder/ manufacturer has not received any reports, nor is there any evidence of spitting/ redosing either in the clinical trials, the expanded access program nor US commercial use. Furthermore, even if spitting would occasionally happen, due to a risk of overdosing, it is considered non-advisable to give "a replacement dose", nor is such guidance provided in the SPC. **Thus, the company maintains the opinion that the base case estimate of zero waste is justified.**
Key issue 6: Application of severity modifier	**Yes**	The company agrees with the EAG that the wording of the NICE Methods Manual on the application of a severity modifier (may be applied to "people living with the condition") leaves room for interpretation. However, CDD is not just a standard difficult-to-treat epilepsy, but an infant-onset, severely disabling, complex developmental and epileptic encephalopathy (DEE). In addition to severe epilepsy, it involves physical and neurocognitive developmental delay and is linked with various other comorbidities. The company believes that no parent who knows of this disorder would doubt that the caregivers are "living with the condition" every day. As already highlighted in the company submission to some degree, there is a meaningful detrimental impact on the quality of life for carers of patients with CDD: In a survey with 49 caregivers of people with CDD, they reported that the profound multisystem complications of CDD such as global developmental delay (consisting of elements such as limited or absent ability for speech/communication, limited ability to use ones hands, to walk or stand unaided, to eat unassisted) as well as the epilepsy/seizures have the most devastating impact on their family life

		requiring adjustment to carers' lifestyles to provide constant support in the management of the patient throughout their journey. The Voice of the [CDD] Patient Report 2020 (Loulou Foundation IFfCR. https://www.cdkl5.com/wp-content/uploads/2020/06/CDD-VoP-REPORT.pdf.) Additionally, these children have multiple comorbidities, such as visual impairment, respiratory issues, scoliosis as well as behavioural issues (e.g. hypersensitivity, agitation, irritability, screaming, or self-injury) as well as sleep disturbance. Thus, it is not surprising that, that studies show that caring for a child with CDD significantly affects parental emotional wellbeing (SF-12) and family quality of life (BCFQOL). Strongest identified drivers of these effects are child sleep problems (also affected by nocturnal seizures) and family financial difficulties. Poor maternal sleep quality, often a sequela of child's sleep disturbances, has been shown to be an important predictor of depression in mothers of children with developmental disabilities. In parents of children needing GI tube feeding, also physical health (SF-12) was impacted. (Mori et al 2017) These findings are further supported by extremely high disability (QI-disability score) and low independence of the patients (Downs, 2022), emphasising the reliance of patients with CDD on carers. Taking care of a person with CDD is a 24/7 task that affects the whole family. As has been considered appropriate in some of the other complex epileptic conditions (e.g TA614, TA615) as well, in our CDD model we account for and average 1.8 caregivers per person with CDD. Furthermore, due to the fairly recent identification of CDD as a separate, distinct condition, and to the prevalence that qualifies CDD as an ultra-rare condition, there is unfortunately no specific information available on CDD mortality. However, as also noted by the EAG, clinical opinion confirms that mortality is likely to be increased in similar fashion as in other DEEs such as LGS, compared to normal population. This would seem a realistic view, since few diagnosed adult CDD cases are known in the UK. Awareness of this excess mortality risk (partially linked to SUDEP), as well as the constant risk of prolonged seizures and status

		epilepticus increase parental stress and the fear of losing their child, or, losing the few but all the more valuable functional abilities their child has gained by then. Based on this background, as well as the near-total dependence of these patients on their caregivers, the company is of the opinion that **also caregivers are impacted by the same, extreme severity of CDD, and thus should be considered "living with the condition". Therefore, the same severity weighting as for the patient QALY gain should be applied on the caregiver QALY gain as well.** The details of the severity modifier calculation are presented in **Attachment 3.**

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Unit cost for hospital admissions (epilepsy)	4.2.8	**Yes**	The EAG highlighted that it was unclear whether the value of 27.4 days referred to an average length of stay per admission, or an overall average length of stay in hospital over an extended period of time potentially covering multiple admissions. Therefore, they suggest applying a short stay unit cost on the epilepsy admissions. The NHS data model and dictionary POINT OF DELIVERY CODE FOR PATIENT LEVEL INFORMATION COSTING (datadictionary.nhs.uk) defines a non-elective short stay as "less than 2 days" and a long stay as "2 days or more". To clarify the length of stay relevant for CDD, the company contacted the research group. We can now confirm that the mean (SD) duration of epilepsy-related hospital admissions in a sample of CDD patients from the same ICDD database as the Mangatt study used, is [redacted] ([redacted]) days (personal communication, [redacted]). This is from a larger sample (N=324) vs Mangatt, with some more recent data included. Furthermore, in this data set it is also confirmed that only a small share of the admissions is shorter than 2 days, meaning that most of the admissions qualify for long stay unit cost. We have revised the model assuming a weighted average unit cost (please see relevant section in **Attachment 3**).

Additional issue 2: Final data/report availability from Marigold open-label extension	page 32	**Yes**	A few patients are still in the OLE follow-up. Thus, the final report/ final OLE data is still not available. We have now received the key seizure outcomes data, the discontinuation and exposure data from the most recent data cut of 30 June, 2022, which includes complete 2 year data. We have utilized these data for the model update. See **Attachment 1.**

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
1–4	Original ICER did not imply stopping rules were beneficial or necessary; no stopping rule was applied.	Addition of stopping rule whereby patients experiencing a minimum 30% reduction in seizure frequency in MARIGOLD double-blind period continue treatment while others revert to ECM alone	Reduced overall ICER
1	Discontinuation rates were calculated using OLE rates; EAG proposed alternative method using exposure from DB only	Incorporated a "split" discontinuation approach, whereby short-term discontinuation matches EAG proposed approach using double blind, whereas long-term discontinuation reflects using the same approach in OLE data (more representative of continuing patients)	Slightly reduced overall ICER
Various including additional issue 1	Used long-term hospitalisation cost from NHS reference costs	Calculated weighted average of long- and short-term hospital stay costs using hospitalisation data from MARIGOLD study	Slightly increased overall ICER
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted]	Incremental costs: [redacted]	£21,715

Sensitivity analyses around revised base case

Deterministic and probabilistic analyses outputs are reproduced for new base case assumptions in **Attachment 3.**

Attachment 1. Further analyses of long-term data from the OLE.

We have now analysed seizure data from the most recent OLE data cut from June 2022, which includes complete data to 2 years for all patients. Based on the OLE data (including missing data analysis using LOCF imputation), the median seizure reduction rate is maintained over time (Fig 1).

Figure 1. Major motor seizure frequency reduction compared to baseline. Analysis on full combined OLE patient cohort with missing data imputed (LOCF).

The maintenance phase difference of ganaxolone vs placebo in median 28-day MMSF reduction was 29.31% (Hodges-Lehmann estimate of location shift) for the overall population, while for the ≥30%-responders it was [redacted] and maintained throughout the open-label extension (Fig 2).

Figure 2. Reduction in 28-day major motor seizure frequency over time in the subgroup of patients who had ≥30% response during the maintenance phase of the DB period vs. baseline (all available data).

We are now presenting a revised base case version of the model, where a stopping rule is adopted. Any patient who did not reach ≥30% reduction in primary (major motor) seizures at week 17 in the DB maintenance dose phase is assumed to stop treatment after the first 6 months (cycles) and immediately from there on to lose the seizure effect and the associated QALY gain of ganaxolone. Therefore, in the model base case we have applied the [redacted]% major motor seizure reduction for the responders on treatment beyond 6 months, while for those who discontinue treatment, a zero-effect is applied from the time of discontinuation.

Figure 3 illustrates how the major motor seizure frequency (reduction) is predicted to develop over time in the full patient cohort (all who enter the model/start GNX treatment) as per the economic model, where the stopping rule is applied.

Figure 3. Major motor seizure frequency reduction vs ECM in full patient cohort *as per the economic model*. Missing values are imputed assuming zero reduction in seizures.

Attachment 2. Seizure distributions

Table 1. CDD associated seizures by type (MARIGOLD study, baseline)

Major motor seizure types in the baseline period (MARIGOLD)	ganaxolone (N=49)	placebo (N=51)
Bilateral tonic	35 (71%)	39 (76%)
Generalized tonic-clonic	24 (49%)	20 (39%)
Atonic	9 (18%)	12 (24%)
Bilateral clonic	6 (12%)	3 (6%)
Focal to bilateral tonic-clonic	7 (14%)	6 (12%)

Source: Pestana Knight et al. Lancet Neurol (21)2022

Table 2. TSC-associated seizures by type (GWPCARE6 study, baseline).
Seizures were defined as generalized seizures (tonic-clonic, tonic, clonic, or atonic), focal seizures evolving to bilateral motor seizures, and focal motor seizures with and without impairment of awareness.

Seizure types during in the baseline period (GWPCARE6)	Placebo (N=76)	CBD-25 (N=75)	CBD-50 (N=73)
Focal with impaired awareness	50 (66%)	46 (61%)	54 (74%)
Focal without impaired awareness	33 (43%)	29 (39%)	39 (53%)
Focal to bilateral motor seizures	24 (32%)	17 (23%)	24 (33%)
Tonic-clonic	14 (18%)	22 (29%)	16 (22%)
Tonic	15 (20%)	27 (36%)	23 (32%)
Clonic	2 (3%)	3 (4%)	3 (4%)
Atonic	13 (17%)	10 (13%)	5 (7%)
Other	15 (20%)	12 (16%)	24 (33%)

Source: Thiele et al. JAMA Neurol. 2021 Mar; 78(3)

Attachment 3: Additional analyses and updates to economic analysis

Parametric bootstrap analysis of MARIGOLD data

To assess alternative structural/methodological approaches, using patient-level data from the double-blind period of the MARIGOLD study, random sampling (n=10,000) from the PBO (n=51) and GNX (n=49) arms, to assess the utility categories – from Lo et al (2022) and Auvin et al. (2021) – into which individual patients fell, so as to calculated mean utility values, changes and relative increments/decrements with GNX. GNX responders (n=21) were also sampled to generate corresponding mean values and increments for this key subgroup. The mid-point of each interval was assumed to represent the cut-off point between categories (at which point patients "switch" between categories).

Scenarios using each source, in addition to a crude average value of both studies, are shown in Table 1.

Table 1. Summary utility values from bootstrap analysis (n=10,000)

Summary values		Study	Auvin et al. (2021)	Lo et al. (2022)	Combined average
PBO	Baseline utility	Patient	[redacted]	[redacted]	[redacted]
		Caregiver	[redacted]	[redacted]	[redacted]
	Average change	Patient	[redacted]	[redacted]	[redacted]
		Caregiver	[redacted]	[redacted]	[redacted]
GNX (all)	Baseline utility	Patient	[redacted]	[redacted]	[redacted]
		Caregiver	[redacted]	[redacted]	[redacted]
	Average change	Patient	[redacted]	[redacted]	[redacted]
		Caregiver	[redacted]	[redacted]	[redacted]
GNX responder	Baseline utility	Patient	[redacted]	[redacted]	[redacted]
		Caregiver	[redacted]	[redacted]	[redacted]
	Average change	Patient	[redacted]	[redacted]	[redacted]
		Caregiver	[redacted]	[redacted]	[redacted]
GNX (all) increment		Patient	[redacted]	[redacted]	[redacted]
		Caregiver	[redacted]	[redacted]	[redacted]
GNX responder increment		Patient	[redacted]	[redacted]	[redacted]
		Caregiver	[redacted]	[redacted]	[redacted]

The outputs from this analysis demonstrate a positive effect on seizure frequency and across QoL increments across all studies using the data from MARIGOLD directly. Furthermore, it investigates the application of other (more traditional) model structures to model CDD, in effect representing a cohort-level and patient-level Markov based approach. To this end, the bootstrapping approach also highlights the limitations of these approaches given the limitations of proxy sources available; with the application of strict categories, and sampling from a small range of patients, a considerable proportion of patients remain in the same frequency category despite clinically relevant seizure

frequency reductions. This is more pronounced with Auvin et al., and particularly regarding caregiver utilities, for which only two states are in effect accessible. This makes the utility calculation an average of just two categories across the entire seizure frequency spectrum, with a high proportion of patients unable to change between them. This dilutes the potential QALY gains for patients experiencing significant reductions in seizure frequency, but unable to realise a utility increment from this.

Further analyses of seizure-free days

To understand potential impacts of changes in seizure-free days, further analyses of the distribution of patients into seizure free days categories described in Auvin et al. were used (no patients fell into the 0 seizures/30 SFD category). These are shown in Table 2. Distribution of MARIGOLD patients into SFD categories (Auvin et al. 2021).

Table 2. Distribution of MARIGOLD patients into SFD categories (Auvin et al. 2021)

Number of SFD per average month	% of patients in SFD categories		
	PBO	GNX	GNX responder
1	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]

These were included in the model to facilitate and option that can ‘weight’ the average utility values of each seizure frequency category by the proportion of patients falling into relevant utility categories, rather than assuming the mean SFD values from Marigold.

In addition, while no patients could feasibly enter the 30 SFD / 0 seizures category for an entire cycle due to the severity of the condition, there is a clear potential for seizure free days associated with reducing the frequency of seizures (especially in patients who experience SFDs at baseline).

As the 28-day cycle length precludes capturing the benefit of SFDs when using Auvin (no patient will experience 28 consecutive seizure free days), the potential to adjust utility values on a population level was considered; an option to weight the average utility values to add an increment for additional SFDs in the cohort was included, whereby the average utility values from Auvin et al. (2021) were adjusted to capture individual SFD increments.

The model considers additional SFDs gained with GNX relative to placebo. The change from baseline in percent of SFDs was compared between groups using the Hodges-Lehmann (HL) Shift. This between-group difference was subsequently converted to represent the number of SFDs gained on a per-year basis.

Considering all GNX patients versus placebo, the HL shift relates to an addition of [redacted] SFDs per year. When considering the subset of GNX patients with at least 30% reduction in seizure frequency (responders), the HL shift relates to an addition of [redacted] SFDs per year.

Assuming these days of a year would be associated with the utility values corresponding to the 30SFD / 0 seizures state (0.83 for patients, 0.78 for caregivers), the weighted average utility was calculated as:

$$U^{Adj} = (\frac{SFD}{365.25}) \times U^{SFD} + ((\frac{365.25 - SFD}{365.25}) \times U^{Base}$$

U^{Adj} = Adjusted utility; SFD = Number of seizure free days per year; U^{SFD} = Utility value of 0 seizures/30 SFD category; U^{Base} = Modelled average utility value from other states

Based on these adjusted values, utility values under all scenarios (with and without adjustment are shown in Table 3.

Table 3. Distribution of MARIGOLD patients into SFD categories (Auvin et al. 2021)

Subgroup/utility method			**Relative/absolute adjusted/unadjusted utility values by category for use in Auvin et al. (2021) calculations**						
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	Relative	U^{Base}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		U^{Adj}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Absolute	U^{Base}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		U^{Adj}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GNX (all)	Relative	U^{Base}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		U^{Adj}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Absolute	U^{Base}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		U^{Adj}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GNX responder	Relative	U^{Base}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		U^{Adj}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Absolute	U^{Base}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		U^{Adj}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For completeness, utility decrements were calculated incorporating the SFD adjustment for the relevant bootstrap analysis calculations (those using Auvin et al. 2021). Calculated utility increments for GNX and GNX responders are shown under each scenario in Table 4.

Table 4. Bootstrap analysis utility increments using SFD adjustments for Auvin *et al.* (2021)

Study/method		GNX increment			
		Average GNX (all)		Average GNX responder	
		Patient	Caregiver	Patient	Caregiver
Auvin et al. (2021)	Without SFD adjustment	[redacted]	[redacted]	[redacted]	[redacted]
	With SFD adjustment	[redacted]	[redacted]	[redacted]	[redacted]
	Average	[redacted]	[redacted]	[redacted]	[redacted]
Lo et al. (2022)		[redacted]	[redacted]	[redacted]	[redacted]
Combined Average (Lo and Auvin)	Without SFD adjustment	[redacted]	[redacted]	[redacted]	[redacted]
	With SFD adjustment	[redacted]	[redacted]	[redacted]	[redacted]
	Average of all options	[redacted]	[redacted]	[redacted]	[redacted]

Further analyses of hospitalisation data

Further analyses of hospitalisation data were conducted to understand length of stay assumptions. These data showed then [redacted]% of hospitalisations in the DB period qualified as long stays per NHS reference costs (≥2 days), and the remaining [redacted]% qualifying as short stays (1 day or less) (AIC; personal communication, [redacted]). A weighted average cost based on the two cost scenarios presented in the EAG report was used in the model (Table 5).

Table 5. Hospitalisation cost scenarios

Cost scenario	Unit cost
NHS reference costs 2020/21; Non elective long-stay; currency Code PRO2A, PRO2B, PRO2C; Paediatric Epilepsy Syndrome	£6,545.75
Short stay equivalent cost	£1,036.71
Weighted average based on MARIGOLD length of stay data ([redacted]% long stay)	[redacted]

The applicable unit cost may still be underestimated, as we have disregarded the excess bed day costing which applies for PRO2B and PRO2C after the trim point of 5 days, and for PRO2A after 11 days. The median LOS in the mentioned real world data set of CDD patients was [redacted] days, while in [redacted]% of the patients the average LOS per admission was 11 days or longer (AIC; personal communication, [redacted]).

Severity weighting

Further consideration was given to the QALY severity weighting. From our interpretation of the intention of the QALY weighting, as a holistic representation of the severity of CDD as a condition, i.e. the weighting that should be applied to its impact as a whole. Furthermore, considering that the value of a QALY is the same irrespective of whether it is that of a patient or caregiver, we consider our base case approach of basing a single overall QALY weighting to be appropriate. This is especially so considering the potential

utility benefits not captured in the current approach (e.g. developmental impact, disability, impact on activities of daily living/education) that would likely considerably increase long term QoL impact for both patients and caregivers above and beyond that estimated in the model.

We understand the principle suggested by the EAG of a potential method of calculating the QALY shortfall for caregivers separately based on the caregiver QALY shortfalls. However, if this were the case, considering there are 1.8 caregivers per patient on average, the shortfall should account for this (i.e.) be multiplied by 1.8, increasing absolute shortfall and allowing for a severity weight of 1.7 to be used, whether basing utilities on Lo et al or Auvin et al.

Seizure effect assumptions in revised model with stopping rule

We are now presenting a revised base case version of the model, where a stopping rule is adopted. Any patient who did not reach ≥30% reduction in primary (major motor) seizures at week 17 in the DB maintenance dose phase is assumed to stop treatment after the first 6 months (cycles) and immediately from there on to lose the seizure effect and the associated QALY gain of ganaxolone.

The following assumptions are used in the revised model for seizure reduction from the six months point onwards for the responders who continue on treatment:

For model assessing major motor seizures: [redacted]% (base case)
For the scenario assessing all seizure types: [redacted]%

These seizure reductions are based on MARIGOLD data, and the HL location shift, for the respective seizure type frequencies, between the GNX responders and placebo in the DB maintenance dose phase vs baseline. There is no change to the seizure reductions applied for the full population in titration phase, or the maintenance phase, compared to the original model submitted.

Base-case incremental cost effectiveness analysis results

Updated Base case results for the CDD population are presented in Table 6.

Table 6: Revised Base-case results

Technologies	Total			Incremental (GNX vs ECM)			Weighted ICER (£/QALY)
	Costs (£)	LYG	QALYs (weighted*)	Costs (£)	LYG	QALYs (weighted)	
ECM alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,715
GNX + ECM	[redacted]	[redacted]	[redacted]	–	–	–	

*1.7 QALY weighting applied to patient and caregiver QALYs

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Sensitivity and scenario analyses

Updated results from sensitivity analyses are presented below.

Deterministic (one-way) analysis

The ten most impactful parameters on the modelled ICER under the updated manufacturer base case are shown in Figure 1.

Figure 1. Tornado chart showing outcomes from deterministic one-way analyses

Probabilistic analysis

A scatterplot showing the spread of sampled incremental costs and QALYs from probabilistic analyses is shown in Figure 2. An updated cost-effectiveness acceptability curve is shown in

Figure 3.

Figure 2. Scatter plot showing sample outputs from probabilistic analyses

Figure 3. Cost-effectiveness acceptability curve generated from probabilistic analyses

Scenario analysis

Scenarios evaluated (steps taking the model from its original to the current manufacturer base case) are summarised in Table 7.

Table 7: Scenario analyses conducted in the paediatric and adult population, and rationale

Scenario	Rationale
Replicating previous manufacturer settings in new structure	Showing initial corrected manufacturer setting
1. Including stopping rule/responder parameters	Retains treatment in patients achieving most clinically relevant seizure reductions (≥30%)
2. Including split discontinuation percentages (pre- and post-stopping rule) (+ scenario 1)	Discontinuation varies post-DB/stopping rule per DB and OLE data; would expect to be higher post given presence stopping rule at 6 months
3.Including weighted hospitalisation cost (+ scenario 2)	Most but not all hospitalisations are long term.
4. Including all rather than primary seizures (like scenario 3 otherwise)	Test impact of using parameters for all seizures

Abbreviations: QALY, quality adjusted life years

Results of scenario analyses are shown in Table 8.

Table 8: Summary of scenario analyses

Scenario	Incremental (GNX + ECM versus ECM alone)			ICER per QALY (£)
	Costs (£)	LYG	QALYs (weighted)	versus ECM alone
Replicating previous manufacturer settings in new structure (full population)	[redacted]	[redacted]	[redacted]	[redacted]
1.Including stopping rule/responder parameters	[redacted]	[redacted]	[redacted]	[redacted]
2.Including split discontinuation percentages (pre- and post-stopping rule) + scenario1	[redacted]	[redacted]	[redacted]	[redacted]
3.Including weighted hospitalisation cost + scenario 2 (**NEW BASE CASE**)	[redacted]	[redacted]	[redacted]	£21,715
4.Including all rather than primary seizures (like scenario 3 otherwise)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECM, Established clinical management; ICER, Incremental Cost-Effectiveness Ratio; LYG, life years gained; QALY, quality-adjusted life year

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **14 March 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Association of British Neurologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	We have nothing to disclose

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding clinical effects in the Marigold open-label extension (OLE)	No	There has been no subsequent secondary analysis to mitigate points raised by EAR, namely 'regression to the mean phenomenon' when assessing effect of GNX on seizure frequency. We would agree that a data cut off of 17 weeks is too short to truly assess long term efficacy. It is expected however that longer data cuts from the trial will be reported in due course. The relatively large withdrawal rate from the GNX arm of the trial (40%), chiefly due lack of efficacy, we agree would have an impact on final analyses.
Key issue 2: Model structure	No	No alternative models or justification of chosen model (Markov state-transition model) has been performed since initial response. Though this model might not reflect the full spectrum of CDD, using *alive/dead* outcome has been adopted in a number of previous comparator studies.
Key issue 3: Application of seizure frequency	No	The trial considered primary seizures alone when formulating the model. Therefor the concern that all types of seizure and their response to ganaxolone remain, with subsequent impact on cost-effectiveness analysis. However as tonic-clonic seizures were considered 'primary', this type would be most associated with

		morbidity and mortality (i.e. SUDEP) and presumably most impact on cost-effectiveness. There would be little reason to not consider US and UK CDD populations as comparable, being such a rare disease.
Key issue 4: Utility values	No	A large section of this response has been blacked out, meaning commenting on it is difficult. It appears utility values (ie assessed epilepsy parameters) were drawn from small studies. As epileptic encephalopathies are rare conditions, comparator studies would be limited to small cohort ones. In addition a study of Lennox-Gastaut was proposed by the EAG to derive utility values; however we would expect that LGS would be a more heterogenous group compared with CDD by nature of its diagnostic criteria.
Key issue 5: Miscellaneous model errors and unsubstantiated assumptions	No	A number of incorrect statistical adjustments were identified and corrected by the EAG. As such we cannot provide further clinical opinion on this issue.
Key issue 6: Application of severity modifier	No	A section of this response has been blanked out, so we are unable to fully comment on appropriate application of severity modifier. However it is not uncommon that QALY measures for patients AND their caregivers are incorporated when assessing intervention.
[insert issue heading from EAR]	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

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

A Single Technology Appraisal

EAG Review of Company's Response to Technical Engagement Response

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Produced by

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Rider on responsibility for document The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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1. INTRODUCTION

This document provides the External Assessment Group's (EAG's) critique of the company's response to the key issues contained within the EAG's report, within the technical engagement (TE) period as part of the National Institute for Health and Care Excellence (NICE) appraisal of ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over [ID3988].

The company has provided updated clinical effectiveness results from the single-arm, open-label extension (OLE) of its pivotal trial, Marigold (with data to 2-years), and has made several modifications to its economic model. A summary of the company's response is provided in Section 2. Each of the issues outlined in the EAG's report are discussed in further detail in Section 3. The EAG's critique of any additional evidence is provided in Section 4. Finally, the EAG's revised base-case analysis is described in Section 5.

2. Overview of company's technical engagement response

The company presented an updated economic model including a revised base-case analysis. The company's revised base-case analysis is presented in Section 2.2.

In its updated base-case, the company has accepted several errors highlighted by the EAG and has not provided any response or rebuttal on these points (i.e., the company's revised base-case analysis has been integrated within the EAG's edited model, including switches implemented by the EAG). The EAG therefore assumes that any changes implemented by the EAG that were not explicitly discussed in the company's response have been accepted, and so are not discussed further within the EAG's response.

2.1. Additional evidence provided by the company

In summary, the company has included the following within its response in relation to the key issues described in the EAG's report:

- **Key issue 1:** Analysis based on longer-term data from the MARIGOLD open-label extension (OLE) study
- **Key issue 2:** Further justification and evidence in support of the company's chosen model structure
- **Key issue 3:** Clarification on the definition of SF as measured in MARIGOLD, and therefore the meaning of the treatment effect estimates
- **Key issue 4:** Updated approach to modelling the health-related quality of life (HRQoL) impact of reducing SF
- **Key issue 5:** Discussion and analysis concerning duration of treatment effect and wastage
- **Key issue 6:** Further justification for the severity modifier relevant to this appraisal

The company's response also highlighted some additional issues that the EAG considered necessary to provide commentary to assist the committee as part of its decision making:

- The company has introduced a stopping rule for GNX, which assumed that all people who do not exhibit a 30% reduction in SF relative to their baseline SF by 6 months would discontinue treatment (see Section 4.1)

- The company has provided additional evidence regarding the length of inpatient stays (see Section 4.2)

All other changes made by the company to its preferred base-case analysis are relatively minor, and therefore are not discussed further in the EAG's response.

Alongside the company's response, the company also provided an updated cost-effectiveness model. The EAG appreciates the efforts made by the company to maintain the functionality implemented by the EAG to inform its report. However, the EAG was unable to fully revert the company's revised base-case analysis back to the EAG's preferred base-case analysis per its report. This is because the company has implemented several changes that compromise the original functionality of the model (e.g., changing specific input values without implementing a switch).

Nevertheless, the EAG was able to revert to its previous base-case analysis with a few small tweaks to specific input cells/ formulae, based on the following edits:

- Costs parameters, cells K34:K39 (revised costs)
- Clinical parameters, cells Q31, AA95, and AA96 (number of caregivers and utility values)
- Trace for GNX, cells M9 and M10 (rounding error)

2.2. Updated company cost-effectiveness results

The updated company base-case ICER is £[redacted]. However, as noted in the EAG's report, there are a number of important assumptions made by the company to obtain this ICER. Therefore, the EAG highlights the following ICERs associated with different settings and/or assumptions that were previously discussed within the EAG's report (but maintaining all other elements of the company's updated base case):

- Without applying the severity modifier to caregiver utilities, the ICER is [redacted]
- Without applying the stopping rule the ICER is £[redacted]
- With no severity modifier for caregivers or the stopping rule the ICER is £[redacted]

- Using Auvin *et al.* utilities instead of the Lo *et al.* utilities the ICER is £[redacted], and when using the bootstrapped combined average utilities (per company Attachment 3), the ICER is £[redacted].
- With the combined average bootstrapped utilities and no caregiver severity modifier, the ICER is £[redacted]

The EAG's updated base-case ICER is presented in Section 5, alongside a description of the changes made.

3. EAG REVIEW OF KEY ISSUES

In this section, each of the key issues described within the EAG's report are discussed alongside the company's TE response.

Key Issue 1: Uncertainty surrounding clinical effects in the Marigold OLE

Summary of the key issue

The EAG considered there to be uncertainty in the clinical effects reported from the Marigold OLE (i.e., all clinical data greater than 17-weeks following treatment) due to a high rate of missing data and a risk of regression to the mean following treatment initiation.

Summary of the company response

In its response to TE, the company provided data for the 28-day change in major motor seizure frequency (MMSF) at 2-years in the ITT population using imputation of missing data. In response to the EAG concerns about a potential regression to the mean effect, the company stated that it did not have access to historical seizure data in participants in Marigold to provide more insight into if / how many participants were experiencing an increase in SF prior to participation in the trial. However, the company provided two additional justifications for the absence of this concern:

- Firstly, the company noted that the baseline period was six weeks, which it argued would mitigate the risk that participants were experiencing a sudden increase in SF.
- Secondly, the company suggested that those participants who switched from placebo to GNX after 17-weeks showed a similar pattern in a reduction in SF, which supported the absence of a regression to the mean effect.

EAG response

The EAG considered that the analysis provided by the company to account for missing data showed that outcomes in the OLE were being affected by attrition bias, and that it was likely that this would affect all OLE outcomes reported in the original CS. The company did not provide updated analyses for other OLE trial outcomes after imputing missing data and therefore the EAG considered that the other OLE outcomes reported in the original CS that did not account for missing data should be considered flawed.

In the original CS, the difference in 28-day MMSF between GNX and placebo was reported to increase over time, from a difference of -27.1% during the 17-week double blind phase to more than a 50% reduction from baseline after 12 months in the OLE. In this updated submission, the company reported the change in seizure frequency after imputing data for missing participants using a last observation carried forward (LOCF) approach (i.e., the last available measurement of SF assessed before the participant discontinued the trial was used at all subsequent timepoints). The results showed that the difference in SF did not increase but was reasonably consistent with the difference recorded at 17-weeks (-29.3%). These data therefore suggested that the median reduction in MMSF shown at 17-weeks could be maintained for up to 2-years. As other anti-seizure medication (ASM) used to treat people with CDKL5 deficiency typically only results in a reduction lasting several months, the stability of the GNX treatment effect could therefore be much improved. However, the EAG cautioned that the LOCF approach may be considered an optimistic approach, for example if any waning of the treatment effect was not evident in participants' last observation or if people were experiencing a benefit of treatment and discontinued for other reasons (e.g. toxicity). In such cases, the treatment effect measured in the last observation was assumed to be maintained throughout the OLE follow-up (i.e. up to 2-years), which may not reflect reality. It was therefore plausible that the MMSF reported using the LOCF approach may be optimistic.

In the original CS, the company reported the number of participants who experienced ≥25% and ≥50% reduction in 28-day MMSF. In the updated submission, the company reported the mean change in MMSF in those who exhibited at least a 30% reduction in MMSF and used this threshold in a new stopping rule for GNX (see Section 4.1). The company did not provide a rationale for the use of this threshold, and the analysis appeared to be post-hoc. As noted in the EAG report, clinical advice to the EAG was that a threshold of 50% was more typically used in epileptic conditions. In the new addendum, the company reported that amongst those participants who experienced ≥30% reduction in MMSF, the median reduction in MMSF was [redacted]% (95% confidence intervals or another measure of variance were not reported). The MMSF in those who did not experience a 30% reduction in MMSF was not reported, and presumably included people with no change, no clinically meaningful change, or an increase in seizure frequency.

With regard to the risk that data were affected by a regression to the mean effect, the EAG did not consider that the company had been able to resolve this issue with the available data. The company argued that a 6-week baseline period could have reduced the risk of a regression to

the mean effect as acute increases in seizure frequency prior to trial entry may have resolved before baseline; however, as noted in the EAG report, this would depend on the typical duration of exacerbations in seizures, and the EAG was unaware of any data to inform this. The EAG understood that the duration of exacerbations may vary greatly across people with CDKL5 deficiency, and so a 6-week period may not be sufficient time for some.

The company further argued that those in the PBO/GNX arm experienced a decrease in MMSF after treatment that was comparable with the GNX/GNX arm, and that this suggested that there was no regression to the mean effect. However, the EAG disagreed and did not consider the single-arm design of the OLE allowed for this be demonstrated. During the DB phase, both arms showed a reduction in MMSF and the difference between arms could be considered to represent the treatment effect of GNX. Without a control arm during the OLE, an unknown proportion of the reduction in MMSF could be caused by factors other than the treatment effect, including a regression to the mean effect. The timing of any regression to the mean effect, including whether this is more likely earlier or later in the OLE follow-up, is related to the typical duration of SF exacerbations, which as noted is currently unknown. The EAG also considered that the calculation of MMSF used in the CS, which converted absolute SF into a median percentage reduction over a 28-day period, made it difficult to interpret any effect of time on SF.

The EAG conclusion on the clinical effectiveness of GNX remained similar to that in the EAG report; i.e. a minority of people with CDKL5 deficiency may experience a meaningful reduction in MMSF following treatment, and new data suggested that this benefit may be sustained for 2 years, which was substantially longer than other ASMs. However, the magnitude of this benefit was somewhat uncertain, given the potential for a natural regression to the mean effect after treatment and the possibility that the missing data analysis in the OLE may be optimistic. The evidence did suggest that the majority of people who receive GNX would not experience a meaningful benefit in seizure frequency. Finally, on the basis of the missing data analysis provided by the company, the EAG considered that other outcomes measured in the OLE that did not account for missing data were flawed, due to the now known attrition bias.

Key Issue 2: The company's model structure

Summary of the key issue

The company's model is a simple Markov state-transition model with two primary health states (alive and dead) which may not capture the full impact of the disease or treatment and may be considered atypical for NICE technology appraisals of genetic epileptic syndromes. The EAG

considered that other model structures could have been considered, but it was unclear to what extent an alternative structure might influence cost-effectiveness results.

Summary of the company response

The company acknowledges that its model is different to models developed for other conditions considered 'similar' to CDD (accepting that CDD has a number of unique features which differentiate it from other conditions, such as TSC, LGS, or DS). However, it explained that the sample size of the Marigold study precluded its ability to reliably construct a model similar to those used for other ('proxy') conditions. Relatedly, the company explained that clinical trials for these other conditions typically recruit larger samples compared with CDD.

In addition, the company explained that specifying a model structure that grouped patients into health states defined by SF (using bounds from other cost-effectiveness analyses in proxy conditions) would also be challenging. This is because the bounds of SF for proxy conditions would not translate well to a CDD population, since a considerable proportion of patients would fall into either the lowest or highest SF categories.

EAG response

The structure of the model remains similar following the company's changes. The previous comments made by the EAG on the company model structure therefore still apply, though the EAG acknowledges the limited data available to inform an alternative structure in the context of this appraisal in CDD.

A major modification to the company's model structure was the introduction of a stopping rule, centred on a response threshold of a 30% reduction in SF. The EAG noted that the definition of response used by the company did not align with that of the MARIGOLD study secondary endpoint (≥50% decrease in SF), or the additional analyses presented in the study CSR (25% and 75% thresholds). Further, the company provided no clinical justification for or clinical testimony in support of a 30% threshold. Therefore, although the EAG supported the use of a stopping rule in principal following clinical advice noted in the EAG report, it had some concerns, which are discussed further in Section 4.1. The EAG was also concerned that an analysis of the HL shift for patients that did not achieve a 30% reduction versus the placebo arm has not been presented. If this showed a non-zero or even worsening shift among those patients, then the model was biased in favour of GNX.

Key Issue 3: Application of seizure frequency

Summary of the key issue

The EAG identified a number of assumptions imposed by the company to reflect SF within its model. These included the decision to capture primary seizures only (i.e., secondary seizures excluded), that the distribution from Marigold reflects UK clinical practice, would not change over time, a treatment effect would apply instantaneously, and that SF distribution was well represented by a lognormal distribution. In addition, the EAG highlighted an apparent error in the application of the treatment effect based on the product rule of logarithms.

Summary of the company response

The company provided analysis of additional data from the OLE of the Marigold study to further support the estimation of SF in the long-term (discussed further in the EAG's response to Key Issue 1). With respect to the instantaneous application of treatment effects, the company agreed with the EAG that the titration and maintenance periods should be modelled separately, but preferred to apply these effects from cycle 2 in the model (i.e., start of the 'maintenance period'), as opposed to from cycle 4 (i.e., approximately Week 17, per the Marigold outcome measure).

Outside of these points, the company provided further information which related mostly to different aspects of the model (e.g., treatment duration) and so these are discussed separately (see Section 4.1).

EAG response

The company did not explicitly confirm in its response if it accepted each of the changes imposed by the EAG within its model linked to SF. However, inferring from the company's revised base-case analysis, the EAG understood that the company accepted its revision of the following settings within the model related to SF:

- Normalised SF distribution densities
- Corrected application of treatment effect (product rule of logarithms)
- Use of EAG's area-under-the-curve function to estimate SF distribution

As noted previously, the company suggested that the full estimated treatment effect should be applied from cycle 2 (week 8) rather than linearly interpolated from baseline to week 16 (to get as close as possible to week 17 per the MARIGOLD evidence). The company explained that

this fit the way that the trial endpoints were calculated more accurately. As stated by the company in its response to key issue 3, the SF quantity at 17 weeks was in fact calculated as *total* seizures over a 17-week period, divided by days ($17 * 7 = 119$ when there is data for each day) and then multiplied by 28. Consequently, the data on which the treatment effect was estimated was in fact the % change in *total* seizures over a 17-week period (with a multiplier of $28/(17 * 7) = 0.235$ applied to it for complete daily data), and *not* the expected change in 28-day SF.

In light of this explanation by the company, the EAG agreed with the company that application of the full treatment effect from cycle 2 was likely to be more appropriate considering that the underlying data was for total seizures over 17 weeks (with a $28/119$ multiplier applied to it) and not per 28-day period.

Key Issue 4: Utility values

Summary of the key issue

Utility values were used to inform estimates of QALYs within the company's model, taken from published vignette studies in proxy conditions. These studies were subject to a number of limitations and were important drivers of the cost-effectiveness results since GNX was modelled to only impact quality and not length of life. Utility values impacted estimates of QALYs for both patients and their caregivers.

Summary of the company response

The company explained that the most suitable source for utility values was the study that best reflected the experience of the CDD population, regardless of how consistent this source was with the other aspects of the company's model (e.g., resource use). Ultimately, the company maintained its preference for the utility values reported by Lo *et al.*, which it considered to be the most suitable source to inform the model. This was based on the following key points:

- The types of seizures experienced by patients with TSC was expected to reflect the experience of a CDD population more closely, versus the participants considered by Auvin *et al.* (people with DS and LGS)
- Estimates of SF for LGS patients were based only on drop seizures in the study by Auvin *et al.*, whereas participants in the Marigold study reported different types of seizures

- The caregiver utilities reported by Auvin *et al.* represented a relatively small number of SF ranges (80 or 110 seizures per month), versus Lo *et al.* which reported four different categories)

In the company's response, it stated: *"*[Company] *have added accuracy to the baseline seizure-free-day (SFD) distribution, to match the Marigold patient level data (previously it was assumed patients are gathered around the mean within the same SFD class)."* (Company's response to Key Issue 2, p.6). While this was not fully explained by the company within its TE response, the EAG understood that the company had undertaken the following analysis:

- In the Auvin *et al.* study, utility values were reported based on SF and the number of SFD within a 30-day period. The SFD categories ranged from 1 (i.e., at least one seizure per day except for 1 day within a 30-day period) to 30 (i.e., no seizures within a given 30-day period)

- Previously, the company assumed all patients with SF between 45 and 130 would have 9 SFD per 30 days. Patients with SF of 20 were assumed to have 12 SFD per 30 days (i.e., 30 – 12 = 18 which is less than 20, compared with 30 – 9 = 21 which is greater than 20), and patients with SF of 0 were assumed to have 30 SFD per 30 days

- The company revised its application by calculating a weighted average of SFD per SF category to re-estimate utility values based on Auvin *et al.* for use within the cost-effectiveness model

- In addition, the company included the option to extract the average number of additional SFD for patients receiving GNX relative to ECM ([redacted]), and estimated a weighted average based on these patients obtaining the highest utility value, whereas all other patients were assigned a value based on SF per the company's original approach

Finally, the company's response also described a further analysis performed to produce alternative utility values: *"In consideration of the EAG´s request we now also present the results from an alternative modelling approach based on microsimulation (bootstrapping) with individual patient data. However, of note even this approach is likely highly conservative for ganaxolone due to the high ceiling and floor effects mentioned above. QALY gains are minimal and in many cases state definitions preclude any QALY gains being demonstrated, even where clinically significant reduction in seizures was experienced. Despite this, the bootstrapping approach largely supports a lower, more narrow range of ICERs."* (Company's response to Key Issue 2,

p.6-7). Some further description of the analysis undertaken was provided in Attachment 3 alongside the company's TE response.

EAG response

The EAG acknowledged the points raised by the company concerning the most suitable source of data to populate the utility values within the model. However, for completeness, the Lo *et al.* study also suffered from a number of limitations, which the EAG explained within its report. Notably, Lo *et al.* did not include an estimate of utility for patients that achieve seizure-free days (SFD) which the EAG considered an important differentiator between the two sources (with SFD noted as an important driver of utility by clinical experts that advised the EAG).

The EAG considered that both options (Lo *et al.*, and Auvin *et al*.) were subject to important limitations, and that neither study exhibited preferred characteristics 'across the board' when considering their applicability to the cost-effectiveness model used in this appraisal. Put another way, each study had its own merits, and both may be suitable to aid decision making. As the EAG stated within its report, utility values from a CDD population specifically would be preferred, as would utility values not based on a vignette study. Nevertheless, the EAG acknowledged the challenges associated with eliciting utility values for people with CDD and their caregivers and considered the ability to explore different options to be helpful for the committee's decision making.

The company's revised approach to considering SFDs represented a re-analysis of the utility values from Auvin *et al.*, which the EAG noted led to broadly similar values – the lower values decreased slightly, whereas the higher values increased slightly. However, the overall impact on the ICER was that the QALY gain was increased by a relatively large amount. This was because the 'poorer' health states (determined by SF) were subjected to a lower utility (favouring GNX, relative to the previous approach), and the 'better' health states (again, determined by SF) were subjected to a higher utility (again, favouring GNX, relative to the previous approach). In other words, making this edit led to a greater QALY gain and therefore a lower ICER, versus the original use of the Auvin *et al.* utilities.

The EAG noted that the company's method assumed that SFD were essentially independent of SF. For example, the same distribution of SFD was used to determine a weighted average utility for the 130 SF category as per the 45 SF category. As per its previous approach, the company accounted for implausible or unlikely combinations (e.g., a patient could not have 20 seizures per month, but also have only 1 SFD per month). If data permitted, the EAG would have

preferred to see a different distribution calculated for each SF category (e.g., one would expect patients in the 130 SF category to be mostly grouped towards the lower end of the SFD distribution, versus the 40 SF category, for which patients may be spread more uniformly across the categories).

With regards to the weighted average approach to account for patients that achieved SFD while receiving GNX, the EAG highlighted that this approach was (to an extent) inconsistent with the company's choice to select a lognormal distribution to model SF, since the support for a lognormal model was $x \in (0, +\infty)$. In other words, the lognormal model cannot estimate a proportion of patients with SF = 0. As such, the company's revised approach represented a somewhat crude adjustment to account for this, as the area-under-the-curve for SF was still estimated to be 100% by virtue of specifying a strictly positive parametric model.

Acknowledging the limited detail provided by the company in its TE response concerning the source data for the distribution of SFD from Marigold (including for GNX responders), and that its revised application was still subject to a number of limitations, the EAG tentatively accepted this alternative approach as a likely more accurate (but still imperfect) estimation of utility values via the Auvin *et al.* study.

In relation to the bootstrapping analysis, while the EAG appreciated the efforts made to provide further analysis of the utility data, it was unable to determine the precise motivation for undertaking the analysis, or how its findings should be interpreted with respect to populating the model. This was because despite the additional work undertaken, the company maintained its preference for the utility values derived from Lo *et al.* Therefore, for this reason, and due to the EAG not having a clear understanding of why the analysis was undertaken, the EAG did not consider these values further.

With the above in mind, the EAG maintained its preference for the study by Auvin *et al.*, but considered that scenarios using either source may be helpful for decision making. The EAG's preference for Auvin *et al.* centred on two main reasons: (i) its arguments set out in its previous report (namely, that this option promotes consistency with the medical resource use estimates and mortality), and (ii) that out of both options this source yields the most conservative estimate of the incremental QALY gain, which given the extent of the structural uncertainty was prudent.

Key Issue 5: Miscellaneous model errors and unsubstantiated assumptions

Summary of the key issue

The EAG identified a number of model errors and assumptions that were unsubstantiated as part of its review, details of which were provided in its report. Where possible, the EAG addressed these by implementing fixes within the company's model, and by eliciting clinical expert opinion to sense check and update key assumptions that it felt were not adequately justified by the company in its submission.

Summary of the company response

The company specifically commented on two components of this key issue: (i) the application and durability of treatment effect, and (ii) the application of wastage for GNX. The first of these points was covered across Key Issues 1 and 3. As such, focus was placed here on the latter point concerning wastage. The company also updated its approach to capturing treatment discontinuation, which the EAG agreed with (i.e., that using exposure time as a basis to calculate discontinuation was appropriate), and so has no further comment.

In short, the company argued that the EAG's clinical expert derived wastage estimate of 10% is inappropriate, since it was not based on empirical evidence (i.e., it is based solely on clinical expert opinion). The company then provided what it considered to be a more realistic estimate of wastage in the region of 0.47% (which, given the lack of a cited source, the EAG understood to be its own opinion). However, because of there being no reports/evidence of spitting/ redosing issues in clinical trials or practice, and because of guidance in the SPC advising against redosing; the company maintained its preference for no wastage within the model.

EAG response

As the company did not provide any further commentary on the other aspects of this key issue, the EAG limits its response to the issue of wastage (with its views on treatment effects covered in its responses to Key Issues 1 and 3). The EAG acknowledged that its base-case assumption was not based on empirical evidence, and that the clinical expert opinion was not based on personal use of GNX (given that it is not currently available in routine NHS practice). However, the EAG also highlighted that the company's opinion was also not based on empirical evidence. Therefore, while the EAG deferred to the clinical opinion it received which suggested that in a 'real-world' setting some wastage was expected, the EAG acknowledged the company's view on this issue.

Ultimately, the EAG considered that this key issue requires further clinical insight to be resolved, given the importance of accurately capturing drug costs on cost-effectiveness results. In the interim, the EAG maintained its preference for 10% wastage, but considered further clinical insight to be critical to determining the most suitable assumption for decision making.

Key Issue 6: Application of a severity modifier

Summary of the key issue

The company applied a severity multiplier to both patient and caregiver QALYs. The NICE methods guidance describes the severity modification applying to those "living with the disease", and the EAG was uncertain if this was also intended to be applicable to caregivers. This has implications for the cost-effectiveness results since severity modifiers can substantially impact the magnitude of the overall QALYs gained.

Summary of the company response

The company reaffirmed its position that both patients and caregivers are *"living with the condition"* (terminology used within the NICE methods guide). Further information concerning the burden of disease on both patients are caregivers was provided to clarify the substantial impact CDD has.

EAG response

The EAG highlighted that the decision of how the severity modifier applies within a cost-effectiveness analysis submitted to NICE ultimately sits with NICE and not the EAG. However, it is the responsibility of the EAG to highlight any potential deviations from the NICE methods guide within a company's submission or cost-effectiveness analysis. A webinar hosted by NICE in early 2023 explained that the modifier should only be estimated based on patient shortfall and should only be applied to patients.[1] However, this precise wording is (to the EAG's knowledge) not explicitly stated within a documented report by NICE. Fundamentally, while the EAG accepted evidence presented by the company that carers of people with CDKL5 deficiency experience significant burden, it considered this to be a separate issue to the design and application of QALY modifiers, which are tied to evidence of societal preferences for spending. The EAG also maintained its position that one caregiver should be used to calculate shortfall,

[1] Centre for Health Technology Evaluation Methods Seminar 2023, hosted by NICE. Relevant section 1:06:33 onward. Available at https://www.youtube.com/watch?v=TVz7pT6DM-U

and that shortfall should be calculated separately from the patient's shortfall as a caregiver is a separate entity from a patient. The EAG could not comment further on this key issue since it required input from NICE.

4. EAG CRITIQUE OF ADDITIONAL ISSUES

Based on the company's response, the EAG has highlighted a number of additional aspects of the company's submission and/or model that warrant attention.

4.1. Treatment discontinuation and stopping rule

As part of its response, the company explained that its model had been updated to include a treatment stopping rule which was not included within its original model. In summary, the model now includes a decision point at six months where only patients that 'respond' are permitted to continue treatment, and those that do not respond are assumed to immediately discontinue treatment. The criterion for response is that patients must achieve at least a 30% reduction in SF at the end of the double-blind phase of the Marigold study (versus baseline). Implementation of this stopping rule in the company's model leads to a notable reduction in the incremental costs for the GNX arm, an increase in the QALYs gained, and therefore a reduction in the ICER.

The company does not provide clear justification for, or a detailed description of, the clinical decision-making mechanism surrounding treatment continuation criterion. The EAG notes that any stopping rule introduced for cost-effectiveness purposes means that some patients may have treatment withdrawn even though they are deriving a modest benefit, and therefore such rules must not be considered lightly. The formulation of a rule to take an effective treatment away from a patient, in the EAG's opinion, should always include careful discussion, refinement, validation and agreement with leading clinical experts to determine whether and how it would work in clinical practice.

Despite this, given the palpable uncertainty associated with modelling CDD, and the clear heterogeneity in both baseline SF and treatment effect at the individual level based on data from the Marigold study, a stopping rule introduced to improve cost effectiveness would appear reasonable. Clinical advisers to the EAG suggested a stopping rule may be suitable (but no specifics were discussed concerning a given rule, beyond the fact that 6 months would seem a reasonable time point). However, this is only if this rule is fully supported by clinicians and patient groups. In addition, it is also important to consider how the stopping rule could reasonably be adhered to in NHS practice.

In addition to the lack of evidence for a clinical consensus for the stopping rule, there are several issues with its implementation in the company's updated economic model. Within the

model, patients that do not respond are assumed to have the same SF distribution as the ECM arm. The EAG does not consider this to be appropriate, since some patients on the ECM arm may theoretically achieve a reduction in SF in accordance with the response criterion defined above. Therefore, an investigation of the SF in the ECM arm should be conducted to identify how many (if any) ECM patients achieved the 30% SF reduction, and the expected SF reduction among that group. If it is found that some patients in the ECM arm do in fact respond according to this criterion, then the implications for the structure of the cost-effectiveness model need to be carefully considered and the current model structure is likely biased in favor of GNX.

The EAG also highlights that response at 17 weeks from Marigold is applied at 28 weeks in the company's model. The EAG suspects this is unintentional, as it would seem inappropriate for a clinician to establish non-response according to response at week 17 and then wait another 11 weeks before discontinuing treatment, irrespective of whether or not the patient achieves response by week 28. Equivalently, the EAG does not understand why a patient achieving response at week 17 and then losing it before 28 weeks would, according to the company's rule, continue treatment despite being a non-responder under the company's definition.

Next, the EAG notices that the company have not presented HL shift estimates for those patients in the GNX arm that did not achieve a 30% reduction in SF at week 17 vs baseline. This could potentially bias the model results in favour of GNX because in reality non-responders per the 30% definition could have *increased* their SF over time. The company would need to perform this analysis for the week 17 data and also for the OLE for 17 week 30% non-responders to provide evidence that those non-responders have an approximately 0% shift in SF over time (to match the unsubstantiated assumption currently being imposed in the cost-effectiveness model).

The EAG notices that the inclusion of the stopping rule has led to an increase in the total QALYs gained for GNX (enabled: + QALYs, disabled: + QALYs), while also leading to a substantial reduction in incremental costs (enabled: +£, disabled: +£). This is despite discontinuing approximately 50% of patients at 28 weeks, leading to and drop in HRQoL (to for patients and to for caregivers, which is then multiplied by 1.8 to , a larger drop than for people with CDD). The underlying reason for this is that the company's updated base case associates a % reduction in SF (the reduction being applied to the SF reduction 30% responders at 28 weeks onwards) with a increase in HRQoL for patients (from to) and a

[redacted] increase in HRQoL for caregivers (from [redacted] to [redacted]) which is then multiplied by 1.8 by the company to [redacted] (i.e., a greater HRQoL increase than for people with CDD). As approximately [redacted]% of patients are discontinued at this point, and the magnitude of the utility gain from the higher effect is larger than the utility loss from losing all effect for non-responders, the net effect is that more QALYs are generated on the population level. This is demonstrated in Figure 1, which shows the expected HRQoL of one patient and one carer over time alongside the proportion of survivors remaining on treatment (in the company's revised base-case).

Figure 1: Expected utility and time on treatment over time - company revised base case

[redacted]

The EAG would expect that inclusion of the stopping rule should theoretically lead to a reduction in the overall lifetime QALYs accrued by patients in the GNX arm, since some patients that achieve some benefit but not enough to be considered 'responders' would discontinue treatment and derive no further benefit (in this case, reverting to the ECM level). Ultimately, the EAG expects this finding is at least partly due to the assumption concerning outcomes achieved by non-responders being assumed to be equivalent to the full ECM arm. This is because the effect for 30% responders is [redacted]%, whilst the effect for all patients is 29.31%, implying that the

effect in 30% non-responders (approximately [redacted]% of the population) is very small, if not negative.

Finally, the larger HL shift in 30% responders at 17 weeks is an indicator that the *shape* of the SF distribution could be affected by the stopping rule. This may then affect how appropriate the previous decision by the company to model SF using a lognormal distribution remains. To alleviate this concern, the company would need to investigate and report the shape of the SF distribution among the subgroup of 17 week 30% responders (should that ultimately be determined to be an appropriate threshold for discontinuing treatment by clinical experts).

Within the timeframe available for the EAG to perform its critique of the company's revised model, it was not possible for the EAG to produce an alternative application of the company's stopping rule. However, based on an exploratory analysis, the EAG presents a heat map to investigate this relationship further (Figure 2).

Figure 2: Heat map for impact of stopping rule on incremental costs and QALY gain

In conclusion, when considering the apparent lack of face validity exhibited by the company's stopping rule application, the EAG does not consider this scenario to be suitable to inform

decision making. The EAG highlights that clinical expert opinion and input from NHS England is required to understand the feasibility of implementing the proposed stopping rule. Without the stopping rule, the ICER in the company's updated base case (without any other EAG alterations or corrections and without the split discontinuation rate post-stopping rule) is [redacted]. Therefore, if the stopping rule proposed by the company is not followed in clinical practice, GNX is unlikely to represent a cost-effective use of NHS resources.

4.2. Justification for long-stay hospitalisations

The company provided additional evidence from the international CDD registry, reporting that the median length of stay (LOS) related to CDD hospitalization events was [redacted] days. When examining the distribution of LOS, the company also report that [redacted]% of CDD related hospital stays had LOS ≥ 2 days, which the company stated constitutes a long-stay in the NHS reference costs. Responding to this additional evidence, the company then updated its base case to calculate a weighted average of short stay and long stay hospitalization costs.

The EAG accepts the updated company's updated approach to hospitalization costs based on the new evidence it has provided. The approach to incorporating this new evidence appears reasonable and the decision to calculate a weighted average appears fair. However, there are two issues which the EAG would like to raise before considering this issue wholly resolved.

The first potential issue is whether the international CDD registry data is representative of the way that CDD patients are treated in the UK. For instance, if the UK approach involves facilitating more at-home care than other countries, including the means to prevent longer inpatient stays or discharge patients from hospital more quickly. Consequently, the EAG suggests that the company presents simple subgroup analysis of the ICDD hospitalization data specifically for UK patients and investigates whether this is different from the full international dataset. The full dataset appears large enough to permit subgroup analyses, and this may alleviate the concern that the EAG has that care for CDD may differ between countries.

The second and relatively minor issue is with NHS reference costs source. The NHS reference cost document used by the company does not report the median or mean length of stay associated with the codes applied by the company in the cost-effectiveness model (PRO2A, PRO2B and PRO2C). It is therefore unknown whether the long-stay codes in NHS reference costs are appropriate for long stays with a median duration of [redacted] days. However, as this is

unlikely to have a large impact on the cost-effectiveness results, the EAG accepts the approach the company has taken and the codes used.

In conclusion, the EAG is satisfied with the additional evidence provided by the company and subject to the presentation of UK subgroup analysis results for LOS accepts the revised company approach to incorporating hospital stays into the cost-effectiveness model.

5. EAG'S REVISED BASE-CASE ANALYSIS

Following the EAG's appraisal of the new evidence submitted by the company, and as explained in the appraisal of the key issues in the previous section, the EAG made several changes to the revised company basecase (Table 1).

Consistent with the EAG report, ICERs are presented both with and without the severity modifier for caregivers, pending NICE advice. Under the updated EAG base case, the absolute and proportional QALY shortfalls calculated for caregivers (i.e., separately to patients) were insufficient to warrant any severity modification, so the exclusion of a severity modifier for carers did not affect the (deterministic) results.

The EAG accepted the use of a treatment discontinuation rule in principle, though it was hesitant to accept the implementation within the cost-effectiveness model for the reasons discussed in Section 4.1. Consequently, ICERs are presented both with and without the stopping rule active: this resulted in an EAG base case ICER of £[redacted] with a stopping rule and £[redacted] without it (note: this was after fixing an error in columns BQ and BR of the "Trace Gan" sheet when using Auvin et al utilities, which was increasing utility for patients per the stopping rule even when the stopping rule was switched off). In both cases, it was unlikely that GNX represented a cost-effective treatment option for people with CDD at the relevant willingness to pay threshold.

Table 1: EAG adjustments to revised company base-case

Change made	Justification	ICER
Revised company base-case	N/A	£[redacted]
Change 1: Auvin *et al.* utilities	Insufficient justification to adjust the EAG position, Lo et al does not take seizure-free days into account, consistency of disease with mortality and HCRU model components	£[redacted]
Change 2: 10% wastage	Company provided no evidence to substantiate its claim of no wastage. EAG position remains the same as it is supported by clinical expert opinion.	£[redacted]
Change 3: Without severity modifier for caregivers	No published clear position from NICE on whether disease severity	£[redacted]

Change made	Justification	ICER
	modification applies to caregivers or not, and on what basis it should be calculated	
Change 4: Caregiver severity modifier calculated based on caregiver QALY shortfall not patient QALY shortfall	Caregivers are separate entities from patients, and so have their own QALY shortfall. Therefore, severity modification (as with all cases) should be based on their own HRQoL	£[redacted]
Change 5: Caregiver QALY shortfall based on 1 caregiver not multiplied by 1.8	QALY shortfall is per expected individual affected by the condition, not the total shortfall of a group of people	£[redacted]
Change 6: No stopping rule	Unclear whether the stopping rule was appropriate, timing issues (stopping rule at week 28 but evaluation at week 17), ubiquitous use of stopping rule assumed, lack of analysis on non-responders.	£[redacted]
EAG base case	Combining changes 1, 2, 4 and 5 is the revised EAG base-case with severity modification. As this results in a severity modifier of 1x for caregivers, the ICER is the same as the scenario without severity modification for caregivers. The scenario combining changes 1, 2, 4, 5 and 6 is the EAG base case with no stopping rule applied.	(1+2): £[redacted] (1+2+3): £[redacted] (1+2+4+5): £[redacted] (1+2+4+5+6): £[redacted]

Abbreviations: EAG, external assessment group; HRQoL, health-related quality of life; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year