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:

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Single technology appraisal

Ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over
[ID 3988]

Addendum to company evidence submission

March 2024

Version 1.0

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Addendum A	1.0	Yes	1st March 2024

Addendum to original STA submission to update the economic model

Introduction

During the second committee meeting for the ganaxolone (GNX) Single Technology Appraisal (STA) held in September 2023, the committee and EAG raised a number of concerns, mostly related to the economic model presented by the Company to estimate the cost-effectiveness of GNX plus established clinical management (ECM) with anti-seizure medications compared with placebo plus ECM for people aged ≥2 years with seizures caused by the cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD).

The uncertainties in the economic model noted by NICE include:

- How well the model describes the course of CDD
- How quality of life is included in the model
- How GNX affects seizure frequency and quality of life
- How stopping GNX treatment is modelled and how well it reflects what would happen in clinical practice

The Company are now pleased to have the opportunity of performing and presenting further analyses to assist the committee in their decision making on GNX. In this document, we provide an overview of the current model and an explanation of the changes implemented to address the uncertainties raised and improve the model's validity. To follow, a brief description of the updated base case and scenario analyses is also presented.

Model description and justification

The company presented a two-health state transition Markov model, with a stopping rule applied at 6 months, to estimate the cost-effectiveness of GNX plus ECM compared with placebo plus ECM for people aged ≥2 years with seizures caused by CDD. The two health states in each arm were alive and dead; in the alive state, people could stop treatment with GNX plus ECM, subsequently continuing to receive ECM alone. The model was informed by the Phase III randomised controlled trial Marigold (1, 2) and by a systematic literature review (SLR) (3) conducted to identify all available clinical and burden of illness evidence in this patient population. Due to the paucity of available data for patients with CDD, the SLR was expanded to cover also other similar forms of developmental and epileptic encephalopathies, to identify suitable proxy data (3). The modelling approach, assumptions, and inputs used have been validated with a key UK clinical expert.

The clinical effectiveness of GNX with ECM and placebo plus ECM was evaluated based on their impact on 28-day seizure frequency in terms of change versus baseline, using Marigold (1, 2) as the main source of evidence. The model focussed on primary seizures (i.e. "major motor seizures" in Marigold) because they are considered the most impactful in terms of resource use and health-related quality of life (HRQoL), and they were the most frequently recorded seizures in the Marigold study (1, 2).

The incremental benefit of GNX over ECM alone was applied to the model leveraging gamma distributions of patient-level Hodges–Lehmann (HL) shift estimate of 28-day seizure frequency reduction from the maintenance dose phase of the double-blind period of Marigold. The benefit of GNX was applied to the pooled distribution of seizure frequency at baseline expressed as a lognormal distribution. This distribution also represented the seizure distribution of ECM for the entire time horizon. Each model cycle was 28 days with a half-cycle correction and a lifetime horizon.

Key model assumptions and inputs are summarised in Table 1.

Table 1: Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Clinical parameters (primary seizures/major motor seizures)		
Average seizure frequency per cycle	Source: Evidence from the Marigold study (1, 2) Assumption: baseline frequency of seizures follows a log-normal distribution based on the pooled data of GNX and placebo arms.	The log-normal distribution has the best statistical (and visual) fit to the baseline trial data among the various distributions tested.
Reduction vs baseline in MMSF with GNX (placebo-adjusted)	Source: Evidence from the Marigold study (1, 2)– Estimate of the HL shift (incremental change [reduction] in 28-day MMSF with GNX + ECM vs placebo + ECM during the maintenance phase of the DB period). Assumption: lifelong duration of effects for those who remain on treatment (i.e. no treatment habituation). Patients discontinuing treatment for any reasons are expected to immediately lose treatment effect.	This outcome was the primary endpoint of the Marigold study (full DB period). The effect in the model is based on the increment in Weeks 5–17
Reduction in epilepsy-related admissions with GNX	Source: Chin et al, 2021 (4) Assumptions: (i) Healthcare resource use in patients with CDD is proxied by respective data in LGS; (ii) Number of epilepsy-related inpatient admissions and acute and emergency visits were assumed to be reduced based on evidence from the Marigold study, with regard to the reduction in seizure frequency (other resource use assumed to be the same between arms).	Most appropriate data source and assumption available, due to the lack of CDD-specific healthcare resource use data. Clinical opinion supported the use of LGS as proxy condition to model healthcare resource use in patients with CDD given the level of similarity between the two conditions. Duration of CDD-related hospitalisations was based on unpublished data on CDD patients in the international CDKL5 register (HL, personal communication).

Model input and cross reference	Source/assumption	Justification
Waste	Base case assumption assumed no waste, while scenarios of 2.5% and 5% were presented.	No indication of waste seen in Marigold nor from US clinical experience.
Discontinuation rate/cycle	Evidence from the Marigold study/DB (1, 2) and OLE phase (5, 6)	Most appropriate data source available.
Standardised mortality ratio in patients with LGS vs general population in the UK	Source: Chin et al, 2021 (4) Assumption: relative survival (vs general population) in patients with CDD is proxied by relative survival in patients with LGS.	Absence of CDD-specific mortality data. Clinical opinion supported the use of LGS as proxy condition to model survival in patients with CDD.
Patient and caregiver utility		
Patient and caregiver utility	Source: Lo et al. 2022. (7) Assumptions: (i) The base case analysis captures the impact of GNX on caregivers' utility; (ii) Seizure frequency is the sole driver of treatment impact on patients' and caregivers' utility in the model; (iii) Seizure-related disutility is proxied by the disutility experienced by patients with TSC.	The condition has a substantial impact on the QoL of patients' caregivers. In the absence of CDD-specific utility values, clinical opinion supported the use of TSC as a proxy condition for informing disutility associated with seizure frequency. While all utility sources had limitations, the Committee concluded that, on balance, Lo et al appears to be the most appropriate source for the utility values.
Average number of caregivers per patient	1.8	This input value was used both for patients younger and older than 18 years, in line with other complex epileptic disorder HTAs.

Abbreviations: CDD, CDKL5 Deficiency Disorder; DB, double blind; ECM, established clinical management; GNX, Ganaxolone; HL, Hodges-Lehmann; HTA, health technology assessment; LGS, Lennox-Gastaut syndrome; MMSF, major motor seizure frequency; OLE, open label extension; QoL, quality of life; TSC, tuberous sclerosis complex.

Continued efficacy assumption

To further validate the model assumptions and better characterise individual patient changes and response patterns over time, we present cycle by cycle data on the GNX effect. Figure 1 illustrates the median difference between GNX responders vs. placebo by cycle. Cycle 1 represents the titration phase, which has been implemented in the model by utilising a correction factor of XXX to patient utility for responders and XXX for non-responders, representing the proportion of MMSF HL effect gained during titration period versus maintenance period.

XXX

Figure 1: Median difference (Hodges-Lehmann location shift) between GNX responders† and placebo by cycle.
Maintenance phase effect has been calculated from cycle 2 up to the end of the double-blind period (17 weeks). Cycle 5 for placebo consists of 1 week on placebo (double-blind) and 3 weeks on GNX (start of OLE).

Cycle 1: Weeks 1–4; cycle 2: Weeks 5–8; cycle 3: Weeks 9-12; cycle 4: Weeks 13–16; cycle 5: Weeks 17–21.
†Responders were defined as patients with ≥30% reduction from baseline in 28-day MMSF during the DB maintenance phase of the Marigold trial.
Abbreviations: GNX, Ganaxolone; OLE, open label extension.

In addition, we present the individual patient-level MMSF data for the GNX responders over the course of the open label extension (OLE) (5, 6) (Figure 2). Overall, the data support the maintenance of the effect during the OLE.

XXX

Figure 2: Individual patient data for the frequency of 28-day MMSF in GNX responders†
†Responders were defined as patients with ≥30% reduction from baseline in 28-day MMSF during the DB maintenance phase of the Marigold trial.
Abbreviations: DB, double blind; GNX, Ganaxolone; MMSF, major motor seizure frequency.

Utility stratification

The EAG raised concerns about the banding of utility values in the model structure, as it resulted in a larger than expected proportion of patients having the utility value of individuals with no seizures, when utilising values from Lo et al (7). Given the relative efficacy approach described below as well as the fact that the patients within the band will have at least one seizure-free day (SFD)/cycle, the model can appropriately capture the *relative benefits* of patients moving between the bands. The choice of utility values is justified since out of the responders experiencing 0–27 seizures/cycle during the maintenance phase of Marigold's double-blind period, approximately XXX had more than XXX within the cycles falling to the respective time period, with the mean in this low seizure frequency class ranging at XXX, and median at XXX. In some of the submissions in similar epileptic conditions (Dravet) it appeared that 15 SFDs in a month was used as a cut off for Seizure free status. The distribution of SFD is illustrated for GNX responders in Table 2.

Table 2: Number of seizure-free days for GNX responders falling to the lowest seizure frequency class 0–27 major motor seizures per cycle

Seizure-free day frequency count								
Planned treatment	**Cycle**	**28-day MMSF class**	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**
GNX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: GNX, Ganaxolone; Min, minimum; Max, Maximum; MMSF, major motor seizure frequency; SD, standard deviation.

In addition, we present data on the Caregiver Global Impression of Change CGI-C (GNX responders: Figure 3; placebo group: Figure 4), where a higher share of GNX responders (XXX at DB) experience improvement compared with placebo plus ECM (XXX) in the DB period, and as the placebo patients switch to GNX after the DB period end at week 17, also they approach similar improvement levels. The share of responders not improving (XXX) is well in line with the model, in which roughly half of the responders did not move from their

prior utility class to a better class. Of these patients, XXX were already in the class of 0–27 seizures at baseline for both treatment arms. The data also indicates that the proportion in whom caregivers report global improvement compared to before treatment remains fairly consistent in the GNX responders over longer term, in those who stay on therapy.

XXX

Figure 3: Parent/caregiver-reported CGI-C over time vs baseline in the GNX responders†
†Responders were defined as patients with ≥30% reduction from baseline in 28-day MMSF during the DB maintenance phase of the Marigold trial.
Abbreviations: CGI, Clinical global impression of change; DB, double blind; GNX, Ganaxolone; MMSF, major motor seizure frequency.

XXX

Figure 4: Parent/caregiver-reported CGI in the placebo group over time vs baseline.
From Week 17, patients on placebo were switched to GNX in the open-label extension.
Abbreviations: CGI, Clinical global impression of change; GNX, Ganaxolone.

The utility classification in the model is based on the utilities/SF class reported by Lo et al., in that the seizure intensity and duration has not been considered. The Similarly to the CGI-C presented above, the Caregiver Global Impression of Change in Seizure Intensity/ Duration/ Severity (CGI-CSID) data also indicate improvement more often for GNX responders (Figure 5), compared with placebo plus ECM (Figure 6) in the DB period, and the proportion with improvement in GNX responders is maintained reasonably well over time.
This improvement has not been incorporated in the GNX economic model.

XXX

Figure 5: Parent/Caregiver reported CGI-CSID over time vs baseline in the GNX responders†
†Responders were defined as patients with ≥30% reduction from baseline in 28-day MMSF during the DB maintenance phase of the Marigold trial.
Abbreviations: CGI-CSID, Clinical global impression of change in seizure intensity and duration; DB, double blind; GNX, Ganaxolone; MMSF, major motor seizure frequency.

XXX

Figure 6: Parent/caregiver-reported CGI-CSID over time vs baseline in the placebo group
Abbreviations: CGI-CSID: Clinical global impression of change in seizure intensity and duration.

Updated model

Changes implemented

The Company reintroduced an up-titration period of one cycle (4 weeks) during which patients receive half dose in accordance with the trial design and dosing guidance in product SmPC. In this cycle thus, the drug acquisition costs are halved. Furthermore, a correction factor of XXX is applied to patient utility for responders and of XXX for non-responders in this cycle, representing the proportion of MMSF HL effect gained during the titration period versus maintenance period in all patients.

The EAG raised concerns about the way in which the stopping rule was implemented in the original company model (*Section 3.12 – FDG*). The key issue was that the total quality-

adjusted life years (QALYs) increased when the stopping rule was implemented. Through a further review of the data in Lo et al (2021) (7) and Auvin et al (2019) (8) (the proxy sources used for utility in CDD), we found that both studies contain nonlinear utility values vs seizure frequency.

Given the nonlinearity of the utility values, the following adjustments were made:

- Instead of the previously used median HL shift value, we added the entire gamma distributions of patient-level HL shift of seizure reduction for both the responder and non-responder sub-groups of patients treated with GNX on the 'Seizure model' sheet, in order to adapt the way the incremental effect of GNX vs ECM is applied.
  To fully incorporate this adjustment:
  - The formulae for the densities of seizure frequency/28 days of patients treated with GNX were updated to incorporate the gamma distributions (see the residual sum of squares [RSS] values as rationale for gamma distribution selection in Table 2)
  - The formulae on the 'Clinical parameters' sheet were updated to weight the estimated GNX generalised seizures/cycle by the gamma distribution of seizure reduction
- Adjustment of the patient distribution in the Markov trace to always split patients as responders or non-responders at beginning of the model as opposed to previous models which only split the patients at the beginning of the model when the stopping rule was utilised as in previous models. This adjustment allows for the clear assignment of utility values for responders/non-responders on the 'Trace Gan' & 'Gan_costsunderstopR' sheets as well as group-specific discontinuation rates.
  To fully incorporate this adjustment:
  - Cost calculation formulae were updated to capture the changes made to the Markov trace
  - Age-adjusted QoL formulae for non-responders were updated to capture the changes made to the Markov trace

The changes listed above along with the maintained assumption that utilities for non-responder patients are equal to OffTx allow for consistent patient QALYs with and without the stopping rule.

The RSS value was utilised to identify the distribution with the best fit, with a lower RSS value indicating a better fit. Due to the low RSS for responders and non-responders, the gamma distribution was selected. The RSS values for the selected gamma distribution as well as for the other distributions evaluated for both responders and non-responders is presented in Table 3.

Table 3: RSS values for the distributions evaluated for both responders and non-responders

Distribution	RSS for Responders	RSS for Non-Responders
XXX	XXX	XXX
XXX	XXX	XXX
XXX	XXX	XXX
XXX	XXX	XXX

Distribution	RSS for Responders	RSS for Non-Responders
XXX	XXX	XXX
XXX	XXX	XXX
XXX	XXX	XXX
XXX	XXX	XXX
XXX	XXX	XXX
XXX	XXX	XXX

Abbreviation: RSS, residual sum of squares.

The patient level HL shift is defined as: HL (x,y) = median $1 \leq i \leq n$, $1 \leq j \leq m$ ($xi - yj$) (see Table 4).

- Median of (n*m pairs of GNX reduction − Placebo reduction)

Table 4: Definition of the variables included in the Hodges-Lehmann shift formula

Variable	Description
xi	Seizure reduction from baseline for patient i treated with GNX
yj	Seizure reduction from baseline for patient j treated with placebo
n	Number of patients treated with GNX
m	Number of patients treated with placebo

Abbreviations: GNX, Ganaxolone.

Additionally, the EAG raised the concern that the division of patients into responders and non-responders at the beginning of the model may break randomisation. However, through the patient-level HL shift and sustained efficacy assumptions above, the utilised approach is equivalent to separating the patients at 6 months. Indeed, the utility utilised for an overall GNX group would be equivalent to the weighted average of the utilities utilised for the GNX responder and non-responder groups. The randomisation of effect is maintained through the adjustment to the proportion of patients considered GNX responders, which can be evaluated through probabilistic sensitivity analysis in the model.

As the GNX responders and non-responders are separated right at the beginning of the model, specific discontinuation rates have been applied for each group, based upon double blind and OLE data in the Marigold study (5, 6). In absence of longer term data, in the base case it is then XXX. The analyses included below evaluate optional discontinuation scenarios after 28 months.

The Patient Access Scheme for GNX has been updated.

The originally applied unit costs of health care resource utilisation (20/21) have not been re-indexed per inflation to 2024, resulting in conservative cost offsets for GNX.

The base case as well as all scenarios below include an assumption of XXX% waste, which has been aligned with EAG´s preference.

The technical error in the cost of GNX in the down-titration period has been corrected. The Company would like to note that, in the recent discussions with the clinical expert, it was confirmed that the assumed duration of the down-titration period in our model (8 weeks) is conservative compared with clinical practice (around 4–5 weeks) with current anti-seizure medications, as well as the Marigold trial (2 weeks).

Base case results

The base case results from the previous and updated model are presented in the Tables below.

Previous base case results

Table 5: Base case results from the previous economic model

	Total costs (undiscounted)	Total costs (discounted)	Total QALYs (undiscounted)	Total QALYs (discounted)	Total QALYs (weighted)	ICER
ECM alone	XXX	XXX	XXX	XXX	XXX	
GNX	XXX	XXX	XXX	XXX	XXX	
Incremental	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Updated base case results

Table 6: Base case results from the updated economic model

	Total costs (undiscounted)	Total costs (discounted)	Total QALYs (undiscounted)	Total QALYs (discounted)	Total QALYs (weighted)	ICER
ECM alone	XXX	XXX	XXX	XXX	XXX	
GNX	XXX	XXX	XXX	XXX	XXX	
Incremental	XXX	XXX	XXX	XXX	XXX	**£20,045**

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Updated base case without stopping rule results

Table 7: Base case results from the updated economic model, without the stopping rule

	Total costs (undiscounted)	Total costs (discounted)	Total QALYs (undiscounted)	Total QALYs (discounted)	Total QALYs (weighted)	ICER
ECM alone	XXX	XXX	XXX	XXX	XXX	
GNX	XXX	XXX	XXX	XXX	XXX	
Incremental	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario analyses

The Committee raised concerns that the model may not fully capture the course of the disease. Therefore, the company has reconnected with the clinical expert to confirm the key modelling assumptions around the disease course, including mortality, age at treatment start, and discontinuation, and presents further scenarios on these parameters of relevance.

Mortality: Based on the accumulating data on deaths in CDD, survival assumption in the model seems very optimistic for this severe condition; based on clinician opinion, a median survival of 30–40 years could be more realistic. Therefore, we present scenarios with a median survival of XXX years (Scenario **S1**, Table 8 for base case).

Discontinuation: In the Company base case, the GNX discontinuation rates in the 0–6 month and 6–28 month periods are based on Marigold double blind (1, 2) and OLE data (5, 6), respectively, and the long-term rate in the "tail" is assumed to remain the same as in 6–28 months. The Committee raised a concern that this would lead to underestimate the share of people who would continue treatment to adulthood. The committee was aware that there are no data available on this proportion and clinicians suggested that some patients would continue if GNX was effective. Therefore, the Company now presents scenarios addressing this topic, using a lower XXX% per 4-week cycle discontinuation rate (scenario **S2**, Table 9) for the long-term tail. For comparison, 5% and 10% discontinuation rates per 3 months have been applied in the STA of the Dravet syndrome (TA614). The lower discontinuation rates would indicate better adherence to GNX.

NICE also proposed that there could be a plateau, after which patients no longer discontinue. Therefore, we have also tested this scenario by introducing a XXX% plateau to the discontinuations on top of the XXX% tail rate (scenario **S4,** Table 11). However, especially with this last scenario, the Company feels it should be taken into consideration that the mortality assumption used in the base case is highly conservative, with a median life expectancy of XXX years (last patient surviving to XXX). Therefore, we have also included both of the above scenarios, using the lower XXX years median life expectancy (scenarios **S3** in Table 10, and **S5** in Table 12). These scenarios are in line with the clinicians' opinion.

Figure 7 illustrates the impact of the scenarios on treatment duration. Note, the percentage of GNX responders alive and on GNX by age overlap for the base case and S1.

XXX

Figure 7: Percentage of GNX responders† alive and on GNX by age

†Responders were defined as patients with ≥30% reduction from baseline in 28-day MMSF during the DB maintenance phase of the Marigold trial.
Abbreviations: DB, double blind; GNX: Ganaxolone; MMSF, major motor seizure frequency.

Scenario S1: Base case with XXX-year median life expectancy

Table 8: Results of the base case with a median life expectancy of XXX years

	Total costs (undiscounted)	Total costs (discounted)	Total QALYs (undiscounted)	Total QALYs (discounted)	Total QALYs (weighted)	ICER
ECM alone	XXX	XXX	XXX	XXX	XXX	
GNX	XXX	XXX	XXX	XXX	XXX	
Incremental	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario S2: XXX% discontinuation from cycle 29 onwards

Table 9: Results of a scenario considering XXX% discontinuation from cycle 29 onwards

	Total costs (undiscounted)	Total costs (discounted)	Total QALYs (undiscounted)	Total QALYs (discounted)	Total QALYs (weighted)	ICER
ECM alone	XXX	XXX	XXX	XXX	XXX	
GNX	XXX	XXX	XXX	XXX	XXX	
Incremental	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario S3: XXX% discontinuation from cycle 29 with XXX-year median life expectancy

Table 10: Results of a scenario considering XXX% discontinuation from cycle 29 with XXX year median life expectancy

	Total costs (undiscounted)	Total costs (discounted)	Total QALYs (undiscounted)	Total QALYs (discounted)	Total QALYs (weighted)	ICER
ECM alone	XXX	XXX	XXX	XXX	XXX	
GNX	XXX	XXX	XXX	XXX	XXX	
Incremental	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario S4: XXX% discontinuation from cycle 29 with XXX% plateau for responders

Table 11: Results of a scenario considering XXX% discontinuation from cycle 29 with XXX% plateau for responders

	Total costs (undiscounted)	Total costs (discounted)	Total QALYs (undiscounted)	Total QALYs (discounted)	Total QALYs (weighted)	ICER
ECM alone	XXX	XXX	XXX	XXX	XXX	
GNX	XXX	XXX	XXX	XXX	XXX	
Incremental	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Scenario S5: XXX% discontinuation from cycle 29 with XXX% plateau for responders and XXX-year median life expectancy

Table 12: Results of a scenario considering XXX% discontinuation from cycle 29 with XXX% plateau for responders and XXX-year median life expectancy

	Total costs (undiscounted)	Total costs (discounted)	Total QALYs (undiscounted)	Total QALYs (discounted)	Total QALYs (weighted)	ICER
ECM alone	XXX	XXX	XXX	XXX	XXX	
GNX	XXX	XXX	XXX	XXX	XXX	
Incremental	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: ECM, established clinical management; GNX, Ganaxolone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

All the above scenarios are based on starting age of XXX years, based on clinician opinion, considering the clinical practice and long-term perspective. However, in addition, we show the ICERs for all scenarios with the starting age of XXX years (Table 13).

Scenario Analysis Results Summary

Table 13: Results of the updated base case and scenario analyses

Scenario	ICER	Change in ICER vs base case
Updated base case	£20,045	n.a.
Updated base case without stopping rule	XXX	XXX
S1: Base case with XXX -year median life expectancy	XXX	XXX
S2: XXX% discontinuation from cycle 29 onwards	XXX	XXX
S3: XXX% discontinuation from cycle 29 with XXX-year median life expectancy	XXX	XXX
S4: XXX% discontinuation from cycle 29 with XXX% plateau for responders	XXX	XXX
S5: XXX% discontinuation from cycle 29 with XXX% plateau for responders and XXX-year median life expectancy	XXX	XXX
S1 with start age XXX	XXX	XXX
S2 with start age XXX	XXX	XXX
S3 with start age XXX	XXX	XXX
S4 with start age XXX	XXX	XXX
S5 with start age XXX	XXX	XXX

Abbreviations: ICER, incremental cost-effectiveness ratio; n.a., not available.

Conclusion

In order to address the uncertainties raised by the committee and EAG on previous iterations of the economic model, the Company has made further updates and completed several scenario analyses to address key concerns. While no economic model can capture the complexity of CDD due to the rare nature of the condition and lack of data available, the Company has made significant efforts to improve the face validity of the model and to run relevant scenario analysis to assist the Committee with their decision making. The base case ICER is £20,045 and the ICER does not rise above XXX in any of the sensitivity analyses provided. This demonstrates the certainty of the ICER and stability of the model.

References[a]

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. Lo SH, Marshall J, Skrobanski H, Lloyd A. Patient and Caregiver Health State Utilities in Tuberous Sclerosis Complex. Pharmacoecon Open. 2022;6(1):105-21.
8. Auvin S, Damera V, Martin M, Holland R, Simontacchi K, Saich A. The impact of seizure frequency on quality of life in patients with Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy Behav. 2021;123:108239.

[a] All references were part of the materials previously submitted to NICE.

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

A Single Technology Appraisal

EAG Review of the company's additional submission

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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.

This TE response is linked to ERG report Burns, Phillips, Matthews, Bullement, Trigg, Briscoe, Symonds, Amin, Hargreaves, Melendez-Torres, Farmer. Ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over [ID3988]. Peninsula Technology Assessment Group (PenTAG), 2023.

1. INTRODUCTION

At a second meeting to discuss ganaxolone for treating seizures caused by CDKL5 deficiency disorder in people 2 years and over [ID3988], ganaxolone received a negative recommendation from the National Institute for Health and Care Excellence (NICE) committee. The company subsequently updated its evidence submission to NICE (1st March 2024). This document provides the External Assessment Group's (EAG's) critique of the company's update.

A summary of the uncertainties raised by the NICE committee in the 2nd appraisal committee meeting is provided in Section 2. An overview and critique of the updated submission is provided in Section 3. Finally, the EAG's revised base-case analysis is described in Section 4.

2. UNCERTAINTIES IN THE APPRAISAL RAISED BY THE NICE COMMITTEE

The final guidance for ganaxolone that was issued after the second appraisal committee meeting was subsequently withdrawn after the company identified an error in calculations in its evidence submission that may have affected the NICE Committee's decision. The uncertainties raised in the second committee meeting, which contributed to the Committee's decision not to recommend ganaxolone, are summarised as follows:

- Uncertainties in the company's economic model, including
    - How well it described the course of CDD
    - How quality of life is included in the model
    - How ganaxolone affects seizure frequency and quality of life
    - If someone stops having ganaxolone, how this is modelled and how well it reflects what would happen in clinical practice
    - Uncertainty about the appropriate starting age in the company's model that would best represent the target population in practice
    - Uncertainty in resource use assumptions associated with a change in seizure frequency
    - Uncertainty in calculating and applying a severity modifier due to limitations in the company model
- Limited evidence for the natural progression of CDD that could explore how seizure frequency changes over time, which may increase uncertainty in the treatment effect of ganaxolone
- Uncertainty in the cause of an increase in seizure frequency in the placebo arm of the clinical trial, which therefore increased uncertainty in the treatment effect of ganaxolone
- Limitations in the long-term data for ganaxolone obtained from the open-label extension of the clinical trial, and therefore uncertainty surrounding assumptions about the long-term treatment effect of ganaxolone used in the company's model.

3. OVERVIEW AND CRITIQUE OF THE UPDATED SUBMISSION

The company did not present new clinical effectiveness evidence with its submission; i.e. no new data were available from the company's clinical trial or from other sources. The company sought advice from its clinical expert to advise on assumptions in its economic model that the Committee considered may lack external validity, but the methods through which advice was elicited were not presented. The company stated that it sought advice from its expert on the "disease course, including mortality, age at treatment start, and discontinuation" (company re-submission, p.12).

While amendments made to the company model lacked transparency, the EAG identified the following key changes to its preferred base case analysis that was discussed at ACM2:

- **Treatment effect and stopping rule:** Adjustment to the modelling of response status and seizure frequency (SF), which (when combined) led to model results where the total QALYs estimated for ganaxolone were the same, whether a stopping rule was specified or not.
- **Cost of ganaxolone:** A revised Patient Access Scheme (PAS) discount for ganaxolone was implemented. In addition, an assumption of [redacted]% wastage for ganaxolone was now applied, and a different approach was taken to estimate discontinuation of ganaxolone over time.
- **Titration:** Included up-titration for ganaxolone in the first 4-week cycle. In addition, the company addressed a technical error in its application of down-titration (which the company noted may be over-estimated in its model versus expected clinical practice).
- **Utility values:** Included an adjustment for utility in the first cycle to reflect the expectation that patients do not immediately experience a drop in MMSF upon treatment initiation (based on the up-titration edit described above). The company maintained its preference for utility values derived from the Lo *et al.*, (2022) study.
- **Life expectancy:** Explored scenarios assuming an average life expectancy of [redacted] years based on clinical expert feedback, as an alternative to the base case assumption of assuming life expectancy in line with the general population.

Each of these points are discussed in turn throughout the sub-sections that follow. For completeness, further model edits not discussed in this response either have a small impact on results or the EAG considered them appropriate without warranting any further commentary.

3.1. Treatment effect and stopping rule

The company retained its approach to modelling responders and non-responders separately from the start in their model. The EAG maintained that this is conceptually inappropriate since response cannot be determined prior to the initiation of treatment. Notwithstanding, the EAG noted additional concerns with the company's revisions to modelling treatment effect and the stopping rule. In brief, the EAG understood the company's revised approach to make use of the individual-level distribution of Hodges-Lehmann estimates of location shift (HL shift), as opposed to the cohort-level HL shift, to capture the effect of ganaxolone on SF. Furthermore, as noted above, the company also edited the model such that response status was established upon model entry, and so the distribution of HL shift was calculated separately for responders and non-responders. To illustrate this, Figure 1 shows the data included in the company's revised model to capture this distribution of HL shift.

Figure 1: Distribution of HL shift included in company's revised model

Note: Plot produced using cell range AH47:AH249 on the 'SeizureModel' sheet of the company's revised model.

The EAG raised several concerns with the company's revised application of treatment effect:

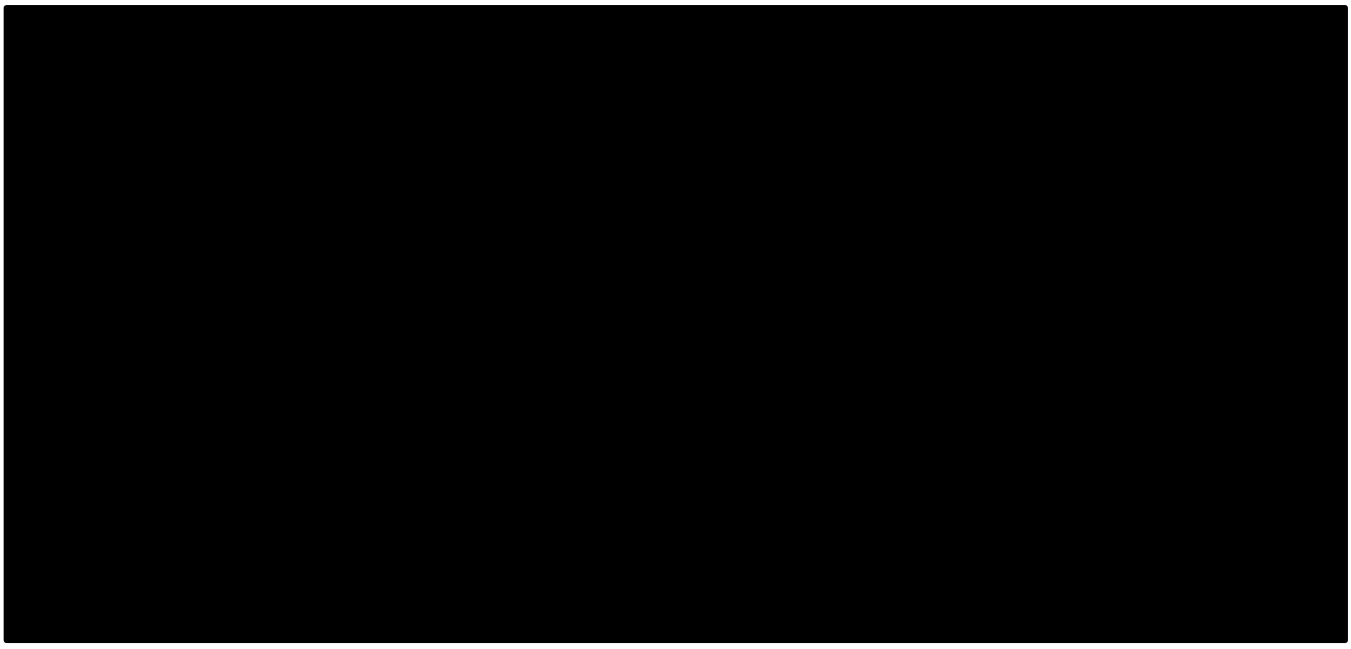
- The values used to inform the distributions shown in Figure 1 were hard-coded, meaning that the EAG had no way of verifying their accuracy.
- The company described the distributions of HL shift as being 'gamma'. A gamma distribution is strictly positive, which is incompatible with a *reduction in seizure frequency* distribution which hypothetically covers the floor [-∞%, +100%] (i.e., patients could potentially have a 100% reduction, but there is no upper limit on the increase in seizures).
- In principle, non-responders should not be capable of achieving a ≥30% improvement in SF. However, a patient could theoretically be defined as a responder, and then be defined as a non-responder at a later time point (and *vice versa*, assuming treatment is continued). The data in the company's model suggested that there were no non-responders that have a [redacted] improvement (cell range AJ173:AJ178 on the 'SeizureModel' sheet). This was not explained by the company. In Figure 1, the distribution stops short of [redacted] response and has an unusual shape that the EAG cannot explain from only the numerical values. The EAG posited that any changes in SF of <30% among people defined to be responders, particularly given the relatively short period of time for which there was follow-up data, provided direct and irrefutable evidence of loss of treatment effect over time (i.e., treatment effect waning). Loss of treatment effect for responders was not included in the cost-effectiveness model, and these patients were assumed to remain responders as long as they continued to receive treatment. The EAG considered this to be a major area of outstanding uncertainty in the model.
- Per the previous point made above, theoretically, responders should not be capable of achieving a <30% improvement in SF or experience a worsening of SF. The data in the company's model (as shown in Figure 1) suggested that this was possible (based on cell range AH49:AJ249 on the 'SeizureModel' sheet), though this may reflect a loss of response. Again, the EAG highlighted that this is concerning given that response status was suggested to be used as a stopping rule specifically at one time point (24 weeks).
- Conceptually, the company's model relied upon combining a distribution of absolute SF (captured by a lognormal distribution) and a distribution capturing relative changes in SF, stratified by response category (though this was applied from baseline when response to treatment is not yet known). The EAG highlighted a persistent issue that affected both this

approach and the previous approach using the median HL shift – that baseline SF was in no way linked to treatment effect. For example, a person experiencing one seizure per month at baseline was applied the same treatment effect as per a person experiencing 1,000 seizures per month at baseline (since the treatment effect was a percentage change).

Ultimately, the EAG had no confidence in the estimation of SF in the company's model because of the anomalies noted above and which are evidenced in Figure 1 (based on hard-coded values for a distribution which the EAG could not verify), and that the EAG did not consider it appropriate to assume that relative changes in SF were independent to baseline SF.

Further to this point, the EAG draws attention to Figure 1 of the company's response, which is re-produced below in Figure 2 of this report. The EAG highlighted that while uncertain, this plot suggested two things: first, that the effect of ganaxolone takes some time to manifest in terms of a reduction in SF (based on this plot, approximately [redacted] cycles for 'peak' efficacy); and second, that there *may* be some evidence of treatment effect waning even in the responder group (based on this plot, the HL shift appeared to reduce after cycle [redacted], though the EAG noted that in cycle 5 the placebo arm received ganaxolone for 3 weeks). This potential reduction in treatment effect over time was further evidenced by Figure 1, which suggested that a considerable proportion of responders at the assessment point were no longer considered responders by the end of follow up. The EAG previously explored functionality to interpolate treatment effect using a combination of Marigold and the Marigold OLE evidence, which was explored again as part of the EAG's analysis (see Section 4).

Figure 2: Median difference (Hodges-Lehmann location shift) between GNX responders† and placebo by cycle (taken from company's response)



Maintenance phase effect has been calculated from cycle 2 up to the end of the double-blind period (17 weeks).
Cycle 5 for placebo consists of 1 week on placebo (double-blind) and 3 weeks on GNX (start of OLE).
Cycle 1: Weeks 1–4; cycle 2: Weeks 5–8; cycle 3: Weeks 9-12; cycle 4: Weeks 13–16; cycle 5: Weeks 17–21.
†Responders were defined as patients with ≥30% reduction from baseline in 28-day MMSF during the DB maintenance phase of the Marigold trial.
Abbreviations: GNX, Ganaxolone; OLE, open label extension.

Related to these points, the EAG identified another issue in terms of how treatment effect was reflected throughout the company's revised model. In Cell AX23 of the "Trace Gan" sheet (note – this refers to part-way down the patient flow sheet calculations, as inconsistent formulae are used in some of the columns in the 'Trace' sheets), 100% of patients that were still alive and on treatment were assigned a per cycle cost of £802.91, which was labelled by the company in cell CostParams!K38 as "Average cost of care per cycle GNX responder (patients aged <12 years)". This cost refers to hospitalisation costs related to SF (i.e., this is a medical resource use [MRU] cost, not a drug cost). This application led to a sudden drop in "Other direct healthcare costs - Ganaxolone" in the "Trace Gan" sheet, from £1,204 in cycle 5 to £732 in cycle 6. This meant that the company's base-case analysis assumed a 100% response rate with respect to MRU, and applied the responder reduction to all patients' epilepsy-related hospital stay rate as long as they remained on ganaxolone. This was an error, as the value should be in keeping with the application of efficacy throughout the model, which at the last ACM was a 0% reduction for non-responders and a larger reduction for responders.

The EAG corrected this error by applying the ECM arm MRU rates to the non-responders after response was assessed, in line with the way that the company applied this incorrectly. Consequently, the ICER was increased by around £3,000, and the drop in monthly MRU at 6 months was considerably reduced from assuming 100% responders to assuming the proportion in line with the MARIGOLD data.

Despite the efforts made by the company to address the EAG's previous concerns with the application of the stopping rule, the EAG was still unable to support the specification of a stopping rule based on the analysis provided by the company. To re-iterate the EAG's previous view on this feature of the model – enabling the stopping rule should lead to a reduction in the total costs *and* QALYs for ganaxolone, versus ECM, yet improve the ICER since the reduction in costs offsets the loss in QALYs. In the company's revised model, enabling the stopping rule only influenced the total costs for ganaxolone, with no impact on QALYs (minus a technical error

which the EAG resolved). The EAG therefore could not accept the company's stopping rule application in its exploratory alternative base-case analysis, and so the stopping rule was disabled in the EAG's exploratory analysis. The EAG highlighted, however, that in principle, a stopping rule *should* improve estimates of cost-effectiveness, relative to results without a stopping rule applied. Therefore, any ICERs excluding the stopping rule may be deemed an upper limit of the ICER were a stopping rule appropriately implemented correctly within the company's model.

3.2. Cost of ganaxolone

In line with the company's edits to handling response in its revised base-case analysis (see Section 3.1.1), the company edited its discontinuation rates for ganaxolone. Previously, the 28-day discontinuation rates were [redacted]% (pre-response assessment at cycle 6 [24 weeks]) and [redacted]% (post-response assessment at cycle 6). The revised values were based on the company's edit to the handling of response, and so there were now two dimensions to consider: response status *and* time:

- For cycles 0 to 5: [redacted]% (responders) and [redacted]% (non-responders).
- For cycles 6 to 28: [redacted]% (responders) and [redacted]% (non-responders).
- For cycles 29+: [redacted]% (responders) and [redacted]% (non-responders).

The EAG was not provided with details of how the discontinuation rates were estimated separately for responders and non-responders. Taken at face value, the EAG was concerned that the 'average' rate of discontinuation appeared to be greater than the previous analysis (since a weighted average of [redacted]% and [redacted]% will be greater than [redacted]% The EAG expected the value for discontinuation of responders to be lower than the previous value for post-response assessment at cycle 6. If a simple 50:50 split was assumed, and the value of [redacted]% for non-responders was considered 'true', then the value for non-responders would need to be [redacted]% Taking this further, if this value was used in the company's revised base-case analysis, the ICER (with stopping rule) increased from £[redacted]% to £[redacted].

As part of its response, the company provided scenarios that applied an assumed [redacted]% discontinuation rate from cycle 29 onwards. These scenarios were provided to address the committee's concern that assuming a constant discontinuation rate based on the observed period of follow-up from MARIGOLD and the LTE study would lead to an underestimate of

patients who would continue treatment into adulthood. While not explicitly described as such, the EAG anticipated that the choice of [redacted]% was arbitrary.

Overall, the EAG considered lower long-term discontinuation to be more realistic than assuming no change in discontinuation after cycle 29. However, there were no data available to robustly estimate this rate. The EAG therefore prefers the use of a [redacted]% discontinuation rate, but notes substantial uncertainty associated with this model input. Furthermore, the EAG explored the 'plateau' scenarios presented by the company, in conjunction with the EAG's other preferred settings and assumptions. The plateau scenarios assumed that a small proportion of patients (e.g., 10%) will remain on treatment indefinitely, whereas the remainder (e.g., 90%) will discontinue at the rate specified from cycle 29+. The EAG considered these scenarios to be helpful for decision making, since they reflect the possibility of some patients continuing treatment with ganaxolone for a period of many years.

The cost-effectiveness results presented in the company's addendum, as well as this response, reflect the revised PAS discount for ganaxolone.

3.3. Titration

The company incorporated two edits to titration within its revised base-case analysis. The first of these accounts for an up-titration period of one cycle (4 weeks) during which patients receive half the dose of ganaxolone, in accordance with the MARIGOLD study design and dosing guidance in the SmPC. The EAG accepted this revised application for up-titration. The second edit accounts for the error in down-titration which the EAG highlighted previously. The company noted that, in practice, the 'true' period over which down-titration would occur may be shorter than that modelled. As such, the costs of ganaxolone may be over-estimated by the model versus practice. However, since there was uncertainty concerning the duration of down-titration, the EAG maintained the current application of an 8-week down-titration period within its exploratory analyses, consistent also with the company's base-case analysis.

3.4. Utility values

The company's response states, with respect to the choice of source for utility values: *"While all utility sources had limitations, the Committee concluded that, on balance, Lo et al appears to be the most appropriate source for the utility values."* (company response, Table 1). The EAG maintained its previous view on the most suitable choice of utility values – that both sources were imperfect, but scenarios considering either source may be helpful for decision making,

since they each had their own strengths and limitations. However, the EAG also noted that the severity modifier for which ganaxolone would qualify changed depending on the source chosen.

In ACM2, an alternative utility source ('CDD utility study') was discussed, which produced a total discounted lifetime QALY estimate for the ECM arm of [redacted] (see slide 35 of the ACM2 slides). This was markedly lower than the total discounted lifetime QALYs estimated for ECM in the economic model using either Auvin *et al.* or Lo *et al.* (range: [redacted]). An equivalent value for the ganaxolone arm was not presented, but the EAG highlighted that if an estimate was produced using utility values similar to the CDD utility study, then the total QALYs for ganaxolone would likely be much lower than the economic model current estimates. Therefore, while ganaxolone may clearly qualify for a x1.7 severity modifier if these alternative utility values were used, the total QALYs gained may be much smaller if a CDD-specific source was available to populate the model with (since each avoided seizure would be associated with a smaller utility benefit, *ceteris paribus*).

Given the committee's expressed preference for the utility values by Lo *et al.*, the EAG presented ICERs using these utility values in its exploratory alternative analysis. However, the EAG highlighted that these utility values, and therefore the cost-effectiveness results relying upon these utility values, were subject to extreme uncertainty. Relatedly, since Lo *et al.* was used for utility values, the EAG's exploratory analysis included a severity modifier of 1.7.

The company's revised base-case analysis included a 'correction factor' of 0.64, which was applied to patient utility for responders and of 0.0 for non-responders in the first 4-week cycle. This was explained by the company to represent the proportion of treatment effect gained during the titration period versus the maintenance period in all patients. In other words, the correction factor aimed to address an important limitation of the revised approach to handling response in the company's economic model, which assumed that patients immediately responded to treatment. In principle, the EAG agreed with adjusting the average utility for responders for the first cycle since patients were not defined as responders until month 6, but no clear explanation was provided for the approach taken to derive the correction factor value of 0.64. Given that the EAG had no alternative data to inform its base-case analysis, this approach was tentatively accepted.

3.5. Life expectancy

In the company's original base-case analysis, patients with CDD were assumed to have life expectancy similar to the general population. As highlighted in the Draft Guidance issued by NICE, there was a dearth of evidence available to quantify the life expectancy of people with CDD. However, the company obtained clinical opinion which considered a median life expectancy between 30 and 40 years to be more realistic, versus assuming life expectancy as per the general population. Accordingly, the company presented scenarios where mortality was calibrated such that life expectancy was approximately [redacted] years. This was achieved by specifying a standardised mortality ratio (SMR) of [redacted], such that at each cycle the probability of death was [redacted]-times the equivalent estimate for the general population. The EAG could not determine how an SMR of [redacted] was determined, nor could it verify the approach used to elicit clinical expert opinion, though the EAG noted that based on this SMR the median survival was estimated to be approximately [redacted] years, which (combined with a starting age of [redacted] years), yielded an estimated life expectancy of [redacted] years.

Since there was no difference in mortality between the two modelled treatment arms, specification of a different life expectancy had a relatively small impact on model results. The EAG considered that a life expectancy estimate which was in-keeping with clinical opinion would seem to be a more reasonable base-case assumption, as compared with using unadjusted general population mortality. Therefore, despite the relatively weak evidence to support the model assumption, and the lack of detail presented concerning the elicitation process, the EAG included an assumed life expectancy of [redacted] years within its exploratory analysis.

4. EAG'S EXPLORATORY ALTERNATIVE BASE-CASE ANALYSIS

Owing to the major outstanding limitations affecting the company's revised model, the EAG was unable to present a definitive preferred base-case analysis. Instead, the EAG presents exploratory indicative results including the EAG's preferences (where possible to specify) within the company's revised model. These results have unknown applicability to real-world use of ganaxolone in the NHS.

The company's revised model included structural edits that could not easily be reconciled with the previous versions of the model submitted by the company. Furthermore, based on the committee's preferences expressed at ACM2, some previous settings and assumptions were no longer applied. Therefore, the EAG applied its adjustments to the company's revised base-case analysis, as opposed to the EAG's previous tentative base-case analysis.

Table 1: EAG adjustments to revised company base-case

Change made	Justification	ICER
Revised company base-case	-	£20,045
1) [redacted]-year life expectancy	Aligned with clinical opinion	£19,979
2) [redacted]% discontinuation rate after cycle 29	More likely to represent real-world practice	£25,623
3) No stopping rule	Issues persist with the face validity of results including a stopping rule	£29,794
4) Re-enable interpolation of treatment effect	Based on evidence to suggest treatment effect waning over time	£20,381
5) Correction of MRU costs	To address inconsistency in treatment effect application	£20,232
Combined result (1+2+3+4+5)	**-**	**£37,774**

Abbreviations: EAG, external assessment group; HRQoL, health-related quality of life; ICER, incremental cost effectiveness ratio; MRU, medical resource use; QALY, quality-adjusted life-year.

The EAG highlighted the following settings and assumptions that remained key uncertainties in the analysis, but were not possible for the EAG to address within the context of its appraisal:

- Inappropriate modelling of treatment effect.
  - The EAG had no confidence in how the company modelled the effect of ganaxolone on SF, described further in Section 3.1.1 of this report.

- Reliance on a proxy condition for vignette-based utility values.
  - On this point specifically, if the total QALYs for the ECM arm were scaled down to align with the estimate of [redacted]previously provided by company to substantiate the 1.7 severity modifier, then the incremental QALY gain would like be [redacted]% of the current value using utility values by Lo *et al.* This would result in an ICER which is [redacted] the current ICER. This is discussed further in Section 3.1.4 of this report.
- Potential for a plateau in treatment discontinuation in the long-term (e.g., [redacted] per scenario 5 presented by the company in its response).
  - The EAG had no clear basis on which to endorse or reject this scenario, but noted that this further increased each of the ICERs presented in Table 1.
- Unclear impact of a likely reasonable stopping rule on the estimated QALY gain produced by the model.
  - While the EAG supported the principal of a stopping rule, its implementation in the model must exhibit face validity. Without this, the EAG was unable to support results including a stopping rule.