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

Produced by

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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.

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

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The final guidance for ganaxolone that was issued after the second appraisal committee meeting was subsequently withdrawn after the company identified an error in calculations in its evidence submission that may have affected the NICE Committee's decision.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)

[redacted]

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.