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

Fully redacted. Contains no confidential information.

Second committee meeting [ACM3]

Technology appraisal committee [B]

Chair: Baljit Singh

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

External assessment group: Peninsula Technology Assessment Group (PenTAG)

Technical team: Summaya Mohammad, Sam Slayen, Adam Brooke, Ian Watson

Company: Orion Pharma

Re-cap from 1st and 2nd committee meetings (ACM1/2)

NICE National Institute for Health and Care Excellence

Patient and carer perspectives

Submission from CDKL5 UK

High unmet need – only symptomatic treatment:

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

Current service provision:

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

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

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

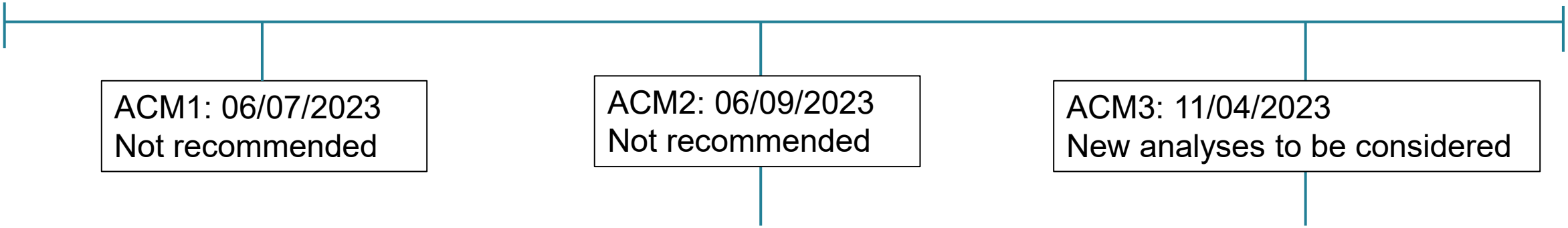
"There's so much joy to be had when your child is well, seizure[s] are minimal…"

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

NICE

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

Appraisal History



- Company identified error in its evidence, and proposed additional analyses to address key uncertainties
- Taking into account all circumstances, appropriate for committee to consider the additional analyses
- Committee has considered in detail nature of the condition, clinical evidence and economic modelling; current discussion focuses on new analyses

Key modelling issues raised at ACM2 to be explored
Key efficacy uncertain – response-based model highlighted issues with splitting ganaxolone arm
Concerns on the validity of the model and whether it fully reflected the condition
Utility values highly uncertain; benefit of reducing seizures likely to be overestimated
Uncertainty around proportions continuing treatment into adulthood

Abbreviations: ACM, appraisal committee meeting

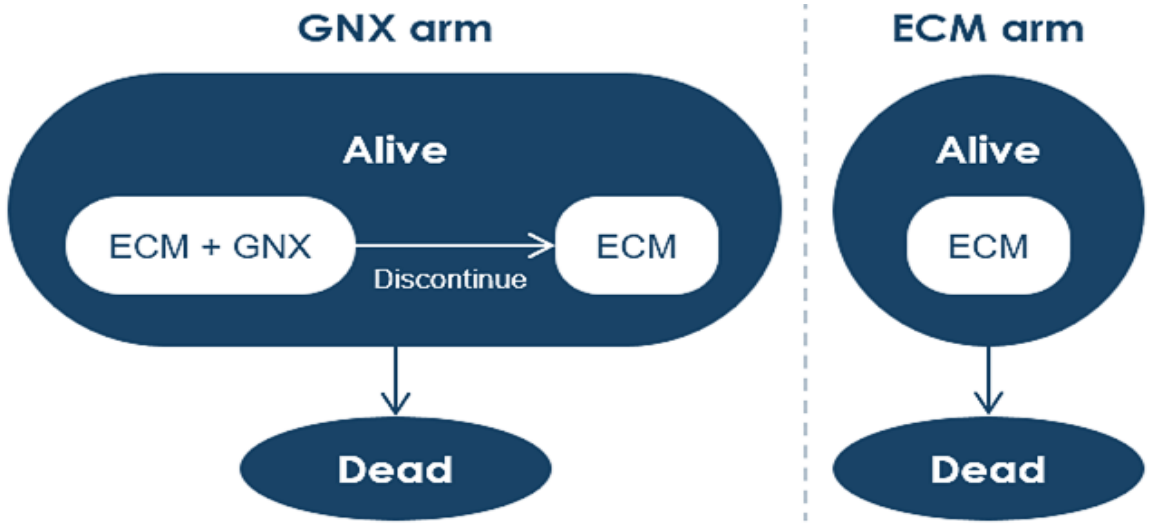
Key issues

Issue	Resolved?	ICER impact
Treatment effect and stopping rule	No – for discussion	Large
Utility estimates used in the model	No – for discussion	Large
Discontinuation (incorporating modelling of discontinuation, life expectancy and starting age)	No – for discussion	Unclear

Company's model overview

Model structure:

Simple Markov state-transition model



- Two health states in the GNX arm. In the GNX arm people can either be having GNX or discontinue
- Discontinuation modelled using extrapolation from trial data and assumptions
- QALYs are generated by applying seizure frequency linked utilities to the ***distribution of seizures*** in each health state

Ganaxolone affects costs by:

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

Ganaxolone affects QALYs by:

- Reducing seizure frequency and improving HRQoL to generate more QALYs than ECM

Assumptions with greatest ICER effect:

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

NICE

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

Overview of treatment effect through seizure frequency

Create baseline SF curve from lognormal fit of baseline period (all people with CDD)

Baseline seizures assumed to stay the same for ECM and non-responders

Establishing relative treatment effect for ganaxolone through changes to the baseline distribution

Utility values applied to banded distributions of seizures dependent on response status/ treatment arm

Individual or cohort level changes in seizure distribution

NICE

Abbreviations: CDD: cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; ECM, established clinical management

Company's model history

Calculation of seizure frequency (relative treatment effect estimation)

ACM1

- For the first 6 months:
  - GNX arm modelled as summary statistic Hodges-Lehman shift change from baseline distribution compared to placebo arm
  - Placebo arm (ECM) assumed to remain as total baseline SF
- Stopping rule added at TE – Non-responders* stop at 6 months. Responders** [redacted] in GNX) have 62% reduction in seizures.
- Committee/EAG – unclear how a stopping rule can increase QALY gain, concerns with validity of the model

ACM2

Updated model structure – explicit responder/non-responder analysis

- EAG - may inflate the treatment effect because all responders are determined at the start of treatment
- Committee - response-based model highlighted issues with splitting the ganaxolone arm (broken randomization)
- EAG – revised model did not resolve the original stopping rule issue due to non-linear relationship between seizure frequency and utility
- FAC – still unclear how responder seizure reduction is calculated

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

**Responders have a 30% or greater reduction in seizure frequency. *Non-responders have a 30% or lower reduction in seizure frequency

Company's model – new submission – HL shift

Generated seizure frequency distributions from individual level HL shifts

Company ACM3 analyses

- Responder and non-responder subgroups maintained. HL shift method updated from cohort to an individual level
- The individual HL shift approach was intended to be a response to the non-linearity of utility values
- Provided visualisation of treatment effect over time (responders) and individual patient MMSF data per cycle

Note: It is unclear which timepoints the reduction in SF in the above graph were calculated from.

EAG comments

"The EAG had no confidence in the estimation of SF in the company's model"

- The seizure frequency distribution underpins the QALY calculations for the ganaxolone responder arm.
- Responder and non-responder HL shift distribution calculated separately at model entry (hard-coded, impossible to verify)
- Unclear how distribution for non-responders* calculated. No non-responders have SF between [redacted] and [redacted] shape not explained
- Distributions of HL shift can't be gamma distributions as they are strictly positive (incompatible with increase in seizure frequency)
- Persistent conceptual issue with combining absolute distribution of SF and one capturing relative changes – assumes relative changes independent of baseline seizure frequency

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

Company's model – new submission – treatment effect

Treatment waning and suitability of responder analysis

[redacted]

[redacted]

Median difference (Hodges-Lehmann location shift) GNX responders† vs placebo by cycle.

EAG comments

- Highlighted area shows direct evidence of treatment waning effect from observed individual level HL shift data – which is not considered in the model (assumed constant treatment response) because the response is only considered at one time point
- This further calls into question validity of a response-based approach to modelling

- Limited use of time series HL shift data because it is for responders only against total placebo arm
- Appears to show that ganaxolone takes [redacted] to achieve "peak" efficiency
- Also suggests plausibility of treatment waning as the HL shift [redacted] Note that cycle 5* includes some placebo crossover and should be interpreted with caution
- EAG scenario reintroduces functionality to interpolate treatment effect using a combination of Marigold and the Marigold OLE evidence. (full treatment effect only applied from cycle 3)

NICE

Abbreviations: ECM: established clinical management; HL, Hodges-Lehman; OLE, open label extension

Company's model – new submission – HL shifts compared

Individual vs cohort level HL shift illustrated

- The shift from the cohort level shift (ACM2) to individual level shift (ACM3) HL shift described in slide 7 had a minimal effect on responder modelled seizure frequency
- It is unclear why there are slight differences between the non-responder modelled seizure frequencies and ECM

[redacted]

NICE

Abbreviations: ACM, appraisal committee meeting; ECM, established clinical management; GNX, ganaxolone; HL, Hodges-Lehman

Company's model – new submission

Appropriateness of stopping rule implementation in the model

Background

- Committee considered a stopping rule appropriate in principle but concerns remained about implementation

Company ACM3 analyses

- Maintains use of a 6-month stopping rule (applied at week 24) – Amended to always split patients as responders or non-responders at the beginning of the model, not only when the stopping rule was utilised.

EAG comments

- Previous implementation of stopping rule increased QALYs, which is counter-intuitive. Stopping rules should reduce costs and QALYs, but generally improve cost-effectiveness (costs reduced more than QALYs)
- In this analysis, implementing stopping rule only affects total costs, with no effect on QALYs (i.e. those that have 1%-29% reduction in SF have no QALY benefit)
- Consequence of response-based analysis – people are modelled alongside those that have an increase in SF.
- EAG considered stopping rule was not appropriate because of concerns with the analysis and potential for treatment waning effect and excluded it from its preferred analyses

Is the responder/non-responder modelling approach appropriate for decision making?
Is the way the treatment effect is modelled appropriate for decision making?

Abbreviations: QALY, quality adjusted life year; SF, seizure frequency;

Modelling treatment effectiveness and response: discussion

ACM1:
- Treatment effect for gnx based on HL shift vs ECM
- Stopping rule: 62% SF reduction for responders

ACM2:
- Treatment effect for responders based on cohort HL shift
- Stopping rule: explicit responder modelling

ACM3:
- Treatment effect for responders based on individual-level HL shift
- Stopping rule: explicit responder modelling

- New analyses further iterate company model: additional complexity aims to address uncertainties and methodological issues (heterogeneity in treatment responses)
- EAG identifies conceptual and methodological limitations:
    - Conceptual issues remains that baseline SF is not linked to treatment effect. People with very different baselilne seizures would have the same response to treatment.
- Model outputs: predicted SF distribution similar to older model; stopping rule affects costs only, not QALYs

Is the modelling of seizure frequency and treatment effect suitable for decision making?
- Responder/non-responder modelling approach?
- Modelling of treatment effect?
- Stopping rule?

Does the model provide sufficiently plausible and robust estimates for decision making?

Abbreviations: HL, Hodges-Lehman; QALY, quality adjusted life year

Utility values

Background

- Two utility value sets have been used so far in this appraisal: Lo et al (utility set from TSC), Auvin et al (utility set from DS/LGS). Also the "CDD utility study" provided a mean overall estimate of utility for people with CDD.
- Both Lo et al and Auvin et al utilities are from different diseases and EAG at ACM2 highlighted the substantial uncertainty associated with applying a utility set from a different disease population

- Lo et al includes utility of 0.73 for 0-27 seizures per 28 days. May be appropriate to people having no seizures but less plausible closer to 27 seizures. Also includes negative utility for people having 3-4 seizures per day.
- Auvin et al utilities not from preference-based method.
- CDD study gives a mean utility for children with CDD (irrespective of seizure frequency) of [redacted]

Auvin et al Seizure frequency

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

Lo et al., (2022) – generalised seizures

Per day	Per 28-day cycle	Mean (SE)
0	0-27	0.73 (0.03)
1	28-55	0.18 (0.06)
2	56-83	0.09 (0.05)
3-4	84-392	-0.11 (0.06)

[redacted]

Abbreviations: TSC, tuberous sclerosis complex; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; CDD, CDKL5 deficiency disorder

Key Issue: Utility values used

Committee at ACM2

- ". . . all sources of utility had substantial limitations but, on balance, Lo et al. may be the most appropriate source for utility values. However, **the benefit of reducing seizures is likely to be overestimated**. . . "
- Very few people in the evidence had 0 or close to 0 seizures per month, applying the 0.73 utility value to the large proportion of people who had <27 seizures a month in the responders arm could bias the model in favour of GNX

Company ACM3 analyses

- Maintains preference for Lo et al. Argues that as patients in the lowest band will have at least one seizure free day per cycle this utility set is appropriate
- Highlights that [redacted] of those experiencing 0-27 seizures a cycles had more than 15 SFDs per 28 days. Considers that this justifies use of the 0.73 utility for this group.

Seizure-free day frequency count								
Treatment	Cycle	28-day MMSF class	N	Mean	SD	Median	Min	Max
GNX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GNX, ganaxolone; SFD, seizure free day; TSC, tuberous sclerosis complex; CDD, CDKL5 deficiency disorder; MMSF, Major Motor Seizure Frequency

Key Issue: Utility values used

EAG comments

- Maintains ACM2 position, both utility sources utility imperfect but considering each may help for decision making
- Alternate "CDD utility study" value of [redacted] suggests modelled QALYs for ECM arm unrealistic
- Consider that if an alternative utility source (derived from a CDD study and used as a scenario for ECM utility in ACM2) was used to inform the GNX arm then total QALYs would be much lower than current estimates.
- The [redacted] of people having [redacted] SFD could still plausible have had 27 seizures a month.
- Lo et al utility values in its exploratory alternative analysis, noting that they are subject to extreme uncertainty

Tech team considerations

- Committee concluded that relative difference in utility values associated with a change in seizure frequency from Auvin et al study may better reflect the impact on HRQoL in CDD
- Lo et al study had a larger utility range (-0.11 to 0.73). When applied to the SF distribution in the GNX arm, it gave a higher mean utility gain between ECM and GNX
- This is less in keeping with the average untreated utility from the "CDD utility study" or [redacted]

	ACM1 model	ACM2 responders only	ACM3 responders only
Auvin et al mean utility **gain**	[redacted]	[redacted]	[redacted]
Lo et al mean utility **gain**	[redacted]	[redacted]	[redacted]

Do the committee consider that the company has addressed concerns around utility raised at ACM2?

Abbreviations: CDD, CDKL5 deficiency disorder; GNX, ganaxolone; QALY, quality adjusted life year; HRQoL, health related quality of life; SF, seizure frequency; ECM, established clinical management; SFD, seizure free days

Key Issue: Discontinuation and modelling assumptions

Background

- At ACM2, per cycle discontinuation was [redacted] in cycles 0 to 5 and [redacted] from cycle 6 for everyone in the model
- Model predicts that [redacted] of people will remain on ganaxalone after 11 years of age, and very few into adulthood. High discontinuation before 11 years benefits ganaxolone as health benefits are gained on lower, cheaper doses

Committee at ACM2

- Requested scenarios to explore the effect of different levels of discontinuation into adulthood, including the possibility that most people who are using ganaxolone at the end of the trial OLE would continue into adulthood.

Company ACM3 analyses

- Base case discontinuation dependent on model cycle and responder status

Cycle	Responder discontinuation	Non-responder discontinuation
0-5	[redacted]	[redacted]
6+	[redacted]	[redacted]

- Company scenarios exploring different levels of discontinuation (including modelling a [redacted] plateau for responders [[redacted] of people in the GNX arm when the stopping rule is enabled]).
- However, no scenario was submitted to explore the possibility that a majority of responders on ganaxolone at the end of the OLE trial would continue into adulthood (i.e a plateau of over ~25%)

Is modelling of discontinuation for responders and non-responders appropriate?

NICE

Abbreviations: OLE, open label extension; GNX, ganaxolone

Key Issue: Discontinuation and modelling assumptions

EAG comments

- Not clear how discontinuation rates were estimated separately for responders and non-responders
- Concerned that average rate is now higher than previous analyses (weighted average of [redacted] and [redacted] will be greater than [redacted] EAG had expected discontinuation value to be lower than in previous analyses.
- Scenarios (which reduce discontinuation from cycle 29 or fix a proportion of responders on ganaxalone indefinitely [plateau scenario]) helpful for decision making
- Noted that the choice of a [redacted] discontinuation from cycle 29 was arbitrary

Tech team considerations

- Unclear why discontinuation for responders increases after cycle 6. Treatment effect waning is not modelled, would logically expect those still on treatment at 6 cycles to be benefiting and therefore stay on treatment.
- Logical inconsistency: treatment benefit continues indefinitely yet large proportions of people discontinue.
- Trial included reinitiation, whereby people discontinuing could restart treatment if it was before age 17, which was not modelled and could plausibly result in more responders using ganaxolone into adulthood.
- Have included scenarios investigating higher plateaus which may better represent a complete absence of treatment effect waning. (Note that in absence of stopping rule, plateau is applied to everyone on ganaxolone)

Has uncertainty around discontinuation been explored appropriately?

Abbreviations: EAG, external assessment group; GNX, ganaxolone

Key Issue: Discontinuation and starting age

Background

- Starting age is a key driver of CE estimates as dose is weight based up to 28kg (~11 years) at which point a fixed dose is used. A later starting age results in a higher dose and overall greater treatment costs.

Company ACM3 analyses

- Company starting age maintained at [redacted] years in base case model. Based on clinical opinion.
- Include scenarios exploring effect of [redacted] year starting age.

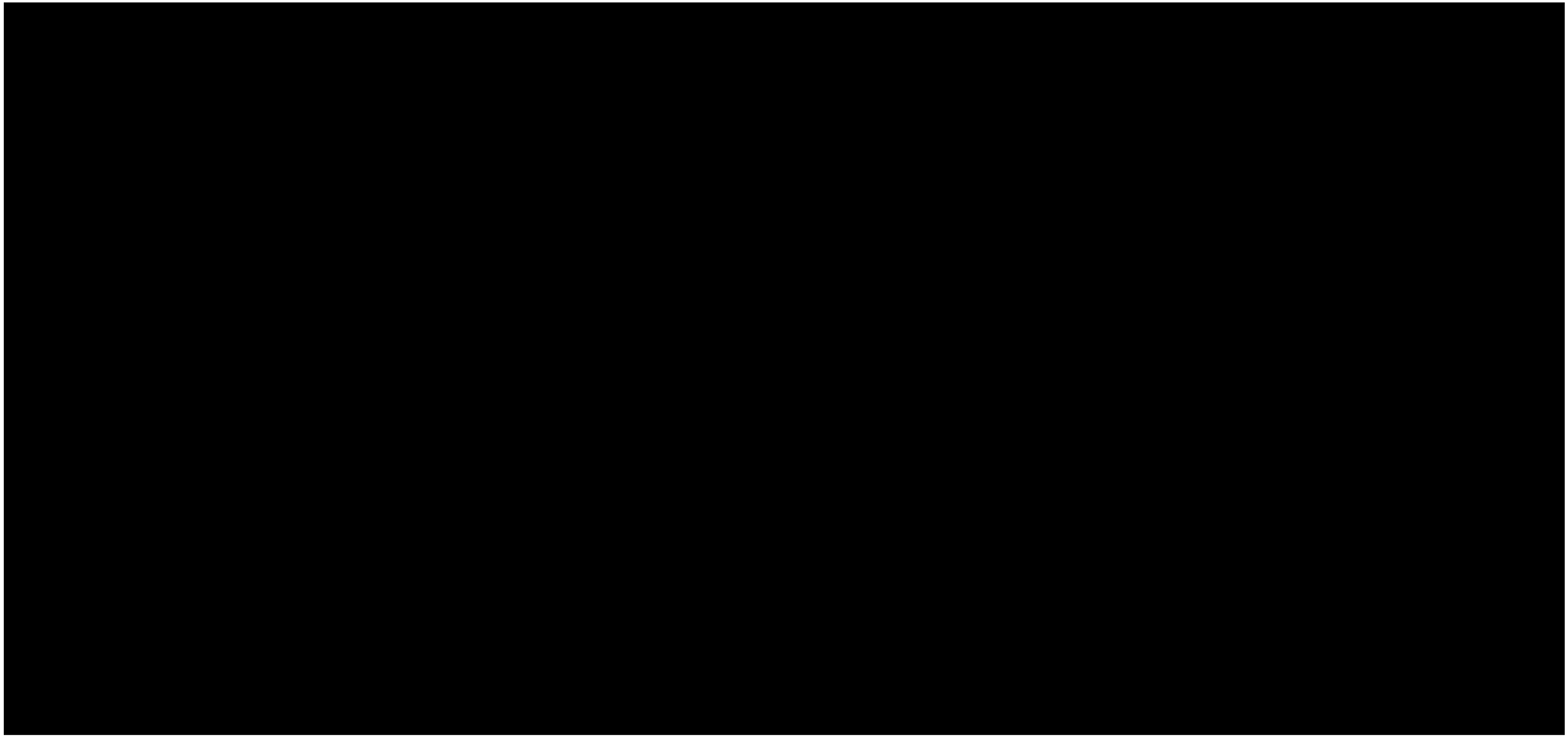
Tech team considerations

- ACM2 committee concluded that costs should be based on the prevalent population although was unclear on what the average starting age of this population was.
- Consider a [redacted] starting age (from MARIGOLD trial) to better reflect estimate of prevalent population although this estimate is uncertain
- Included [redacted] starting age scenarios on discontinuation graph (see next slide) to explore effect on overall treatment use

What do the committee consider as the appropriate starting age?

Abbreviations: CE, cost-effectiveness

Key Issue: Discontinuation



NICE ICERs for scenarios presented in Slide 24

Summary of company and base case and EAG exploratory base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG exploratory base case
Starting age	[redacted]	[redacted]
Treatment effect	Response based SF applied to baseline curve	As per company base case but noting extreme uncertainty
Stopping rule	Applied. All non-responders stop at 6 months.	Not applied in base case. (no face validity)
Discontinuation	Responder status and cycle dependent rates (see slide 15)	Add [redacted] discontinuation for all post cycle 29
Utility	Lo et al utility set	Lo et al utility set
Life expectancy	General population with [redacted] year median life expectancy as a scenario	[redacted] year median life expectancy
MRU costs	N/a	Inconsistencies in model corrected

EAG comments: Owing to the major outstanding limitations affecting treatment effect in 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."

Abbreviations: SF, seizure frequency

Company base case and scenario results

Company revised base case results

Technology	Total costs (£)	Total QALYs (weighted)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
Ganaxolone	[redacted]	[redacted]	[redacted]	[redacted]	£20,045	-0.002	0.355
ECM	[redacted]	[redacted]	[redacted]	[redacted]			

Company scenario analyses around discontinuation and life expectancy (deterministic)

No.	Scenario (applied to company base case)	Incremental costs (£) versus ECM	Incremental QALYs versus ECM	ICER (£/QALY) versus ECM
1	**Company revised base case**	[redacted]	[redacted]	£20,045
2	Without stopping rule	[redacted]	[redacted]	£29,792
3	With [redacted] year median life expectancy	[redacted]	[redacted]	£19,979
4	[redacted] discontinuation from cycle 29	[redacted]	[redacted]	£25,623
5	Scenarios 3 and 4 combined	[redacted]	[redacted]	£25,141
6	Scenario 4 with [redacted] responder plateau	[redacted]	[redacted]	£29,090
7	Scenario 5 with [redacted] responder plateau	[redacted]	[redacted]	£26,799

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; ECM, established clinical management

EAG exploratory base case results

Deterministic base case results

Technology	Total costs (£)	Total QALYs (weighted)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
Ganaxolone	[redacted]	[redacted]	[redacted]	[redacted]	£37,774	-1.441	-0.418
ECM	[redacted]	[redacted]					

No.	Scenario (applied to company base case)	Incremental costs (£) versus ECM	Incremental QALYs versus ECM	ICER (£/QALY) versus [insert comparator]
0	**Revised company base case**	[redacted]	[redacted]	£20,045
1	[redacted]year life expectancy	[redacted]	[redacted]	£19,979
2	[redacted] discontinuation after cycle 29	[redacted]	[redacted]	£25,623
3	No stopping rule	[redacted]	[redacted]	£29,794
4	Re-enable interpolation of treatment effect	[redacted]	[redacted]	£20,381
5	Correction of MRU costs	[redacted]	[redacted]	£20,232
6	Combined 1 to 5	[redacted]	[redacted]	£37,774

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; ECM, established clinical management

Tech team additional deterministic scenario analysis

Tech team scenario analyses around discontinuation – conditional on EAG exploratory base case

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus [insert comparator]	Incremental QALYs versus [insert comparator]	ICER (£/QALY) versus [insert comparator]
1	**EAG exploratory base case**	[redacted]	[redacted]	£37,774
2	With 10% responder plateau	[redacted]	[redacted]	£48,569
3	With 20% responder plateau	[redacted]	[redacted]	£58,110
4	With 30% responder plateau	[redacted]	[redacted]	£64,484
5	With 40% responder plateau	[redacted]	[redacted]	£68,154
6	Model starting age set to 6 years	[redacted]	[redacted]	£49,059
7	Scenario 2 plus 6 year starting age	[redacted]	[redacted]	£58,449

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; ECM, established clinical management

Committee key questions and preferred assumptions

- Is the modelling of seizure frequency and treatment effect suitable for decision making?
  - Responder/non-responder modelling approach?
  - Modelling of treatment effect?
  - Stopping rule?
- Does the model provide sufficiently plausible and robust estimates of SF for decision making?
- Does the committee consider that the company has addressed concerns around utility raised at ACM2?
- Has uncertainty around discontinuation been explored appropriately?

Parameter	Key Question	Scenarios	Preference
Utility	Which utility set best shows the relative effect of ganaxolone treatment?	Lo et al utility set	?
		Auvin et al utility set	
Treatment effect	Has the individual level HL shift analysis resolved uncertainty?	Cohort level HL responder analysis Individual level HL responder analysis	?
Discontinuation	How should discontinuation be applied to responders and (if stopping rule removed) non-responders?	Fix discontinuation to [redacted] after cycle 29?	?
		Apply a ___% plateau to discontinuation?	
Starting age	What starting age should be used in the model?	[redacted] years	?
		[redacted] years	
		Other starting age	

Backup slides

NICE National Institute for Health and Care Excellence

Other Issue: Utility correction factor

Background

- Noted that treatment effect may take some time to appear. Does not instantly accrue in Cycle 1
- See graph of responder treatment effect by cycle (not this has not been provided for “all-comers GNX” group.

Company ACM3 analyses

- Company new analysis includes a correction factor of 0.64 which is applied to responders in the first cycle and is intended to represent the fact that the treatment effect appears gradually throughout the first cycle.

[redacted]

EAG comments

- Agree in principle with adjusting first cycle utility as responders were not defined until month six. However, no clear explanation given for assuming a correction factor of 0.64. This approach was only accepted tentatively.
- Provide scenario with interpolated treatment effect for the first 3 cycles

Abbreviations: GNX, ganaxolone;

Key Issue: Discontinuation and life expectancy

Background

- Lack of evidence on life expectancy in CDD, previously assumed to be equal to general population
- Starting age is a key driver of CE estimates as dose is weight based up to 28kg (~11 years)

Company ACM3 analyses

- Clinical opinion considers median life expectancy between 30 and 40 realistic. Modelled median at [redacted] years as scenario.
- This was modelled by applying an SMR of 90 per cycle to estimates from the general population

EAG comments

- There is relatively weak evidence to support the assumption of a [redacted] year median life expectancy but included in exploratory base case. Noting it does not have a large effect on cost-effectiveness estimates.

What do the committee consider as the appropriate median life expectancy to model?

Abbreviations: SMR, standardised mortality ratio; CDD, cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

Marigold primary results – seizure frequency (reproduced from ACM1)

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

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

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

NICE

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