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Effects of ganaxolone on non-seizure outcomes in CDKL5 Deficiency Disorder: Double-blind placebo-controlled randomized trial

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Abstract

CDKL5 deficiency disorder (CDD) is a rare developmental and epileptic encephalopathy. Ganaxolone, a neuroactive steroid, reduces the frequency of major motor seizures in children with CDD. This analysis explored the effect of ganaxolone on non-seizure outcomes. Children (2–19

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years) with genetically confirmed CDD and ≥ 16 major motor seizures per month were enrolled in a double-blind randomized placebo-controlled trial. Ganaxolone or placebo was administered three times daily for 17 weeks. Behaviour was measured with the Anxiety, Depression and Mood Scale (ADAMS), daytime sleepiness with the Child Health Sleep Questionnaire, and quality of life with the Quality of Life Inventory-Disability (QI-Disability) scale. Scores were compared using ANOVA, adjusted for age, sex, number of anti-seizure mediations, baseline 28-day major motor seizure frequency, baseline developmental skills, and behaviour, sleep or quality of life scores.
101 children with CDD (39 clinical sites, 8 countries) were randomized. Median (IQR) age was 6 (3–10) years, 79.2 % were female, and 50 received ganaxolone. After 17 weeks of treatment, Manic/Hyperactive scores (mean difference 1.27, 95%CI −2.38,−0.16) and Compulsive Behaviour scores (mean difference 0.58, 95%CI −1.14,−0.01) were lower (improved) in the ganaxolone group compared with the placebo group. Daytime sleepiness scores were similar between groups. The total change in QOL score for children in the ganaxolone group was 2.6 points (95%CI −1.74,7.02) higher (improved) than in the placebo group but without statistical significance. Along with better seizure control, children who received ganaxolone had improved behavioural scores in select domains compared to placebo.

Keywords

CDKL5 deficiency disorder; Epilepsy; Anti-Seizure medication; Patient-reported outcomes

1. Introduction

CDKL5 deficiency disorder (CDD, MIM: 300203) is an X-linked developmental and epileptic encephalopathy caused by pathological variants in the *CDKL5* gene [1,2]. CDD is an extremely rare condition [3], with the incidence estimated to be approximately 1 in 40,000 live births [4]. It is characterized by early onset refractory seizures, global developmental impairments, cortical visual impairment, and other associated symptoms such as poor sleep and gastrointestinal dysfunction [2,5].

Epilepsy is the most prominent feature of CDD with onset of seizures during early infancy in most children [5–7]. Polypharmacy is common with nearly half in an international study using three or more antiseizure medications (ASM) [8], yet seizures remain difficult to manage and adverse effects are common [8]. Other treatment modalities include the ketogenic diet and vagal nerve stimulation and while benefits have been reported [9,10], seizures typically persist.

Addititive to the effects of the genetic variant [11], seizures may have adverse impacts on child development such as periods of developmental regression and other symptoms. Compared with a low seizure burden (<5 seizures/day), a high seizure burden (≥ 5 seizures/day) was associated with a small reduction in developmental skills after three to four years in a longitudinal study of 143 children and adults with CDD [12]. Seizures impose additional impacts on the child's alertness, sleep, behaviours and mood [13,14]. Together, seizures, functional impairments and associated symptoms have adverse effects on the child's quality of life (QOL) [8,15,16].

Ganaxolone is a synthetic analog of the neuroactive steroid allopregnanolone that acts as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors [17], and has demonstrated anticonvulsant properties in preclinical and clinical epilepsy studies [18]. Further, ganaxolone has been shown to improve behavioural abnormalities in a pre-clinical model of Angelman Syndrome [19] and improve depressive symptoms in women with postmenopausal depression [20] suggesting a potential for effects beyond just antiseizure properties. A recent multi-site international randomized placebo-controlled randomized controlled trial was conducted to evaluate the safety and efficacy of ganaxolone for the treatment of seizures in CDD [21]. The primary outcome was the percentage change in the 28-day frequency of major motor seizures (MMS), where the median change of −30•7 % (IQR −49•5 to −1•9) in the ganaxolone group compared to a median change of −6•9 % (IQR −24•1 to 39•7) in the placebo group (p = 0•0036) [21]. Ganaxolone is now the first approved medication specifically for CDD in patients two years of age and older. (https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treatment-seizures-associated-rare-disease-patients-two-years-age-and-older).

There is the possibility that ganaxolone could improve other aspects of the child's wellbeing, secondary to better control of seizures [21] or behaviours [22,23]. In this manuscript, we describe the effects of ganaxolone on non-seizure outcomes of behavior, sleep and QOL in CDD patients.

2. Materials and methods

2.1. Study design, participants and procedures

This was a multicentre, international double-blind, placebo-controlled, phase 3 clinical trial conducted at 39 outpatient clinics in eight countries (Australia, France, Israel, Italy, Poland, Russia, the UK, and the USA; NCT03572933). The trial was undertaken in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice and applicable national and local regulatory requirements. The protocol was approved by independent ethics committees or institutional review boards at each participating site, and written informed consent was provided for all patients by their guardians or legal representatives before screening or at the screening visit [21].

Full details of the trial are described elsewhere [21]. This trial included a double-blind phase followed by an open-label phase and findings from the double-blind phase are presented here. To summarize, 2-to-21-year individuals with genetically confirmed CDD were recruited if they had (1) had a history of early-onset seizures that were uncontrolled despite at least 2 ASMs, (2) 16 or MMS per month in the 8-week period before screening, and (3) a stable regimen of up to 4 ASMs during the month before screening [21].

The sample size was estimated from seizure frequency data obtained in a previous phase 2 trial (NCT02358538) of adjunctive ganaxolone in patients with rare genetic epilepsies, including CDD. A sample size of 100 patients (50 per group) was required to give 92 % power at a onesided α of 0•025 to detect a between-group difference of 30 % in the percentage change in 28-day major motor seizure frequency, assuming that the SD for the percentage change in 28-day seizure frequency was 44•5 %. Percentage change in 28-day

major motor seizure frequency was the primary outcome for the clinical trial. Participants were randomized (1:1) to receive either ganaxolone or placebo, as adjunctive therapy to their existing antiseizure medications, which was administered 3 times daily over a 17-week period. Randomization occurred between June 2018 and July 2020. Trial staff, patients and caregivers, investigators, and the sponsor (other than the investigational product manager) were masked to treatment allocation. Outcomes were assessed at baseline and at intervals across the treatment period [21].

2.2. Measures

2.2.1. Covariates—Covariates included child age at recruitment, sex, and the number of concomitant ASMs. Baseline 28-day frequency of MMS was measured using an electronic diary where parent caregivers documented daily seizure frequency and type. The development score was adapted from the CDKL5 Development Score [21]. The CDKL5 Development Score is a 7-item scale where items identify the acquisition of gross motor, hand and expressive communication milestones and the maximum score is 7 [24]. For this study, we modified the CDKL5 Development Score to describe smiling and eye contact; gross motor skills of sitting, crawling, standing and walking with and without support; and communication skills of making identifiable sounds for specific items, repeating sounds, saying single and multiple words, making a sentence and replying to a question with an identifiable word. For the Modified CDKL5 Development Score, data were collected during routine clinical exams and one point was allocated per item giving a maximum possible score of 15.

2.2.2. Outcome variables—Behaviour was measured using the Anxiety, Depression and Mood Scale (ADAMS), developed as a proxy-report measure to screen mental health in individuals with intellectual disability [25]. The ADAMS includes 28 items that are rated on a four-point Likert scale. Items group into five domains: Manic/Hyperactive Behaviour (n = 5), Depressed Mood (n = 7), Social Avoidance (n = 7), General Anxiety (n = 7) and Compulsive Behaviour (n = 3) [25]. Higher scores indicate more problematic behaviors [25].

Sleep was measured by the Children's Sleep Habits Questionnaire (CSHQ) [26]. The CSHQ includes 33 items which group into eight subscales. The CSHQ is widely used in paediatric populations and recent exploratory studies have explored its validity in genetic epilepsy conditions [27–29]. The Daytime Sleepiness (n = 8) subscale was used in this analysis because of its clinical relevance, with higher scores indicating more problematic sleep problems [26].

Quality of Life (QOL) was measured using the Quality of Life Inventory-Disability (QI-Disability) scale, developed for children with intellectual disability [30] and with validation data for CDD [8,15,16,31]. QI-Disability is a parent-reported measure, comprising 32 items which group into six domains: Physical Health (n = 4), Positive Emotions (n = 4), Negative Emotions (n = 7), Social Interactions (n = 7), Leisure and the Outdoors (n = 5) and Independence (n = 5). Domains are scored out of 100 with higher scores indicating better QOL. A total QI-Disability score is computed as the average of the domain scores [30].

2.2.3. Analysis—The effects of ganaxolone on post treatment scores for behaviour, sleep and QOL were assessed with Analysis of Covariance (ANCOVA) in their original assigned groups, adjusting for the relevant baseline score in addition to the following covariates: child age, sex, number of ASMs, baseline 28-day frequency of MMS and baseline developmental skills. We used Full Information Maximum Likelihood (FIML) to account for missing data in the post treatment scores and the confounding variables[32]. This method produces similar results to multiple imputation in reducing bias but has many advantages, notably ease of implementation[33]. Pearson correlation coefficients were used to explore within group relationships between % change in seizure frequency (primary outcome) and changes in non-seizure outcomes (secondary outcomes) for each group. Statistical analyses were performed using Stata 15.1 (StataCorp 2019) and statistical significance was assessed at the p = 0.05 level. Cohen's d values were calculated to indicate the magnitude of treatment effects.

3. Results

There were 101 participants in the trial, 50 in the ganaxolone group and 51 in the control group. Fig. 1 shows the flow of patients in the trial for analysis of primary [21] and secondary outcome variables. The characteristics of the trial participants are presented in Table 1. The median age was 6 (IQR 3–10) years, and the majority were female. The groups were similar at baseline for MMS frequency and the number of concurrent ASMs. There was an imbalance between the groups for this variable, but we adjusted for baseline values in the ANCOVA analyses. Baseline scores for the ADAMS, daytime sleepiness and QI-Disability scores were similar (Table 1). Table 1 also presents the post-treatment ADAMS, daytime sleepiness and QI-Disability scores and the number of completed post-treatment questionnaires.

Adjusted post treatment ADAMS subscale scores, except for Depressed Mood, were lower in the ganaxolone group, indicating fewer behaviour problems. Effects were statistically significant for the Manic/Hyperactive subscale (effect size = −1.27, 95 % Confidence Interval (CI) −2.38 to −0.16, p = 0.025) and for the Compulsive Behavior subscale (effect size = −0.58, 95%CI −1.14 to −0.01, p = 0.046), and the Cohen's d effect size values were between small and medium. Depressed Mood scores were increased but not significantly (effect size = 0.82, 95%CI −0.22 to 1.86, p = 0.122) (Table 2, Fig. 2).

Daytime sleepiness scores were similar in the ganaxolone and placebo groups (effect size = 0.65, 95%CI −0.44 to 1.74, p = 0.245). The post treatment total QI-Disability score was 2.64 (95%CI −1.74, 7.02) points higher in the ganaxolone group. Subscale scores were higher in the ganaxolone group post treatment, except for a very slight decrease in the Negative Emotions domain score, but none of these effects were statistically significant. The Cohen's d effect size values suggested small effects for the Social Interactions, Leisure and the Outdoors, and Independence domains, and the Total score. (Table 2, Fig. 3).

For the primary outcome, there was a 30.7 % median reduction in 28-day major motor seizure frequency in the ganaxolone group compared with a 6.9 % median reduction in the placebo group (p = 0•0036) [21]. Relationships between the change in the primary

outcome (% change in seizure frequency) and change in secondary outcome measures were mostly weak ($r < 0.3$). However, there was a significant positive relationship in the ganaxolone group and a significant negative relationship in the placebo group between % change in seizure frequency and Compulsive Behaviour domain scores, indicating better compulsive behaviour with larger reductions in seizures in the ganaxolone group. There was a moderate negative relationship for Anxiety in the placebo group but no relationship for the ganaxolone group. The QOL total and domain scores were higher indicating better QOL with greater % reductions in seizures for the ganaxalone but not the placebo group. However, the relationships were weak and non-significant (Table 3).

4. Discussion

This study is the first to evaluate the effect of ganaxolone, a new ASM for CDD in patients 2 years of age and older [21], on non-seizure outcomes. Adjusting for covariates, children in the ganaxolone group had significantly better behaviours in Manic/Hyperactive and Compulsive Behaviour domains. Overall, the ganaxolone group achieved slightly higher QOL scores but these differences did not reach significance. Understanding the effects of new medicines on how patients *feel and function* is a Food and Drug Administration (FDA) priority [34]. We know from a recent FDA Patient Focused Drug Development meeting for CDD, that families live with multiple impacts from their child's developmental and health challenges, and that day-to-day functioning is prioritized [35]. The presence of co-occurring neurodevelopmental and other symptoms is almost a rule in DEEs, ranging from intellectual disabilities to behavioural disorders, attention deficit and autistic spectrum disorders [36]. Interventions should aim not only to reduce seizure frequency but also improve other outcomes. Our study is contemporary in this regard and evaluates aspects of the child's functioning beyond seizures for children with CDD.

Altered mood and behaviours are recognized in many genetically caused neurodevelopmental disorders [37]. Mood and behaviour scores using the ADAMS have been reported for 129 individuals with CDD registered with the International CDKL5 Disorder Database and scores were generally comparable with our trial data [8]. In a case series of 127 individuals with CDD, 13 % had received medications to manage behavioural issues, the most common issue being irritability [38], suggesting that difficult behaviours have implications for how children with CDD live and their medical management. In this trial, ganaxolone led to small reduction in manic/hyperactive and compulsive behaviours although the effect sizes were between small and medium and the upper CI values for both domains were close to the line of no effect. Neuroactive steroids influence GABAergic and glutamatergic pathways and the production of serotonin and dopamine. There is evidence that neuroactive steroids modulate obsessive compulsive behaviours in the rat model [39] and in adults with obsessive compulsive disorder [23]. There is also evidence in the paediatric literature that dysregulation of neuroactive steroids is associated with schizophrenia, depression, eating disorders, aggressive behaviour and attention deficit disorder [22]. Additionally, we observed that greater % change in seizure frequency was associated with less compulsive behaviours for the ganaxolone and not the placebo, offering another potential explanation of the effect on behaviour. These findings provide evidence for

the plausibility of the ganaxolone effect on behaviour in CDD although the exact mechanism remains unclear.

Ganaxolone was associated with increased daytime napping as a binary outcome measure, 36 % in the ganaxolone group compared to 18 % in the placebo group [21]. Our analysis shows a very small effect size on daytime sleepiness scores from the CSHQ, an eight-item subscale that more fully represents the construct of daytime sleepiness (e.g. difficult to wake, seems tired, falls asleep easily in day). Sleep disturbances are common in CDD, necessitating medication use in approximately one quarter of individuals attending the CDKL5 Centre of Excellence clinics in the USA (40/126, 32 %) [38] and in a similar proportion of individuals in an international sample (38/129, 29 %) [16]. It is reassuring to observe that while there was some additional napping reported in the trial, there was no broader effect on additional daytime sleepiness behaviours.

There were positive effects on QOL scores following ganaxolone compared to placebo, but the effects were small and confidence intervals were wide and spanned the line of no effect. We had hypothesized that less frequent MMS would have positive impacts on QOL scores. Correlations between % change in seizures and changes in QOL suggested better QOL scores with greater seizure reduction, but effects were small and relationships were weak. It is feasible that it takes longer than 17 weeks to observe differences in QOL and that ongoing surveillance of ganaxolone could indicate different effects. Alternatively, QOL could be more dependent on other impairments relating to the child's functional abilities [8] or comorbidities such as insomnia or daytime sleepiness [16].

There are several limitations to this study. The sample size was calculated to evaluate a 30 % reduction in the primary seizure outcome, but this sample size may be inadequate to detect meaningful differences in non-seizure outcomes such as behaviour and QOL. The sample size was too small for mediation analyses to explore linkages between ganaxolone use and effects on seizures and non-seizure outcomes, although our analysis afforded some compensation by examining correlations between the primary outcome and changes in secondary outcomes by treatment group. We accounted for missing data in the post treatment scores and the confounding variables by using FIML, a recommended method for managing missing data [40], to reduce compromise on interpreting causal inferences. There could be potential confounding effects of other ASMs used by the children. Further, we do not know what differences in the outcomes are clinically meaningful for patients and their families.

This clinical trial was the first to evaluate a seizure medication for CDD, an ultra-rare and complex DEE causing refractory seizures and other comorbidities, and severe neurodevelopmental impairments. Beyond the evidence that ganaxolone was well-tolerated and effective in reducing MMS in CDD [21], we now report that ganaxolone slightly reduced hyperactivity and obsessive compulsive behaviours suggesting a potential role of ganaxolone in improving behaviour in CDD. Beyond evidence of more frequent daytime napping [21], ganaxolone was not associated with increased daytime sleepiness as measured in this study. There was a modest increase in QOL scores. To our knowledge, this is the first clinical trial for CDD to report non-seizure outcomes, critical information to understand

more fully how patients are living when using a new medicine [34,35]. Ongoing monitoring of the effects of ganaxolone on seizure and non-seizure outcomes is needed to confirm benefits.

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Declaration of competing interest

Jenny Downs: Consultancy for Marinus, Ultragenyx, Orion and Taysha; Clinical Trials with Anavex; All remuneration has been made to her department.

Peter Jacoby: No conflicts of interest to report.

Nicola Specchio: served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus and Takeda; has received speaker honoraria from Eisai, Biomarin, Livanova, Sanofi; has served as an investigator for Zogenix, Marinus, Biomarin, UCB, Roche.

Helen Cross: acted as an investigator for studies with GW Pharma, Ovid Therapeutics, Zogenix, Vitaflo, Marinius and Stoke Therapeutics. She has been a speaker and on advisory boards for GW Pharma, Zogenix, UCB and Nutricia; all remuneration has been paid to her department. She holds an endowed chair at UCL Great Ormond Street Institute of Child Health; she holds grants from NIHR, EPSRC, GOSH Charity, ERUK, the Waterloo Foundation and the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital.

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Alex Aimetti: Employee of Marinus Pharmaceuticals.

Gregory Busse: Previously an employee of Marinus Pharmaceuticals.

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Abbreviations

ADAMS	Anxiety, Depression and Mood Scale
ASM	Anti-seizure medication
CDD	CDKL5 Deficiency Disorder
CSHQ	Children's Sleep Habits Questionnaire
FIML	Full Information Maximum Likelihood
MMS	Major motor seizures
QI-Disability	Quality of Life Inventory - Disability
QOL	Quality of life

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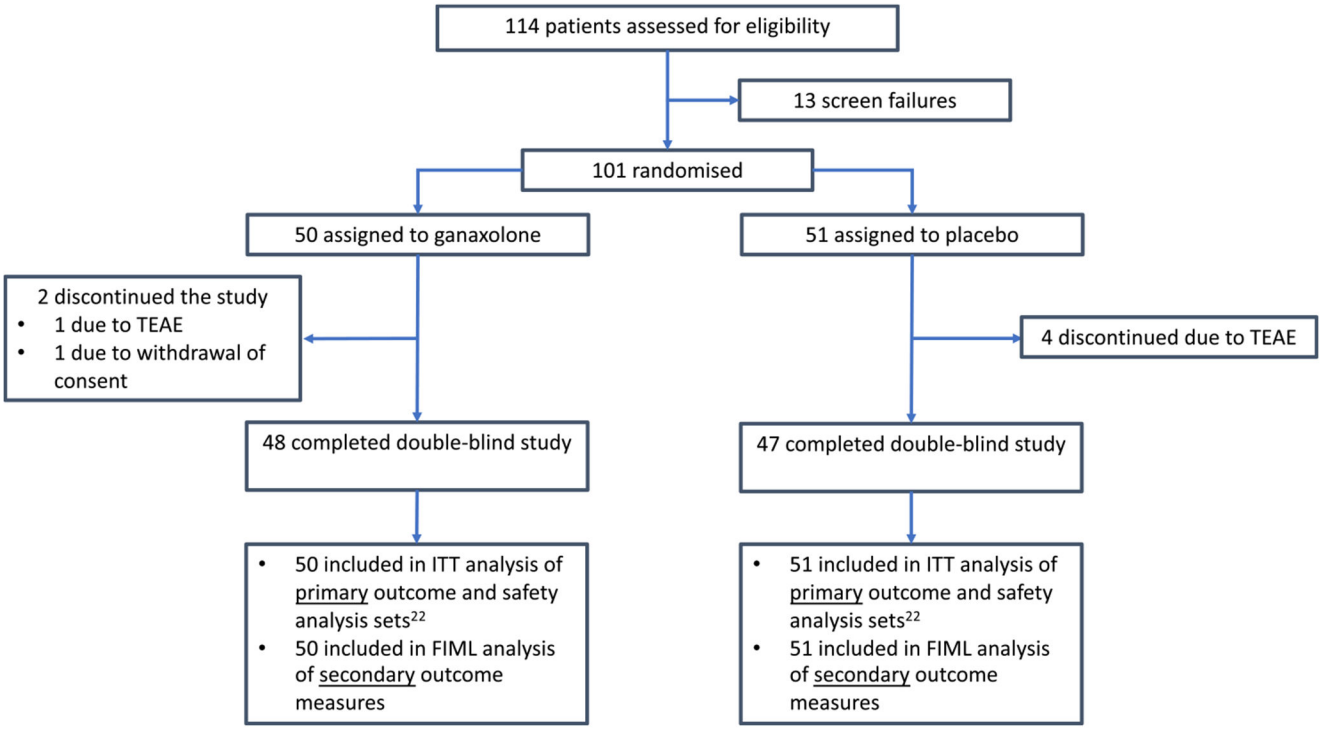

Fig. 1.
Trial profile. TEAE = treatment-emergent adverse events.

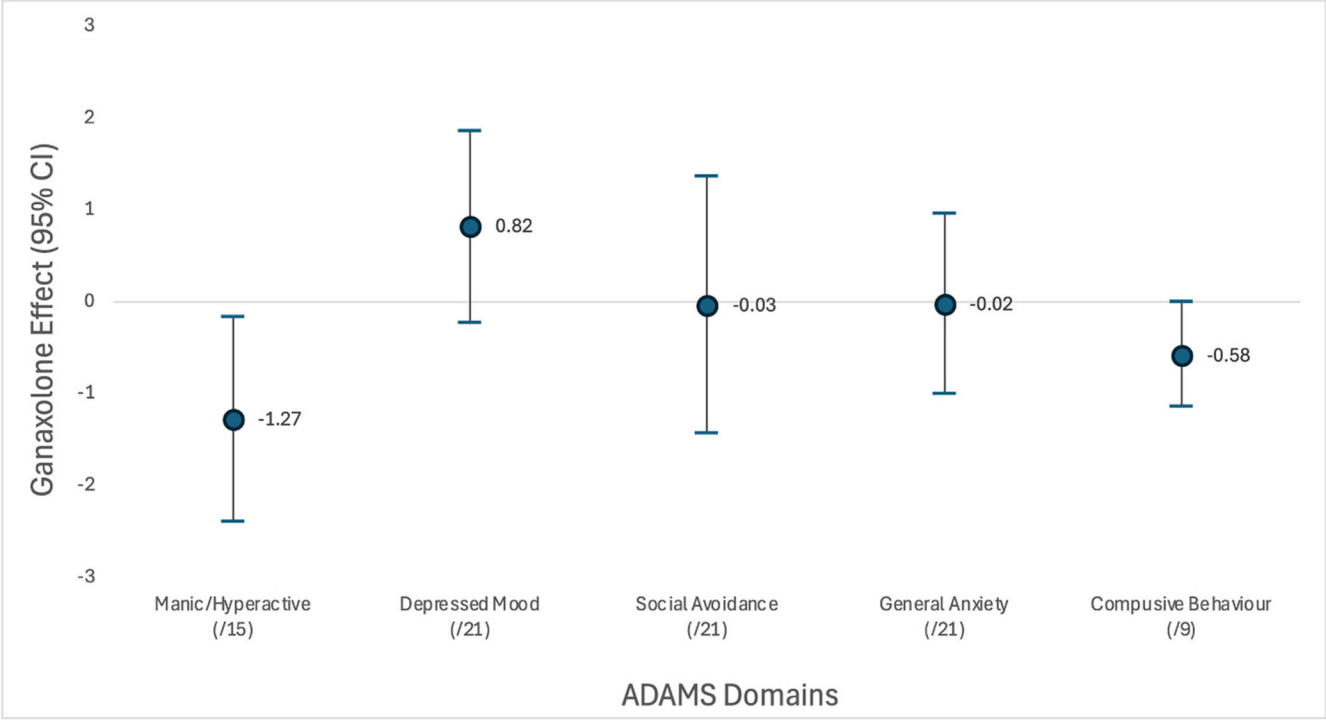

Fig. 2.

Forest plot indicating the adjusted post-treatment mean differences in ADAMS scores between ganaxolone and placebo groups. Negative differences indicate better behaviours in the ganaxolone group.

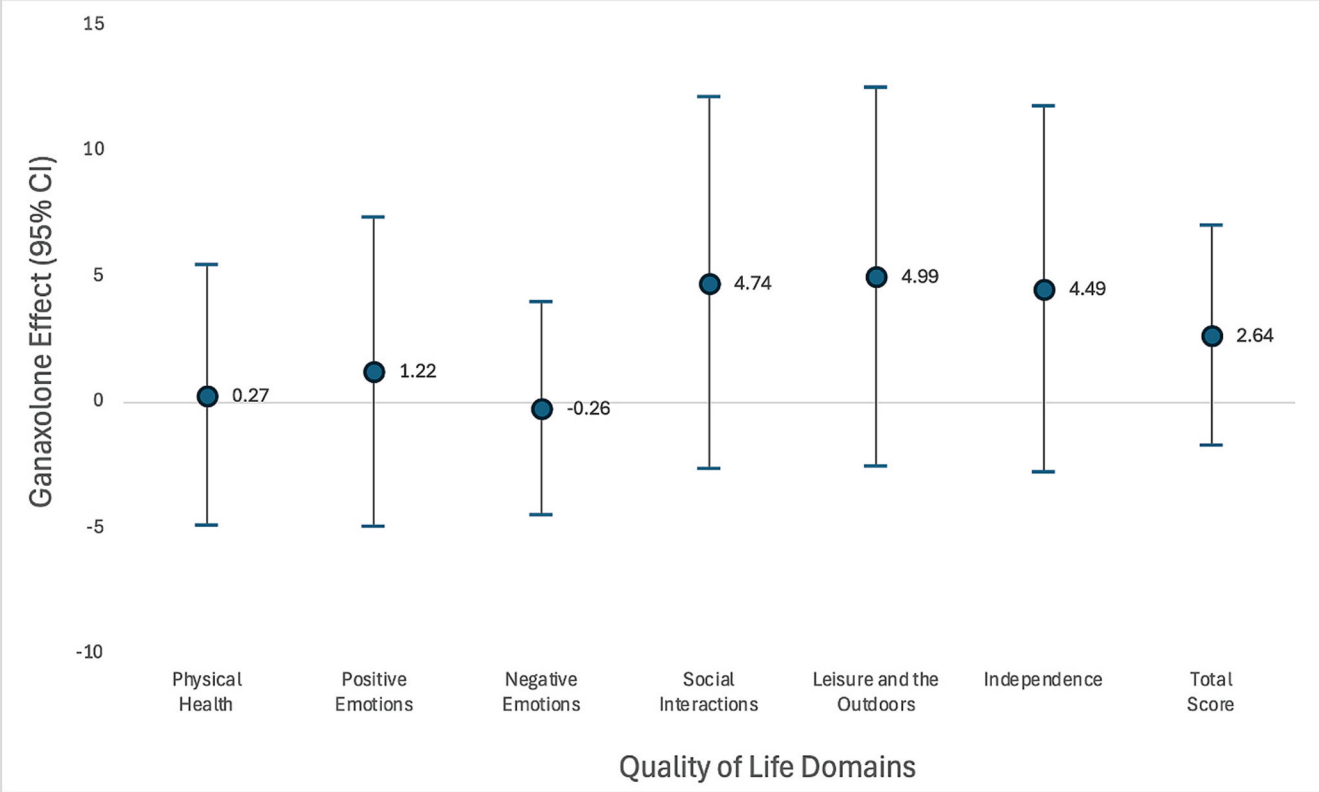

Fig. 3.

Forest plot indicating the adjusted post-treatment mean differences in QI-Disability domain and total scores between the ganaxolone and placebo groups. Positive differences indicate better quality of life in the ganaxolone group.

Table 1

Characteristics of trial participants at baseline and 17-week assessments by treatment group.

		Ganaxolone (N = 50)	Placebo (N = 51)
	Median (IQR) age (years) N = 101	5 (3–10)	7 (4–11)
	Female (%) sex N = 101	39 (78.0)	41 (80.4)
	Median (IQR) Baseline Development Score (/15)[a] N = 100	2 (1–5)	4 (1–7)
	Median (IQR) number of concurrent ASMs[b] N = 96	2 (2–4)	2 (1–3)
	Median (IQR) baseline 28-day seizure frequency N = 100	54.0 (31.3–147.3)	49.2 (18.7–120.0)
Anxiety, Depression and Mood Scale (ADAMS)	Mean (SD) Baseline ADAMS scores		
	Manic/Hyperactive (/15)[a] N = 97	7.0 (4.3)	6.3 (4.0)
	Depressed Mood (/21)[a] N = 97	5.7 (3.8)	4.8 (3.7)
	Social Avoidance (/21)[a] N = 96	7.7 (4.6)	6.3 (4.4)
	General Anxiety (/21)[a] N = 97	4.0 (3.6)	4.5 (4.1)
	Compulsive Behaviour (/9)[a] N = 97	2.2 (2.3)	2.2 (2.6)
	Mean (SD) Post-treatment ADAMS scores		
	Manic/Hyperactive (/15)[a] N = 89	4.8 (3.8)	5.2 (4.1)
	Depressed Mood (/21)[a] N = 90	5.5 (3.2)	4.0 (3.7)
	Social Avoidance (/21)[a] N = 87	6.8 (4.5)	5.8 (4.7)
	General Anxiety (/21)[a] N = 90	2.8 (3.0)	2.9 (3.6)
	Compulsive Behaviour (/9)[a] N = 88	1.3 (1.4)	1.8 (2.3)
Children's Sleep Habits Questionnaire	Mean (SD) Baseline Daytime Sleepiness subscale score (/24)[a] N = 78	12.1 (2.7)	12.3 (3.0)
	Mean (SD) Post-treatment Daytime Sleepiness subscale score (/24)[a] N = 78	12.6 (2.7)	12.2 (3.6)
Quality of Life Inventory – Disability	Mean (SD) Baseline QI-Disability scores[c]		
	Physical Health N = 100	62.6 (16.5)	63.8 (20.7)
	Positive Emotions N = 99	55.7 (25.6)	59.6 (24.7)
	Negative Emotions N = 99	79.5 (14.7)	77.9 (16.1)
	Social Interactions N = 98	43.0 (26.9)	42.1 (27.0)
	Leisure and Outdoors. N = 98	49.6 (27.3)	48.2 (30.8)
	Independence N = 100	23.1 (20.7)	27.0 (21.4)
	Total N = 98	53.0 (15.4)	53.3 (15.7)
	Mean (SD) Post-treatment QI-Disability scores[c]		
	Physical Health N = 91	64.3 (15.3)	65.0 (16.1)
	Positive Emotions N = 89	55.7 (19.4)	57.6 (22.3)
	Negative Emotions N = 89	84.0 (12.2)	82.8 (16.3)
	Social Interactions N = 89	47.4 (24.2)	42.5 (26.6)
	Leisure and the Outdoors N = 89	52.7 (23.2)	47.2 (29.5)
	Independence N = 89	28.7 (22.2)	27.3 (22.2)
	Total N = 87	56.3 (13.7)	54.3 (16.3)

[a] Maximum possible score presented in brackets.

[b] ASM – Anti-Seizure Medication.

[c] /100 for all QI-Disability scores.

Table 2

Non-seizure outcomes treatment effects from regression analysis using Full Information Maximum Likelihood.

	Effect size[a]	95 % Confidence Interval	Cohen's d[b]	p-value
ADAMS [c]				
Manic/Hyperactive (/15)	−1.27	−2.38 to −0.16	0.32	0.025
Depressed Mood (/21)	0.82	−0.22 to 1.86	0.24	0.122
Social Avoidance (/21)	−0.03	−1.43 to 1.37	0.01	0.968
General Anxiety (/21)	−0.02	−0.99 to 0.96	0.01	0.970
Compulsive Behavior (/9)	−0.58	−1.14 to −0.01	0.30	0.046
CSHQ [d]				
Daytime sleepiness subscale (/24)	0.65	−0.44 to 1.74	0.21	0.245
QI-Disability (/100)				
Physical Health	0.27	−4.91 to 5.45	0.02	0.918
Positive Emotions	1.22	−4.93 to 7.36	0.06	0.698
Negative Emotions	−0.26	−4.49 to 3.97	<0.01	0.903
Social Interactions	4.74	−2.65 to 12.13	0.19	0.209
Leisure and the Outdoors	4.99	−2.54 to 12.53	0.19	0.194
Independence	4.49	−2.78 to 11.76	0.20	0.226
Total Score	2.64	−1.74 to 7.02	0.17	0.237

[a]The effect size is the mean difference between post-treatment ganaxolone and placebo groups scores after adjustment for baseline score, age, sex, development score, number of concurrent ASMs and baseline seizure frequency.

[b]Cohen's d scores are commonly interpreted as small (d = 0.2), medium (d = 0.5), and large (d = 0.8).

[c]ADAMS - Anxiety, Depression and Mood Scale.

[d]CSHQ - Children's Sleep Habits Questionnaire.

Table 3

Pearson correlation coefficients between the primary outcome (% change in seizure frequency) and change in the secondary outcomes (behavior, daytime sleepiness, quality of life) for the treatment and placebo groups.

Measure	Domain	Correlation with % change in seizure frequency	
		Ganaxolone group	Placebo group
ADAMS[a]	Manic/Hyperactive	0.03 (p = 0.88)	−0.18 (p = 0.23)
	Depressed Mood	0.12 (p = 0.45)	−0.03 (p = 0.86)
	Social Avoidance	0.15 (p = 0.35)	−0.08 (p = 0.59)
	General Anxiety	0.01 (p = 0.97)	−0.61 (p < 0.001)
	Compulsive Behaviour	0.33 (p = 0.04)	−0.35 (p = 0.02)
CHSQ[b]	Daytime sleepiness	−0.05 (p = 0.80)	−0.18 (p = 0.33)
QL-Disability[c]	Physical Health	−0.09 (p = 0.55)	0.16 (p = 0.30)
	Positive Emotions	−0.26 (p = 0.11)	−0.06 (p = 0.69)
	Negative Emotions	−0.07 (p = 0.65)	0.13 (p = 0.39)
	Social Interactions	−0.16 (p = 0.30)	−0.03 (p = 0.86)
	Leisure and Outdoors	−0.26 (p = 0.09)	−0.06 (p = 0.71)
	Independence	0.18 (p = 0.26)	0.05 (p = 0.77)
	Total	−0.16 (p = 0.31)	0.03 (p = 0.86)

[a]ADAMS - Anxiety, Depression and Mood Scale, positive correlations indicate lower problematic behaviour scores with greater % reduction in seizure frequency.

[b]CSHQ - Children's Sleep Habits Questionnaire.

[c]QI-Disability – Quality of Life Inventory – Disability, negative correlations indicate better quality of life scores with greater % reduction in seizure frequency.