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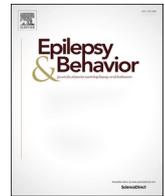
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Placebo response in patients with Dravet syndrome: Post-hoc analysis of two clinical trials

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ABSTRACT

Objective: Dravet syndrome is a rare, early childhood-onset epileptic and developmental encephalopathy. Responses to placebo in clinical trials for epilepsy therapies range widely, but factors influencing placebo response remain poorly understood. This study explored placebo response and its effects on safety, efficacy, and quality of life outcomes in patients with Dravet syndrome.

Methods: We performed exploratory post-hoc analyses of pooled data from placebo-treated patients from the GWPCARE 1B and GWPCARE 2 randomized controlled phase III trials, comparing cannabidiol and matched placebo in 2–18 year old Dravet syndrome patients. All patients had ≥ 4 convulsive seizures during a baseline period of 4 weeks.

Results: 124 Dravet syndrome-treated patients were included in the analysis (2–5 years: $n = 35$; 6–12 years: $n = 52$; 13–18 years: $n = 37$). Convulsive seizures were experienced by all placebo group patients at all timepoints, with decreased median convulsive seizure frequency during the treatment period versus baseline; the number of convulsive seizure-free days was similar to baseline. Convulsive seizure frequency had a nominally significant positive correlation with age and a nominally significant negative correlation with body mass index. Most placebo-treated patients experienced a treatment-emergent adverse event; however, most resolved quickly, and serious adverse events were infrequent. Placebo treatment had very little effect on reported Caregiver Global Impression of Change outcomes versus baseline.

Interpretation: Placebo had little impact on convulsive seizure-free days and Caregiver Global Impression of Change versus baseline, suggesting that these metrics may help differentiate placebo and active treatment effects in future studies. However, future research should further assess placebo responses to confirm these results.

1. Introduction

Dravet syndrome (DS) is a rare, early childhood-onset, developmental and epileptic encephalopathy (DEE), often caused by loss-of-function *SCN1A* gene mutations [1]. Generalized clonic or prolonged hemiclonic seizures typically begin in the first year of life, often triggered by fever or other causes of hyperthermia [2,3].

Placebo responses in epilepsy clinical trials vary widely, with 4–27% of placebo-treated patients achieving ≥ 50 % reduction in seizure frequency in epilepsy trials [4]. However, the factors that drive the diversity of placebo-related effects in safety, efficacy, and quality of life

(QoL) measurements in DS or other epilepsies are poorly defined.

Placebo response differed between children and adults in a systematic literature review (SLR) and meta-analysis (MA) of randomized controlled trials (RCT) investigating anti-seizure medications (ASM) in drug-resistant focal epilepsies, which found that placebo response was 19.0 ± 2.3 % in children compared with 9.9 ± 4.6 % in adults [5]. This increased placebo response in children, similar to trials for other medical and psychiatric medications [6,7], confounds accurate assessment of their active treatment responses in clinical trials.

Placebo responses have changed over time, with a recent SLR demonstrating an increase in the placebo response over time since 1990

Abbreviations: ASM, antiseizure medications; CGIC, Caregiver Global Impression of Change; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; MA, meta-analysis.

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in randomized clinical trials of adjunct antiseizure medications for medication-resistant focal onset epilepsy [8]. An earlier SLR and MA conducted in 2011 also identified a trend for higher placebo response rates in studies published between 1989 and 2009 in other, more common epilepsies [9]. The proportion of patients achieving a reduction in seizure rates during a clinical trial as a result of treatment with placebo nearly doubled over the 30-year period ($p = 0.001$) [9]. This trend was observed together with a parallel increase in response to active treatments, and was theorized to be related to changes in trial patient characteristics and monitoring procedures over time [9]. A 2023 study investigated regression to the mean as a potential cause for placebo response in epilepsy patients using a seizure diary simulator, and found that manipulation of eligibility criteria for RCTs had a predictable impact on regression to the mean, and therefore the placebo response [10].

Randomized, placebo-controlled trials are the ‘gold standard’ to assess ASM efficacy. However, demonstrating ASM superiority to placebo can be challenging since factors driving placebo responses are not fully understood. Assessing treatment effects in rare pediatric-onset epilepsies such as DS is further confounded by small, heterogeneous populations that vary in age and disease severity.

An improved understanding of placebo response drivers in DS in a trial setting could provide insight into the disorder as well as aid in designing clinical trials and interpreting the effects of novel therapies. Improved understanding may also help researchers identify therapeutic benefits by developing novel strategies to reduce placebo response and optimize outcome assessments of potential therapies.

We investigated placebo response by age group by performing exploratory post-hoc analyses of safety, efficacy, and QoL outcomes from the placebo arms of two pivotal trials of cannabidiol in patients with DS (GWPCARE 1B and 2) [11,12].

2. Material and methods

2.1. Data sources

These pooled post-hoc analyses used data from GWPCARE 1B (GWEP1332B; NCT02091375) and GWPCARE 2 (GWEP1424; NCT02224703), two phase III RCTs comparing cannabidiol and placebo in patients with DS. All patients had a confirmed DS diagnosis, were taking ≥ 1 ASM and had ≥ 4 convulsive seizures during a 4-week baseline period [11,12]. The GWPCARE 1B trial was a 1:1 double-blind, multicenter, 14-week comparison of treatment with 20 mg/kg/day cannabidiol versus matched placebo in 2–18 year old patients with DS [11], while GWPCARE 2 was a 2:2:1:1 double-blind, 14-week comparison of two dose levels of cannabidiol (10 mg/kg/day and 20 mg/kg/day) versus matched placebo (in two equivalent volumes) in children with DS aged 2–18 years [12]. Both studies compared adjunctive cannabidiol versus placebo for change from baseline in convulsive seizure frequency per 28 days or monthly during treatment.

Both trials included 4-week baseline, 14-week treatment (2 weeks of dose titration followed by 12 weeks of dose maintenance), 10-day taper, and 4-week safety follow-up periods. Visit 1 marked the start of the 4-week baseline period, throughout which caregivers recorded the number and types of seizures each day. Following the baseline period, patients were randomized to active treatment or placebo at Visit 2 (day 1). The end of the treatment period was the earlier of either day 99 or the day of last dose up to and including the end of treatment visit. The maintenance period was day 15 to the earlier of either day 99 or the day of last dose up to and including the end of treatment visit (Table S1). Across both studies, 124 patients were treated with placebo; full details were reported previously [11,12].

Both trials were approved by the review board or ethics committee at participating institutions [11,12]. All trials were conducted in accordance with the principles of the Declaration of the Helsinki and the International Conference on Harmonization Good Clinical Practice

guidelines. Patients and their parents or legal representatives provided written informed consent, and children mature enough to understand the trials provided assent. Parents or patients could withdraw from the trials at any time without prejudice.

2.2. Statistical analysis

As these analyses were exploratory and post-hoc, the studies were not designed to assess placebo response, and statistical testing was performed to examine relationships, but only provided nominal values. The analysis set was stratified by the following age groups: **2–5 years** ($N = 35$), **6–12 years** ($N = 52$) and **13–18 years** ($N = 37$).

Convulsive seizure frequency for each period (baseline and treatment) was calculated and analyzed as a 28-day average which was calculated as:

$$\frac{\text{Number of seizures reported during the period}}{\text{Number of days that seizure data were collected during the period}} \times 28$$

To examine the association of covariates and the potential interactions with convulsive seizure frequency, a multivariate stepwise analysis of covariance (ANCOVA) based on log-transformed data was performed. Seizure frequency during the treatment period and baseline period were log-transformed prior to analysis. If any values of 0 were observed, a value of 1 was added to all patients’ seizure frequency data prior to log transformation. The log-transformed seizure frequency during the treatment period was then analyzed using a hierarchical stepwise-selection model. The criteria for entry into and exit from the model was $p < 0.05$. The selection model was hierarchical, and an interaction term required that all corresponding lower-order terms were included. Log-transformed baseline seizure frequency was forced into the model. Table S2 reports all variables considered in the analysis. Convulsive seizure frequency was further stratified by concomitant ASM use for ASMs used by $>25\%$ of patients of the overall analysis population (i.e. clobazam, stiripentol, topiramate, valproate, levetiracetam). The correlation between convulsive seizure frequency during the baseline period and percentage change from baseline in convulsive seizure frequency during the treatment period was assessed using a Pearson correlation coefficient.

The number of convulsive seizure-free days during each period (baseline and treatment) was based on 28-day averages and calculated as:

$$\frac{\text{Number of seizures} - \text{free days reported during the period}}{\text{Number of days that seizure data were collected during the period}} \times 28$$

The change from baseline in convulsive seizure-free days per 28 days was analyzed for the treatment period using an ANCOVA. The model included baseline and age groups as covariates and treatment group as a fixed factor.

Incidences of treatment-emergent adverse events (TEAE; an adverse event [AE] that occurs only after treatment has begun) were assessed by time to first onset during the 2-week titration period, for Weeks 1–4, 5–8, and 9–12 of the maintenance period and for the safety follow-up. The time to first onset of an AE was calculated as “start date of an AE – the date of first dose of study medication + 1”; if patients had multiple occurrences of an AE, then the AE was counted once for the first occurrence only. The analysis of time to AE resolution summarized incidence of AEs that resolved within 4 weeks or after 4 weeks but before end of treatment. The time to AE resolution was calculated as “stop date of an AE - start date of an AE + 1”. If patients had multiple occurrences of an AE, then the AE was counted once for the occurrence with the longest time to AE resolution; if any AE did not resolve by treatment end, it was categorized as ongoing.

Proxy-reported patient outcomes and QoL were assessed with the Caregiver Global Impression of Change (CGIC) 7-point Likert scale using three categories of improvement (slightly, much or very much improved), three categories of worsening (slightly, much or very much

worse) or “no change”.

3. Results

3.1. Patient disposition and baseline characteristics

The 124 patients were divided into three age groups (2–5 years, 6–12 years, and 13–18 years) for the pooled analysis. The mean age (standard deviation; SD) across all age groups was 9.7 (4.7) years and the median (range) number of convulsive seizures per 28 days at baseline was 15.5 (3.0–770.5). The most commonly used ASMs were valproate ($n = 82$, 66.1 %), followed by clobazam ($n = 79$, 63.7 %) and stiripentol ($n = 45$, 36.3 %). Full baseline characteristics are described in [Table 1](#).

ASMs used during the baseline period were similar across age groups and sex, except for valproate and levetiracetam use between sexes ([Table 2](#)). Valproate was used by 72.4 % (42/58) of males and 60.6 % (40/66) of females, while levetiracetam was used by 32.8 % (19/58) of males and 18.2 % (12/66) of females. Among all patients, those experiencing atonic seizures had the lowest use of stiripentol (19.1 %; 4/21) and higher use of levetiracetam (42.9 %; 9/21) than other patients,

Table 1
Baseline demographics.

Characteristic	Placebo patients included (N = 124)
Age in years, mean (SD)	9.7 (4.7)
Age group, n (%)	
2–5 years	35 (28.2 %)
6–12 years	52 (41.9 %)
13–18 years	37 (29.8 %)
Sex, n (%)	
Female	66 (53.2 %)
Male	58 (46.8 %)
Race, n (%)	
White/Caucasian	105 (84.7 %)
Black/African American	6 (4.8 %)
American Indian or Alaska Native	6 (4.8 %)
Asian	5 (4.0 %)
Not Applicable	2 (1.6 %)
Country, n (%)	
USA	69 (55.6 %)
Poland	14 (11.3 %)
Spain	13 (10.5 %)
Netherlands	9 (7.3 %)
United Kingdom	8 (6.5 %)
France	6 (4.8 %)
Australia	3 (2.4 %)
Israel	2 (1.6 %)
Weight at baseline, kg, mean (SD)	34.6 (16.6)
BMI at baseline, kg/m ² , mean (SD)	18.9 (4.3)
Baseline convulsive seizures per 28 days, median (range)	15.5 (3–771)
Number of prior ASMs, mean (SD; range)	4.5 (2.9; 0–14)
Number of current ASMs, mean (SD; range)	3.0 (0.9; 1–5)
Current ASMs (≥ 25 %), n (%)	
Valproate	82 (66.1 %)
Clobazam	79 (63.7 %)
Stiripentol	45 (36.3 %)
Topiramate	32 (25.8 %)
Levetiracetam	31 (25.0 %)

Abbreviations: ASM: anti-seizure medication; BMI: body mass index; SD: standard deviation.

while patients with tonic-clonic seizures had the highest use of stiripentol (38.6 %; 44/114).

3.2. 2–5 Years age group

3.2.1. Convulsive seizure frequency

Median convulsive seizure frequency, calculated and analyzed as a 28-day average, decreased for patients aged 2–5 years during the placebo treatment period, with a median (range) percent change from baseline of -47.5 % (-68.4 to -5.3); the median (range) baseline seizure frequency was 11.4 (4.8–60.2), while the median (range) seizure frequency during the placebo treatment period was 5.8 (3.1–44.7; [Table S3](#)). When considering seizure frequency by concomitant ASM use, stiripentol was associated with the lowest median (range) convulsive seizure frequency during baseline (4.8 [4.0–6.0]) and placebo (3.5 [2.0–5.3]) treatment periods; the highest percentage change from baseline (-55.4 %; -70.4 – 0.0) was observed for patients treated with clobazam ([Table S4](#)).

3.2.2. Convulsive Seizure-Free days

Consistent with the decrease in median convulsive seizure frequency, median (range) number of convulsive seizure-free days per 28 days increased from baseline to treatment period (1.7 [0.3–5.4]; [Table 3](#)) for patients aged 2–5 years. The median (range) number of convulsive seizure-free days per 28 days was 21.0 (16.8–24.0) at baseline and increased to a median (range) of 24.0 (14.3–25.7) days during the treatment period.

3.2.3. AEs

Thirty of 35 (85.7 %) placebo-treated patients aged 2–5 years experienced at least one TEAE during the study period ([Table S3](#)). In total, 5/35 (14.3 %) patients experienced at least one serious TEAE, and treatment-related TEAEs (an adverse event attributed to the study drug, as assessed by the study investigator) were reported for 14/35 (40.0 %) patients. One patient discontinued the study medication due to a TEAE; no treatment-related serious TEAEs or treatment-related TEAEs leading to discontinuation were reported.

Among patients in the 2–5 years age group, 17/35 (48.6 %) reported the first onset of an AE during the 2-week titration period. The number of patients that experienced the first onset of an AE decreased over the 12-week maintenance period, from 8/35 (22.9 %) in Weeks 3–6 to 2/35 (6.7 %) beyond Week 14. Of the patients reporting AEs, 13/35 (37.1 %) resolved in 1–3 weeks and 7/35 (20.0 %) of patients reported AEs that resolved after > 4 weeks. Overall, 10/35 (28.6 %) of patients in this age group reported an ongoing AE at the end of treatment ([Table S3](#)).

3.2.4. CGIC

CGIC scores in the 2–5 years age group were relatively stable throughout the treatment period, with caregivers reporting ‘slightly improved’, ‘no change’ or ‘slightly worse’ for most patients (76.5–93.9 %) from day 15 to the last visit ([Table S3](#)).

3.3. 6–12 Years age group

3.3.1. Convulsive seizure frequency

Patients aged 6–12 years had a median (range) convulsive seizure frequency of 17.4 (8.7–68.0) at baseline and 19.9 (6.1–53.1) during the treatment period ([Table S5](#)). Median convulsive seizure frequency declined during the placebo treatment period versus baseline, with a median (range) percent change from baseline of -13.3 % (-37.3 – 19.9). Patients treated with topiramate had the highest percentage decrease (-37.8 %; -64.7 – 14.5 %) in convulsive seizure frequency from the baseline to placebo treatment period ([Table S6](#)).

3.3.2. Convulsive Seizure-Free days

The baseline median (range) number of convulsive seizure-free days

Table 2Antiseizure medication at baseline, by age group, sex, and seizure types experienced by patients (ASMs used by $\geq 25\%$ of patients).

		n (%)				
		Valproate	Clobazam	Stiripentol	Levetiracetam	Topiramate
Age	2–5 years (n = 35)	24 (68.6 %)	23 (65.7 %)	11 (31.4 %)	10 (28.6 %)	10 (28.6 %)
	6–12 years (n = 52)	35 (67.3 %)	31 (59.6 %)	20 (38.5 %)	13 (25.0 %)	11 (21.2 %)
	13–18 years (n = 37)	23 (62.2 %)	25 (67.6 %)	14 (37.8 %)	8 (21.6 %)	11 (29.7 %)
Sex	Female (n = 66)	40 (60.6 %)	44 (66.7 %)	27 (40.9 %)	12 (18.2 %)	16 (24.2 %)
	Male (n = 58)	42 (72.4 %)	35 (60.3 %)	18 (31.0 %)	19 (32.8 %)	16 (27.6 %)
Seizure type	Tonic (n = 38)	24 (63.2 %)	20 (52.6 %)	11 (29.0 %)	9 (23.7 %)	24 (63.2 %)
	Clonic (n = 25)	17 (68.0 %)	13 (52.0 %)	5 (20.0 %)	8 (32.0 %)	17 (68 %)
	Tonic-clonic (n = 114)	74 (64.9 %)	72 (63.2 %)	44 (38.6 %)	28 (24.6 %)	74 (64.9 %)
	Atonic (n = 21)	11 (52.4 %)	14 (66.7 %)	4 (19.1 %)	9 (42.9 %)	11 (52.4 %)

Abbreviations: ASM: anti-seizure medication.**Table 3**

Median number of convulsive seizure-free days per 28 days, patients aged 2–5 years (n = 35).

Age (n)	Median number of convulsive seizure-free days per 28 days (IQR)	
2–5 years (n = 35)	Baseline	21.0 (16.8–24.0) [n = 29]
	Treatment period	24.0 (14.3–25.7) [n = 35]
	Change from baseline to treatment period	1.7 (0.3–5.4) [n = 35]

Abbreviations: IQR: interquartile range.

for patients aged 6–12 years was 18.5 (12.0–23.0). Median (range) convulsive seizure-free days increased to 19.1 (13.1–24.0) during the placebo treatment period (Table 4).

3.3.3. AEs

Of patients aged 6–12 years, 42/52 (80.8 %) experienced at least one TEAE during the study. Treatment-related TEAEs and serious TEAEs were reported by 16/52 (30.8 %) and 7/52 (13.5 %) patients in this age group, respectively; no TEAEs led to discontinuation (Table S5).

More than half of patients (30/52; 57.7 %) experienced the first onset of an AE during the 2-week titration period, which decreased to 12/52 (23.1 %) reporting the first onset of AEs during the 12-week maintenance period. No patient in the 6–12 years age group reported the first onset of an AE after the 12-week maintenance period. Overall, 19/52 (36.5 %) of patients in this age group reported an AE that resolved within 1–3 weeks; a smaller proportion (14/52; 26.9 %) experienced an ongoing AE at the end of treatment (Table S5).

3.3.4. CGIC

In the 6–12 years age group, caregivers reported that only a small proportion of patients were ‘much/very much improved’ (6.0–12.2 %) or ‘much/very much worse’ (0.0–5.9 %) from day 15 to the last visit, with most indicating ‘no change’ or that patients were ‘slightly improved or worse’ (Table S5).

Table 4

Median number of convulsive seizure-free days per 28 days, patients aged 6–12 years (n = 52).

Age (n)	Median number of convulsive seizure-free days per 28 days (IQR)	
6–12 years (n = 52)	Baseline	18.5 (12.0–23.0) [n = 50]
	Treatment period	19.1 (13.1–24.0) [n = 51]
	Change from baseline to treatment period	1.0 (-1.4–3.2) [n = 51]

Abbreviations: IQR: interquartile range.

3.4. 13–18 Years age group

3.4.1. Convulsive seizure frequency

Median (range) convulsive seizure frequency was similar at baseline (13.0; 7.0–30.9) and during the treatment period (14.0; 7.0–31.1) for patients aged 13–18 years (Table S7). The median (range) percent change from baseline in convulsive seizure frequency was -17.9 % (-46.1–5.4 %) for this group. Patients treated with topiramate had the lowest median (range) convulsive seizure frequency during the baseline (8.0; 7.0–36.0) and treatment (10.0; 7.0–35.7) periods, and also experienced the highest percentage decrease from baseline to treatment period (-20.9 %; -51.4–10.7) together with clobazam-treated patients (-20.9 %; -46.1 to -3.9) (Table S8).

3.4.2. Convulsive Seizure-Free days

Patients aged 13–18 years had a median (range) of 20.0 (11.6–22.0) convulsive seizure-free days per 28 days at baseline and a median (range) of 19.8 (13.0–22.9) convulsive seizure-free days per 28 days during the treatment period (Table 5).

3.4.3. AEs

Most patients aged 13–18 years (30/37; 81.1 %) experienced at least one TEAE during the study period. Treatment related TEAEs were reported for 18/37 (48.6 %) patients in this age group, while 1/37 (2.7 %) experienced a serious TEAE; no TEAEs led to discontinuation (Table S7).

During the two-week titration period, 13/37 (35.1 %) patients reported the first onset of an AE, and 17/37 (45.9 %) experienced the first onset of an AE in the 12-week maintenance period. No patients in this age group reported the first onset of an AE following the study period. Time to AE resolution was 1–3 weeks for 14/37 (37.8 %) patients, while 4/37 (10.8 %) patients experienced an AE that required more than four weeks to resolve, and 12/37 (32.4 %) reported an ongoing AE at the end of treatment (Table S7).

3.4.4. CGIC

Most caregivers reported that patients aged 13–18 years were ‘slightly improved’ (16.2–32.4 %), ‘slightly worse’ (2.7–11.1 %) or had

Table 5

Median number of convulsive seizure-free days per 28 days, patients aged 13–18 years (n = 37).

Age (n)	Median number of convulsive seizure-free days per 28 days (IQR)	
13–18 years (n = 37)	Baseline	20.0 (11.6–22.0) [n = 37]
	Treatment period	19.8 (13.0–22.9) [n = 37]
	Change from baseline to treatment period	1.1 (-1.4–4.1) [n = 37]

Abbreviations: IQR: interquartile range.

'no change' (43.2–56.8 %) from day 15 to the last visit (Table S7).

3.5. Multivariate stepwise selection ANCOVA

To explore potential relationships between convulsive seizure frequency and other factors, a multivariate stepwise selection ANCOVA of log-transformed convulsive seizure frequency during the treatment period was performed (Table 6). Log-transformed baseline seizure rate demonstrated a nominally statistically significant positive association with log-transformed convulsive seizure frequency during the treatment period ($\beta = 0.990$, nominal $p < 0.0001$). However, further analysis showed that baseline seizure rate was *not* nominally significantly correlated with the percentage change from baseline in seizure frequency during the treatment period ($\beta = -0.073$, nominal $p = 0.4201$). This suggests that whilst a patient's convulsive seizure frequency during the study was likely influenced by seizure frequency at baseline, whether this frequency changed or not during the study was unlikely to be affected by their seizure frequency at baseline.

Further to this, age was positively associated with log-transformed convulsive seizure frequency ($\beta = 0.042$, nominal $p = 0.0017$), while body mass index (BMI) was negatively associated with log-transformed convulsive seizure frequency ($\beta = -0.038$, nominal $p = 0.0086$).

4. Discussion

Post-hoc analyses of the placebo arms of two pivotal DS cannabidiol trials found that placebo-treated patients experienced convulsive seizures across all timepoints, but that the frequency of seizures declined during the treatment period when compared with baseline. This decrease was most pronounced for the youngest patients, aged 2–5 years (–47.5 %). While some or most of the decline in convulsive seizure frequency may be attributable to placebo response, patients commonly enter a clinical trial when their disease is most severe [13,14]. This suggests that decreased convulsive seizure frequency during the placebo or active treatment period may hypothetically represent a regression to the mean. However, the decrease in convulsive seizure frequency was smaller for patients aged 6–12 years (–13.3 %) and 13–18 years (–17.9 %) during the treatment period. Therefore, whilst some patients may have individually demonstrated regression to the mean, in aggregate any regression in these groups, which comprised 71.8 % of our study population, was less pronounced.

In contrast, convulsive seizure-free days remained largely unchanged in this placebo group during the treatment period as compared with baseline, with the possible exception of patients aged 2–5 years. The apparent stability of convulsive seizure-free days throughout the treatment period of these two trials suggests that this outcome was less influenced by placebo response than convulsive seizure frequency. These results contrast to those in the active treatment groups in the randomized clinical trials, whereby seizure frequency was reduced and a greater number of patients receiving active treatment became seizure-free [11,12]. This indicates the potential use of this metric to

Table 6

Multivariate stepwise selection ANCOVA of log-transformed convulsive seizure frequency in patients receiving placebo during the treatment period.

Parameter	Parameter estimate (log ratio)	95 % CI	P-value
log(baseline seizures per 28 days)	0.990	(0.90, 1.08)	<0.0001
Age	0.042	(0.02, 0.07)	0.0017
BMI	–0.038	(–0.07, –0.01)	0.0086

GWEP1332 Part B and GWEP1424, ITT Analysis Set; convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures. All p-values are nominal.

Abbreviations: ANCOVA: analysis of covariance; BMI: body mass index; CI: confidence interval; ITT: intention to treat.

differentiate active and placebo groups in future studies, though further exploration of this initial insight is required. However, it should be noted that regression to the mean in patients receiving placebo in epilepsy trials may also be affected by other factors such as eligibility criteria of the trial, as shown by Goldenholz *et al.* and therefore these factors should be considered carefully in clinical trial design [10].

High levels of placebo-treated patients (~80 %) reported a TEAE, the incidence of which peaked during the titration period; most AEs resolved within four weeks and only one patient (in the 2–5 years age group) discontinued due to a TEAE. These results contrast with those of an SLR assessing AE incidence in placebo-treated patients in RCTs for refractory focal epilepsy, where 60 % of patients report AEs and almost 1 in 30 patients withdrew from study medication [15]. Some AEs in these placebo-treated patients may have resulted from baseline ASMs or sesame oil in the placebo formulation, especially regarding gastrointestinal-related AEs [16]. The higher frequency of first AE onset during the titration period, followed by resolution during the maintenance phase for most AEs, is consistent with mild effects to which the subject developed tolerance (e.g., gastrointestinal effects of sesame oil) or heightened caregiver vigilance during the initial study period.

Although AE incidence varied throughout the treatment period, caregivers largely reported that patients were 'slightly improved', 'slightly worse' or had 'no change', indicating that their perception of the patient's QoL was stable throughout the study period irrespective of AEs. However, the negative effects of AEs may have been countered by positive effects of reduced seizure frequency, observed across all age groups. Some level of improvement was reported for slightly more than half of the patients in youngest age group at the end of treatment and last visit, which may indicate a perceived improvement due to placebo response during the treatment period. The stability of the CGIC responses suggests that caregiver-reported QoL measurements may have been less influenced than other outcomes by placebo treatment in the two explored trials, and may help distinguish between placebo response and response to active treatment as a trial outcome. However, an improved QoL in the cannabidiol versus placebo group was not consistently reported by the randomized placebo-controlled trials [11,12], suggesting that QoL cannot wholly substitute for convulsive seizure frequency or measures in DS patients.

We examined the relationship between seizure frequency and other factors in a multivariate ANCOVA and found that age was positively correlated with convulsive seizure frequency, while BMI was negatively correlated. This may reflect the observation that patients aged 2–5 years had the lowest median convulsive seizure frequency at baseline and during the treatment period. However, independent of age group, a correlation between baseline seizure frequency and subsequent percentage change in seizure frequency could not be observed.

The negative correlation observed between BMI and convulsive seizure frequency could be related to ASM use, which can cause weight change. Sodium valproate, used by 66.1 % of patients in this study, is commonly associated with weight gain, while topiramate, used by 25.8 % of patients, can cause weight loss [17]. Combinations of medications associated with improved seizure control may correlate with a tendency for weight changes, and vice versa. Differences in median convulsive seizure frequency were also observed for all age groups when stratified by concomitant ASM use, including sodium valproate and topiramate; however, multivariate ANCOVA did not result in a statistical correlation of valproate use and convulsive seizure frequency. Seizures and seizure patterns can also affect weight, for example by impacting hormones involved in appetite regulation [18], and patients' body weight may have been further influenced by AEs such as decreased appetite. Since age was adjusted for in the multivariate analysis and would have biased the correlation in the opposite direction, it is unlikely that this was related to the association of BMI and convulsive seizure frequency.

This post-hoc analysis had some limitations. First, we performed post-hoc analyses of data from the placebo arms of two clinical trials of cannabidiol that were not designed to explore placebo response.

Complementary analyses of recent trials of other ASMs in DS, such as fenfluramine [19,20], or additional research specifically designed to assess placebo response may further support these findings. Further, while the patients were not receiving any active treatment, they were still enrolled in a clinical trial and received an intervention, i.e. placebo treatment. This could have resulted in selection bias, as patients with a more severe disease history may have been more likely to be recruited, as well as possible observer bias based on caregivers' corresponding expectations or hopes for a positive treatment effect. Similarly, these analyses were based on a relatively short observation period (up to ~20 weeks); data from longer periods of follow-up could be informative. Finally, inherent difficulties in measuring non-convulsive seizures led us to primarily focus on convulsive seizures; our findings may not represent the number of non-convulsive seizures experienced by patients.

5. Conclusions

Overall, this post-hoc analysis provides insight into possible placebo response and its effects on convulsive seizures, AEs and QoL for patients with DS. Placebo had minimal impact on convulsive seizure-free days and CGIC versus baseline, suggesting that these metrics may help differentiate placebo and active treatment effects in future studies, though further study is required. These findings are especially relevant for younger patients, where previous research on the topic is lacking. [5] It will be valuable to compare these results with similar analyses for other epilepsy syndromes, such as Lennox-Gastaut syndrome.

Data accessibility statement

Full study details and data have been previously reported [11, 12].

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Authors' contributions

Substantial contributions to study conception and design: **RN, KH, RL, CN, OD**; substantial contributions to analysis and interpretation of the data: **RN, KH, CN, OD**; drafting the article or revising it critically for important intellectual content: **RN, KH, RL, CN, OD**; final approval of the version of the article to be published: **RN, KH, RL, CN, OD**.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CRediT authorship contribution statement

Orrin Devinsky: Writing – review & editing, Methodology, Conceptualization. **Kerry Hyland**: Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Rachael Loftus**: Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Charlotte Nortvedt**: Writing – review & editing, Methodology, Conceptualization. **Rima Nabbout**: Writing – review & editing, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary material

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