Supplementary Online Content

Miller I, Scheffer IE, Gunning B, et al; GWPCARE2 Study Group. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome: a randomized clinical trial. Published online March 2, 2020. *JAMA Neurol.* doi:10.1001/jamaneurol.2020.0073

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Eligibility Criteria

Inclusion Criteria	
1.	Patient and/or parent(s)/legal representative must be willing and able to give informed assent/consent for participation in the study.
2.	Patient and their caregiver must be willing and able (in the investigator's opinion) to comply with all study requirements.
3.	Patient must be male or female aged between two and 18 years (inclusive).
4.	Patient must have a documented history of DS which is not completely controlled by current AEDs.
5.	Patient must be experiencing four or more convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the first 28 days of the baseline period.
6.	Patient must be taking one or more AEDs at a dose which has/have been stable for at least four weeks.
7.	All medications or interventions for epilepsy (including ketogenic diet and VNS) must have been stable for four weeks prior to screening and patient and caregiver are willing to maintain a stable regimen throughout the study. The ketogenic diet and VNS treatments are not counted as an AED.
8.	Patient and/or parent(s)/legal representative is willing to allow his or her primary care practitioner and consultant to be notified of participation in the study.
9.	Patient has completed their IVRS telephone diary on at least 25 days of the baseline period; patients who are non-compliant will be deemed ineligible to continue.
Exclusion Criteria	
1.	Patient has clinically significant unstable medical conditions other than epilepsy.
2.	Patient has clinically relevant symptoms or a clinically significant illness in the four weeks prior to screening or randomization, other than epilepsy.
3.	Patient has clinically significant abnormal laboratory values, in the investigator's opinion, at screening or randomization.
4.	Patient has clinically relevant abnormalities in the ECG measured at screening or randomization.
5.	Patient has any concurrent cardiovascular conditions which will, in the investigator's opinion, interfere with the ability to assess their ECGs.
6.	Patient has a history or presence of alcohol or substance abuse within the last two years prior to the study or daily consumption of five or more alcohol-containing beverages.
7.	Patient is currently using, or has in the past used, recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex®) within the three months prior to study entry.
8.	Patient is unwilling to abstain from using recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex) during the study.
9.	Patient has a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure due to postural changes.
10.	Patient has ingested alcohol in the 24-hour period prior to the first study visit and/or is unwilling to abstain from drinking alcohol throughout the treatment period.
11.	Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMPs (e.g., sesame oil).
12.	Female patient is of childbearing potential or male patient's partner is of childbearing potential; unless willing to ensure that they or their partner use highly effective contraception for the duration of the study and for three months thereafter. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.
13.	Female patient who is pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the study and for three months thereafter.
14.	Patient has been part of a clinical trial involving another IMP in the previous six months.
15.	Patient is taking felbamate and they have been taking it for less than one year prior to screening.
16.	Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, may influence the result of the study, or affect the patient's ability to participate in the study.

17.	Patient had significantly impaired hepatic function at screening (Visit 1) or randomization (Visit 2), defined as any of the following: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN); ALT or AST >3 × ULN and [total bilirubin (TBL) >2 × ULN or international normalized ratio (INR) >1.5]; ALT or AST >3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). This criterion could only be confirmed once the laboratory results were available; patients randomized into the trial who were later found to meet this criterion were withdrawn from the trial.
18.	Following a physical examination, the patient has any abnormalities that, in the opinion of the investigator, would prevent the patient from safe participation in the study.
19.	Patient is unwilling to abstain from donation of blood during the study.
20.	There were plans for the patient to travel outside their country of residence during the trial.
21.	Patient had previously randomized into the trial.
22.	Any history of suicidal behavior or any suicidal ideation of type four or five on the C-SSRS at screening.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, 12-lead electrocardiogram; IMP, investigational medicinal product; INR, international normalized ratio; TBL, total bilirubin; ULN, upper limit of normal.

eTable 2. Other Secondary Outcomes

	Placebo	Cannabidiol, 10 mg/kg/day	Cannabidiol, 20 mg/kg/day	Cannabidiol, 10 mg/kg/day vs. Placebo	Cannabidiol, 20 mg/kg/day vs. Placebo
Percentage of patients with increase or reduction in convulsive seizure frequency during the treatment period	**n/N (%)**	**n/N (%)**	**n/N (%)**		
> 25% increase	8/65 (12.3)	12/66 (18.2)	8/67 (11.9)	n/a	n/a
≥ 0% to ≤ 25% increase	9/65 (13.8)	4/66 (6.1)	4/67 (6.0)	n/a	n/a
> 0% to < 25% reduction	16/65 (24.6)	13/66 (19.7)	8/67 (11.9)	n/a	n/a
≥ 25% to < 50% reduction	15/65 (23.1)	8/66 (12.1)	14/67 (20.9)	n/a	n/a
≥ 50% to < 75% reduction	13/65 (20)	9/66 (13.6)	21/67 (31.3)	n/a	n/a
≥ 75% reduction	4/65 (6.2)	20/66 (30.3)	12/67 (17.9)	n/a	n/a
Percentage of patients with ≥ 25%, ≥ 75%, and 100% reduction in convulsive seizure frequency during the treatment period	**n/N (%)**	**n/N (%)**	**n/N (%)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
≥ 25% reduction	32/65 (49.2)	37/66 (56.1)	47/67 (70.1)	1.32† (0.66, 2.62)	2.42† (1.19, 4.95)
≥ 75% reduction	4/65 (6.2)	20/66 (30.3)	12/67 (17.9)	6.63† (2.12, 20.73)	3.33† (1.01, 10.92)
100% reduction	1/65 (1.5)	2/66 (3.0)	3/67 (4.5)	2.00† (0.18, 22.61)	3.00† (0.30, 29.61)
Change in non-convulsive seizure frequency during the treatment period	**n/N**	**n/N**	**n/N**	**Percentage reduction from placebo (95% CI)[a]**	**Percentage reduction from placebo (95% CI)[a]**
	51/65	50/66	48/67	40.7† (12.4, 59.9)	20.6† (-18.1, 46.6)
Change in subtype of convulsive seizures during the treatment period	**n/N**	**n/N**	**n/N**	**Percentage reduction from placebo (95% CI)**	**Percentage reduction from placebo (95% CI)**
Tonic-clonic	62/65	57/66	62/67	20.0† (-9.6, 41.6)	18.5† (-11.5, 40.4)
Tonic	26/65	24/66	31/67	23.6† (-52.6, 61.7)	3.7† (-85.3, 50.0)
Atonic	10/65	9/66	11/67	89.6† (63.0, 97.1)	52.1† (-37.6, 83.3)
Clonic	14/65	18/66	17/67	48.6† (-6.7, 75.2)	51.0† (-6.5, 77.4)
Myoclonic	34/65	24/66	26/67	37.9† (-12.7, 65.7)	36.4† (-13.8, 64.4)
Countable partial	27/65	21/66	20/67	-29.5 (-162.8, 36.2)	-118.1 (-351.8, -5.3)
Other partial	8/65	1/66	9/67	100† (n/a, 100)	-97.1 (-1605, 77.2)
Absence	23/65	26/66	35/67	44.8† (-9.9, 72.2)	0.4† (-86.3, 46.7)
Caregiver global impression of change in seizure duration[b]	**n/N**	**n/N**	**n/N**	**Odds Ratio (95% CI)[c]**	**Odds Ratio (95% CI)[c]**
Tonic-clonic	50/65	50/66	50/67	3.27† (1.48, 7.24)	1.68† (0.78, 3.62)
Tonic	19/65	20/66	19/67	1.78† (0.51, 6.16)	1.67† (0.48, 5.82)
Atonic	11/65	5/66	9/67	2.70† (0.29, 25.03)	0.76 (0.12, 4.90)
Clonic	15/65	17/66	15/67	3.61† (0.80, 16.31)	4.53† (0.94, 21.74)
Myoclonic	29/65	24/66	21/67	2.51† (0.83, 7.60)	2.20† (0.70, 6.90)
Countable partial	22/65	15/66	14/67	0.84 (0.22, 3.17)	1.70† (0.43, 6.67)

	Placebo	Cannabidiol, 10 mg/kg/day	Cannabidiol, 20 mg/kg/day	Cannabidiol, 10 mg/kg/day vs. Placebo	Cannabidiol, 20 mg/kg/day vs. Placebo
Other partial	6/65	4/66	7/67	0.91 (0.08, 10.68)	0.96 (0.10, 9.70)
Absence	17/65	18/66	29/67	4.44[†] (1.13, 17.39)	3.01[†] (0.88, 10.30)
Change from baseline in sleep disruption 0–10 numerical rating scale score	**n/N**	**n/N**	**n/N**	**Treatment Difference (95% CI)[d]**	**Treatment Difference (95% CI)[d]**
Last visit	64/65	66/66	65/67	0 (-0.9, 0.8)	-0.1 (-0.9, 0.8)
Change from baseline in Epworth Sleepiness Scale score	**n/N**	**n/N**	**n/N**	**Treatment Difference (95% CI)[d]**	**Treatment Difference (95% CI)[d]**
Last visit	64/65	66/66	66/67	-0.55 (-1.86, 0.75)	0.74 (-0.57, 2.05)
Change from baseline in Quality of Life in Childhood Epilepsy score	**n/N**	**n/N**	**n/N**	**Treatment Difference (95% CI)[d]**	**Treatment Difference (95% CI)[d]**
End of treatment	49/65	57/66	53/67	3.8[†] (-0.1, 7.8)	1.8[†] (-2.2, 5.8)
Change from baseline in Vineland Adaptive Behavior Scales (Second Edition) Adaptive Behavior Composite Standard Score	**n/N**	**n/N**	**n/N**	**Treatment Difference (95% CI)[d]**	**Treatment Difference (95% CI)[d]**
Last visit	37/65	32/66	27/67	-0.4 (-2.5, 1.7)	0.0 (-2.2, 2.2)

Abbreviation: n/a, not applicable; CI, confidence interval.

All of the above other secondary outcomes are from the intention-to-treat analysis set and are considered exploratory as there was no adjustment to account for multiple comparisons.

[a] Calculated using negative binomial regression.

[b] For each seizure type, only patients with at least one seizure for the corresponding seizure type, reported at any time during the study, are included.

[c] Analyzed using an ordinal logistic regression model with age group (2–5, 6–12, and 13–18 years) as a covariate and treatment group as a fixed factor.

[d] Analyzed using an ANCOVA model with baseline and age group (2–5, 6–12, and 13–18 years) as covariates and treatment group as a fixed factor.

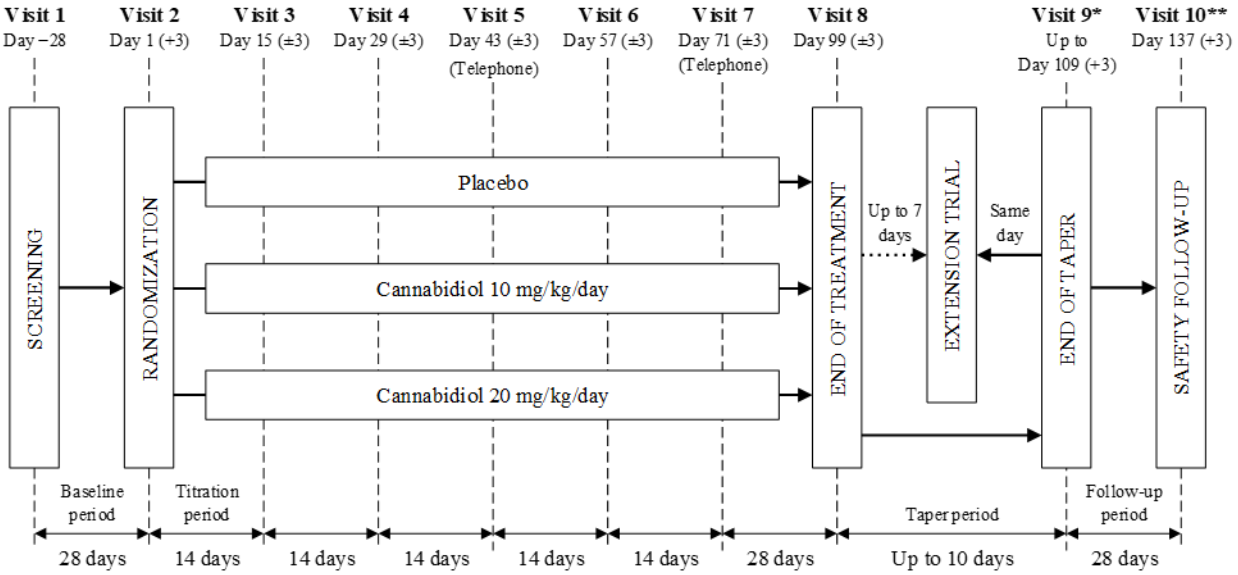
[†] Favors cannabidiol.

eTable 3. Adverse Events of Special Interest in Patients With and Without Clobazam and AED Dose Adjustments From the Safety Analysis Set

Number of patients n (%)	**Placebo** n=65	**Cannabidiol 10 mg/kg/day** n=64	**Cannabidiol 20 mg/kg/day** n=69
With clobazam[a]	41	44	42
Somnolence, Fatigue, Lethargy, or Sedation	12 (29.3)	19 (43.2)	24 (57.1)
Rash[b] or Generalized maculopapular rash	1 (2.4)	6 (13.6)	3 (7.1)
Pneumonia[c]	1 (2.4)	6 (13.6)	3 (7.1)
Aggression or Irritability	2 (4.9)	3 (6.8)	5 (11.9)
Without clobazam[a]	24	20	27
Somnolence, Fatigue, Lethargy, or Sedation	4 (16.7)	2 (10.0)	5 (18.5)
Rash[b] or Generalized maculopapular rash	0	0	1 (3.7)
Pneumonia[c]	1 (4.2)	0	1 (3.7)
Aggression or Irritability	1 (4.2)	0	4 (14.8)
Clobazam adjustment	1	8	11
	1 increase	7 decreases 1 initiation	8 decreases 1 temporary decrease 1 increase 1 cessation
Valproate adjustment	4	4	11
	1 increase 1 decrease/ increase 2 decreases	3 decreases 1 decrease/ increase	8 decreases 1 increase 1 interruption 1 initiation/increase

[a] For percentages of patients with AEs, the denominator is the number of patients treated with or without CLB.
[b] Defined as any MedDRA preferred term containing the word rash.
[c] Defined as any MedDRA preferred term containing the word pneumonia.
Note: In CBD patients, ASD dose adjustments occurred during the treatment period and were due primarily to AEs (15 of 19 patients for VPA and 14 of 20 for CLB).

eFigure 1. Trial Schematic Overall trial design/diagram.



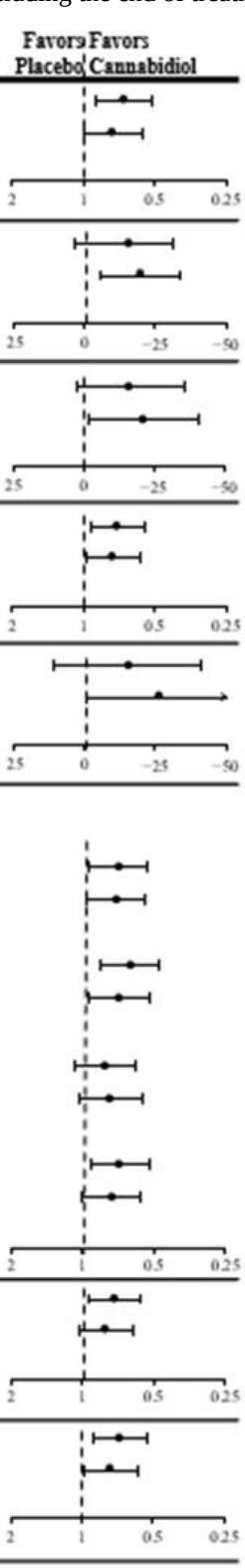
* For patients who did not enter the open-label extension trial at Visit 8 or for those who withdrew early and tapered trial medication. Patients who completed treatment but opted not to enter the open-label extension trial, or who withdrew from the trial early, had weekly (±3 days) safety telephone calls from Visit 9 (or date of final dosing) until Visit 10.

** For patients who did not enter the open-label extension trial or who withdrew from the trial early; could be conducted by telephone.

eFigure 2. Sensitivity Analyses of the Primary End Point and Percentage Reductions in Convulsive and Total Seizure Frequency During the Maintenance Period

(a) Sensitivity Analyses of the Primary End Point. Convulsive seizures include tonic, clonic, tonic–clonic, and atonic seizures. Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit. Maintenance period was defined as Day 15 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit

Model	Cannabidiol vs. Placebo	Cannabidiol (n)	Placebo (n)	Treatment Difference/Ratio (95% CI)
NBR[a] (PP)	10 mg/kg/day	61	62	0.673 (0.510, 0.888)
	20 mg/kg/day	59	62	0.746 (0.563, 0.987)
WRST[b] (ITT)	10 mg/kg/day	66	65	−15.74 (−31.27, 3.68)
	20 mg/kg/day	67	65	−19.88 (−33.92, −5.29)
Rank ANCOVA[c] (ITT)	10 mg/kg/day	66	65	−16.9 (−36.3, 2.4)
	20 mg/kg/day	67	65	−21.3 (−40.7, −1.9)
Log ANCOVA[d] (ITT)	10 mg/kg/day	66	65	0.717 (0.550, 0.935)
	20 mg/kg/day	67	65	0.742 (0.569, 0.968)
ANCOVA[e] (ITT)	10 mg/kg/day	66	65	−15.20 (−41.17, 10.77)
	20 mg/kg/day	67	65	−26.25 (−52.16, −0.35)
NBR[a,e] (Maintenance ITT)				
Maintenance Period	10 mg/kg/day	66	65	0.711 (0.539, 0.938)
	20 mg/kg/day	63	65	0.719 (0.542, 0.954)
Maintenance Period (Weeks 1–4)	10 mg/kg/day	66	65	0.629 (0.471, 0.839)
	20 mg/kg/day	63	65	0.702 (0.523, 0.941)
Maintenance Period (Weeks 5–8)	10 mg/kg/day	66	65	0.802 (0.592, 1.087)
	20 mg/kg/day	62	65	0.757 (0.554, 1.035)
Maintenance Period (Weeks 9–12)	10 mg/kg/day	64	65	0.693 (0.520, 0.923)
	20 mg/kg/day	62	65	0.755 (0.565, 1.009)
NBR[a,f] (ITT, Worst)	10 mg/kg/day	66	65	0.729 (0.563, 0.943)
	20 mg/kg/day	67	65	0.798 (0.616, 1.033)
NBR[a] (Safety Analysis)	10 mg/kg/day	64	65	0.688 (0.526, 0.899)
	20 mg/kg/day	69	65	0.756 (0.579, 0.986)



Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; NBR, negative binomial regression; PP, per protocol analysis set; ITT, intent-to-treat analysis set; WRST, Wilcoxon Rank-Sum Test.

[a] Model includes total number of seizures as a response variable, age group (2-5, 6-12, and 13-18 years), time (baseline and treatment or maintenance period), treatment, and treatment by time interaction as fixed effects, and patient as random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

[b] The treatment differences are median differences; estimated median difference and 95% CI were calculated using the Hodges–Lehmann approach.

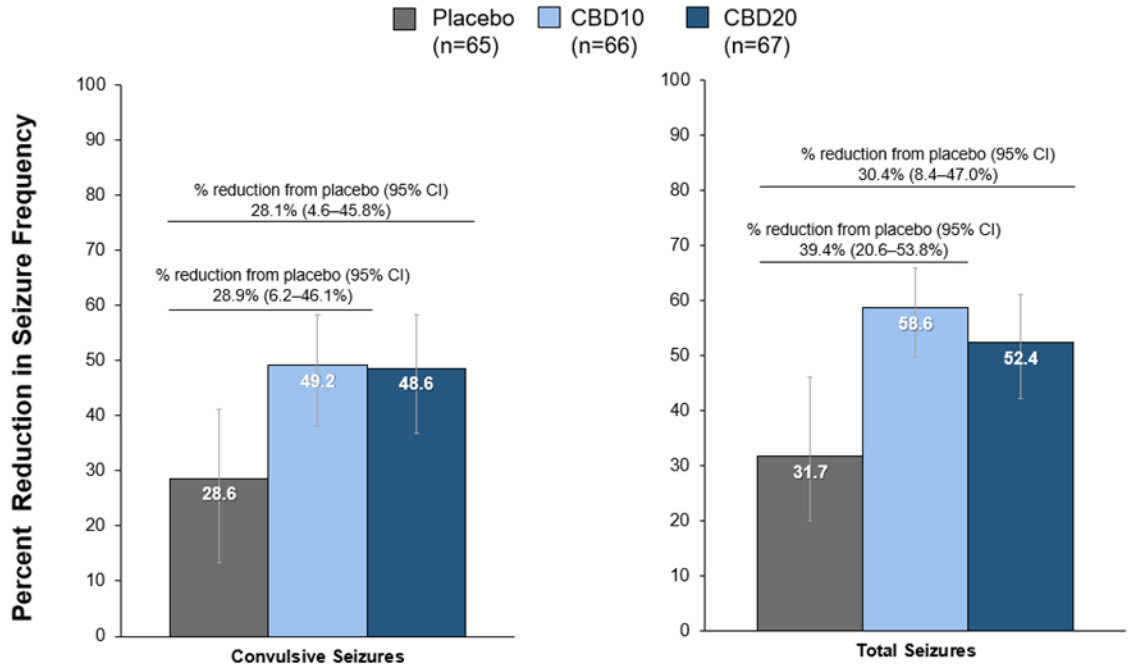
[c] The treatment differences are least squares mean differences. The rank of the percent change from baseline convulsive seizure frequency was analyzed using an ANCOVA model with the rank of the baseline convulsive seizure frequency and age group (2-5, 6-12, and 13-18 years) as covariates and treatment group as a fixed factor.

[d] Analyzed with the log-transformed rank of the baseline convulsive seizure frequency and age group (2-5, 6-12, and 13-18 years) as covariates and treatment group as a fixed factor. A value of 1 was added to the convulsive seizure frequency for all patients prior to log-transformation. The least squares means, treatment ratio, and 95% CI have been back-transformed.

[e] Includes only patients with at least 7 days of seizure data within the corresponding period.

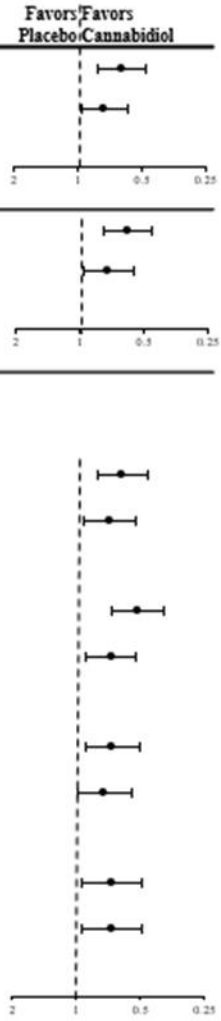
[f] Missing data from the treatment period arising from unreported days in interactive voice response system were imputed using the worst (highest number of seizures) of the following for each patient: last observation carried forward, next observation carried backward, and the mean daily number of seizures during the treatment period (using the non-missing data).

(b) Percentage Reductions in Convulsive and Total Seizure Frequency During the Maintenance Period. The estimated percentage reduction in seizure frequency and 95% confidence intervals (CI) are shown for each treatment group. Cannabidiol doses of 10 mg/kg/day (CBD10) and 20 mg/kg/day (CBD20) were associated with greater reductions in convulsive and total seizure frequency compared with placebo. Convulsive seizures include tonic, clonic, tonic-clonic, and atonic seizures and total seizures include convulsive and non-convulsive seizures (myoclonic, countable partial, other partial or absence seizures).



eFigure 3. Sensitivity Analyses of Change in Total Seizure Frequency Compared to Baseline Total seizures include all seizure types combined. Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit. Maintenance period was defined as Day 15 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.

Model	Cannabidiol vs. Placebo	Cannabidiol (n)	Placebo (n)	Treatment Ratio (95% CI)
NBR[a] (ITT)	10 mg/kg/day	66	65	0.620 (0.481, 0.799)
	20 mg/kg/day	67	65	0.749 (0.581, 0.965)
NBR[a] (PP)	10 mg/kg/day	61	62	0.590 (0.454, 0.768)
	20 mg/kg/day	59	62	0.732 (0.562, 0.955)
NBR[a,b] (Maintenance ITT)				
Maintenance Period	10 mg/kg/day	66	65	0.606 (0.462, 0.794)
	20 mg/kg/day	63	65	0.696 (0.530, 0.916)
Maintenance Period (Weeks 1–4)	10 mg/kg/day	66	65	0.512 (0.388, 0.675)
	20 mg/kg/day	63	65	0.687 (0.519, 0.908)
Maintenance Period (Weeks 5–8)	10 mg/kg/day	66	65	0.676 (0.504, 0.906)
	20 mg/kg/day	62	65	0.735 (0.546, 0.989)
Maintenance Period (Weeks 9–12)	10 mg/kg/day	64	65	0.681 (0.493, 0.940)
	20 mg/kg/day	62	65	0.687 (0.496, 0.950)

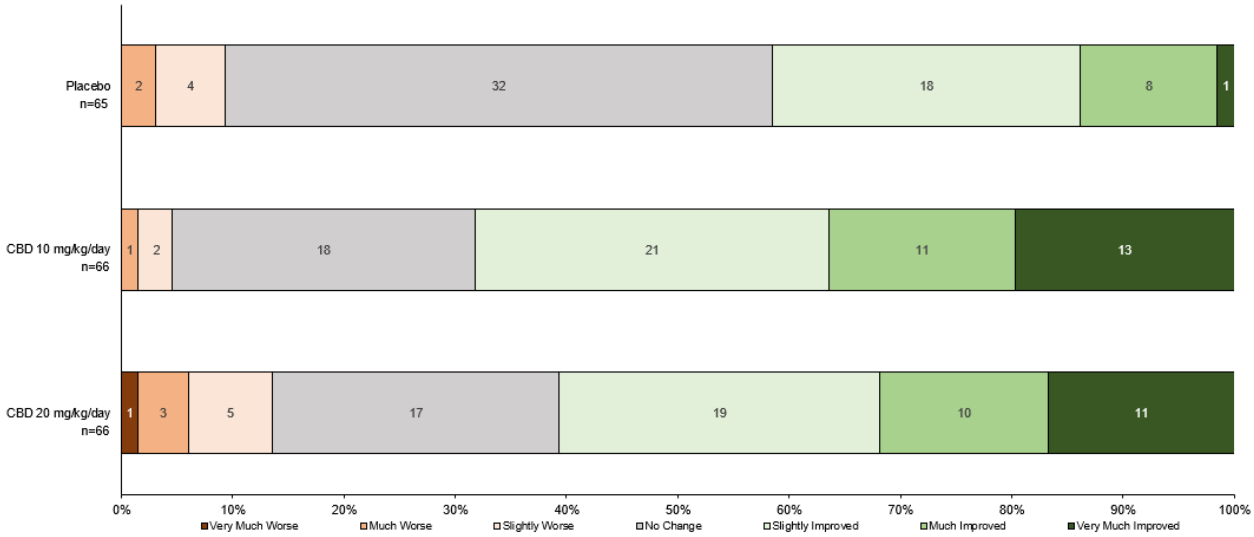


Abbreviations: CI, confidence interval; NBR, negative binomial regression; PP, per protocol analysis set; ITT, intent-to-treat analysis set.

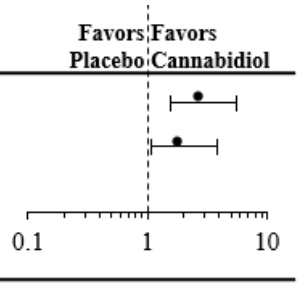
[a] Model includes number of seizures as a response variable, age group (2-5, 6-12, and 13-18 years), time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and patient as random effect. Log-transformed number of days in which seizures were reported by period in included as an offset.

[b] Includes only patients with at least 7 days of seizure data within the corresponding period.

eFigure 4. Caregiver Global Impression of Change in Overall Condition at Last Visit An improvement from baseline in overall condition (slightly improved, much improved, or very much improved) was reported in 27 of 65 patients (41.5%) in the placebo group, 45 of 66 patients (68.2%) in the CBD10 group, and 40 of 66 patients (60.6%) in the CBD20 group (1 patient in the CBD20 group did not have a CGIC reported at last visit). The differences in proportions favored both doses of cannabidiol over placebo.



Model	Cannabidiol vs. Placebo	Cannabidiol (n)	Placebo (n)	Odds Ratio (95% CI)	P value
(ITT)	10 mg/kg/day	66	65	2.93 (1.56, 5.53)	0.0009
OLR	20 mg/kg/day	66	65	2.02 (1.08, 3.78)	0.0279



Note: Caregiver global impression of change is assessed on a 7-point Likert-like scale with three categories of improvement (slightly improved, much improved, or very much improved), three categories of worsening (slightly worse, much worse, or very much worse), and "no change". The number of patients in each category is presented for each treatment group. CI, confidence interval; OLR, ordinal logistic regression; ITT, intention-to-treat.

eMethods. Statistical Analysis for Sample Size, Other Secondary Outcomes, and Sensitivity Analyses

Sample size: Based on a two-sided non-parametric Mann-Whiney-Wilcoxon test with a significance level of 5%, we calculated that a sample size of 62 patients per group would provide 80% power to detect a difference in response distributions. This is based on a gamma distribution for the cannabidiol groups with scale parameter of 65.614 and shape parameter of 1.0886, and a gamma distribution for the placebo group with scale parameter of 40.887 and shape parameter of 2.3059. Maximum likelihood estimates using the Newton-Raphson approximation were computed for the scale and shape parameters using data from the previous Dravet syndrome trial GWEP1332 Part B (GWPCARE1).

Other secondary outcomes: The proportion of patients experiencing worsening or improvement with a > 25% increase, ≥ 0 to ≤ 25% increase, > 0 to < 25% reduction, ≥ 25 to < 50% reduction, ≥ 50 to < 75% reduction, or ≥ 75% reduction from baseline and the proportion of responders (≥25%, ≥75%, and 100% reductions in seizure frequency) were analyzed using a Cochran-Mantel-Haenszel test stratified by age group (2-5, 6-12, and 13-18 years) and expressed as an estimated odds ratio (where applicable) with 95% confidence intervals. Percentage change in seizure frequency (total, non-convulsive, and individual seizures by type) was analyzed using the same methods as the primary outcome. CGIC (overall condition and seizure duration) was analyzed using ordinal logistic regression with treatment and age group (seizure duration only) as factors. Sleep disruption, Epworth Sleepiness Scale, and Quality of Life in Childhood Epilepsy were analyzed using an analysis of covariance with baseline and age group as covariates and treatment group as fixed factor. The domains of Vineland-II were analyzed by either analysis of covariance or ordinal logistic regression as above, depending on the domain, with baseline adaptive level as a covariate.

Sensitivity analyses: Prespecified sensitivity analyses of the primary and first key secondary outcome included repeat analyses of the intention-to-treat analysis set (eFigure2, Supplement 2) using the per-protocol analysis set; sensitivity analysis was also done on the safety analysis set (primary outcome only), analysis during the maintenance period (Day 15 onwards), and analysis during each 4-week block of the maintenance period. Additional sensitivity analyses of the primary outcome included Wilcoxon rank-sum

test, and the estimated median difference between treatments, together with 95% confidence intervals, calculated using the Hodges-Lehmann approach, parametric analyses following transformation of data to account for non-normality, and analyses imputing missing data from unreported days using (1) the worst case of last observation carried forward, next observation carried backward, or the mean daily number of seizures during the treatment period, based on non-missing data; and (2) multiple imputation to impute data under the missing not at random assumption. Prespecified sensitivity analyses of the CGIC at last visit included analysis by caregiver only and was repeated using the end-of-treatment CGIC scores and the per-protocol analysis sets.