Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
eAppendix. Study Design, Outcome Measures, Statistical Analysis, Additional Safety, Tolerability, and Laboratory Parameters, and Pharmacokinetics

METHODS

Study Design
Clinic visits occurred on days 15, 29, 43, 57, 85, and 113 after randomization, with a telephone visit on day 71 (eFigure 1). Additional telephone calls to access safety were conducted every 2 days during the titration period and 1 week after the end of titration.

Patients began a 4-week baseline observation period after screening (eFigure 1), during which patients or their caregivers reported daily the number and type of seizures using an interactive voice-response system (IVRS), completing at least 90% of the calls. The seizures were classified with verification by the Epilepsy Study Consortium.

Outcome Measures
Other secondary outcomes included the following: percentage of patients who had at least a 25%, at least a 75%, or a 100% reduction from baseline in the number of primary end point seizures; percentage of patients who had worsening or improvement in primary end point seizure frequency; a change in the number of days without primary end point seizures; a percent reduction from baseline in absence, myoclonic, and focal sensory seizures, as well as infantile or epileptic spasms; growth and development in patients less than 18 years of age (change in serum insulin-like growth factor-1 levels and change in Tanner Staging score for patients between 10 and 17 years of age); change in the quality of life of patients, evaluated using changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2-18 years) or Quality of Life in Epilepsy (QOLIE; patients 19+ years) score; and a change in Physician Global Impression of Change (PGIC) score. Safety was assessed primarily by evaluation of adverse events and clinical laboratory parameters. Other safety and tolerability end points were 12-lead electrocardiogram, physical examination parameters, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS; for 19+ years) or C-SSRS Children’s (6-18 years) score, number of inpatient hospitalizations due to epilepsy, abuse liability, and the effect on menstruation cycle in female patients.

Cannabidiol pharmacokinetics was evaluated by measuring the plasma concentrations of cannabidiol and its major metabolites. Blood samples were taken on the day of the first dose, and at the end of treatment or the withdrawal visit (if possible). A sample was taken before administration of the medication and at 2-3 hours, 4-6 hours, and 8-10 hours post-dose. The 8-10 hours sample was taken only from patients aged 18 years and older.

Statistical Analysis
Negative Binomial Regression Analysis

A mixed-effect model with repeated measures was performed to model the reported number of seizures in the baseline and treatment periods, implemented within the framework of general linear models, using the negative binomial response distribution. The model included stratified age groups (1-6, 7-11, 12-17, and 18-65 years), time, treatment arm, and treatment arm by time interaction as the fixed effects, and patient as a random effect. The log-transformed number of days in which seizures were reported was included as an offset. The estimated ratio of least squares means for the treatment period to baseline period and the 95% confidence intervals (CIs) are presented for each treatment arm. In addition, the estimated ratio of each cannabidiol group to placebo and 95% CIs are presented with the $P$ value testing of the null hypothesis that this ratio was 1. Prespecified sensitivity analyses of the primary outcome included repeat analysis using the per-protocol analysis set, analysis over the maintenance period alone, analyses accounting for missing values with alternative methodologies, and parametric analyses.

Secondary Outcomes Analyses

The percentages of patients with a $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, and 100% reduction in the number of primary end point seizures were analyzed using a Cochran–Mantel–Haenszel test stratified according to the same age groups as used for randomization; odds ratios (OR) with 95% CIs are presented. The subject/caregiver global impression of change in the overall condition from baseline was analyzed with ordinal logistic regression using the proportional odds model (ordinal values 7-1 [very much worse to very much better]). The change in total seizures was analyzed similarly to the primary outcome. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).
RESULTS

Additional Safety, Tolerability, and Laboratory Parameters
Overall, no consistent difference was observed between the placebo and the cannabidiol groups in most laboratory parameters (except liver parameters) other than the hematological parameters and creatinine. Mean hemoglobin baseline values were 130.0 g/L for 25-mg cannabidiol, 130.3 g/L for 50-mg cannabidiol, and 130.2 g/L for placebo. Mean changes from baseline at the end of treatment were -3.5 g/L for 25-mg cannabidiol, -3.8 g/L for 50-mg cannabidiol, and 0.7 g/L for placebo. The pattern of changes in hematocrit was consistent with the hemoglobin changes. Anemia events were reported in 9 patients: 1 on placebo, 5 on 25-mg cannabidiol, and 3 on 50-mg cannabidiol. No patient required transfusion. Mean creatinine levels at baseline were 35.0 µmol/L for 25-mg cannabidiol, 34.9 µmol/L for 50-mg cannabidiol, and 34.0 µmol/L for placebo. At the end of treatment, the mean changes from baseline were 0.9 µmol/L for 25-mg cannabidiol, 2.1 µmol/L 35.0 for 50-mg cannabidiol, and -1.1 µmol/L for placebo.

Cannabidiol treatment had little or no effect on vital signs, physical examination parameters, or other assessments, including electrocardiograms. No suicidal ideation or behavior was reported during the trial, and there was no evidence of differences in growth and development, menstruation, abuse liability, or signs of a potential or actual withdrawal syndrome across the treatment groups.

Pharmacokinetics
Plasma concentrations of cannabidiol and its major metabolites were analyzed in samples from 104 patients (57 patients from the 25-mg cannabidiol group and 47 patients from the 50-mg cannabidiol group). At the end of treatment (day 113, at steady state) cannabidiol exposure was similar between the 25-mg cannabidiol (mean [CV%] AUC_{(0–t)}, 2520 h•ng/mL [52.4]) and 50-mg cannabidiol (mean [CV%] AUC_{(0–t)}, 2730 h•ng/mL [87.2]) groups, suggesting that the absorption may be saturated at these dose levels. Exposure to metabolite 7-carboxy-cannabidiol (mean [CV%] AUC_{(0–t)}, 47,200 h•ng/mL [78.3] for 25-mg cannabidiol and 62,000 h•ng/mL [79.8] for 50-mg cannabidiol) and 7-hydroxy-cannabidiol (mean [CV%] AUC_{(0–t)}, 723 h•ng/mL [52.3] for 25-mg cannabidiol and 773 h•ng/mL [79.7] for 50-mg cannabidiol) were also consistent between the 2 cannabidiol doses.
# eTable 1. Eligibility Criteria

## Inclusion Criteria

|   |   |
|---|---|
| **1.** | Patient was male or female aged between 1 and 65 years inclusive. |
| **2.** | Patient and/or parent(s)/legal representative was willing and able to give informed consent/assent for participation in the study. |
| **3.** | Patient and their caregiver were willing and able (in the investigator’s opinion) to comply with all study requirements (including accurate diary and IVRS completion). |
| **4.** | Well-documented clinical history of epilepsy, which was not completely controlled by their current AEDs. |
| **5.** | Clinical diagnosis of TSC according to the criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference. |
| **6.** | Patient was taking one or more AEDs at a dose that had been stable for at least 4 weeks prior to screening. |
| **7.** | All medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for 1 month prior to screening, and the patient was willing to maintain a stable regimen throughout the study. |
| **8.** | Patient was willing to keep any factors that are expected to affect seizures (such as the level of alcohol consumption and smoking) stable. |
| **9.** | Patient and/or parent(s)/legal representative was willing to allow the responsible authorities to be notified of participation in the study, if mandated by local law. |
| **10.** | Patient and/or parent(s)/legal representative was willing to allow his or her primary care practitioner and consultant (if they had one) to be notified of participation in the study, if mandated by local law. |
| **11.** | By the end of baseline period, patients must have experienced at least 8 TSC-associated seizures during the first 28 days of the baseline period, with at least one seizure occurring in at least 3 of the 4 weeks. |
| **12.** | Patients/caregivers must have completed at least 90% of calls to IVRS during the first 28 days of the baseline period (a minimum of 25 completed calls). |

## Exclusion Criteria

|   |   |
|---|---|
| **1.** | Patient had a history of non-epileptic seizures. |
| **2.** | Patient had clinically significant unstable medical conditions other than epilepsy. |
| **3.** | Patient had an illness other than epilepsy in the 4 weeks prior to screening or randomization which, in the opinion of the investigator, could affect seizure frequency. |
| **4.** | Patient had undergone general anesthetic in the 4 weeks prior to screening or randomization. |
| **5.** | Patient had undergone surgery for epilepsy in the 6 months prior to screening. |
| **6.** | Patient was being considered for epilepsy surgery or any procedure involving general anesthesia during the blinded phase of the study. |
| **7.** | Patient had been taking felbamate for less than 1 year prior to screening. |
| **8.** | Patient was taking an oral mTOR inhibitor. |
| Exclusion Criteria |
|--------------------|
| 9. Patient had, in the investigator's opinion, clinically significantly abnormal laboratory values. |
| 10. Patient had any known or suspected hypersensitivity to cannabinoids or any of the excipients of the trial medication, such as sesame oil. |
| 11. Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale in the last month or at screening. |
| 12. Patient was currently using or had in the past used recreational or medicinal cannabis or cannabinoid-based medications within the 3 months prior to screening and was unwilling to abstain for the duration for the study. |
| 13. Patient had tumor growth which, in the opinion of the investigator, could affect the primary end point. |
| 14. In the opinion of the investigator, the patient had clinically significant abnormalities in the ECG measured at screening or randomization, or any concurrent cardiovascular conditions that would interfere with the ability to read their ECGs. |
| 15. Patient had significantly impaired hepatic function at the screening visit (visit 1) or the randomization visit (visit 3), defined as any of the following: serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5X upper limit of normal (ULN); serum total bilirubin (TBL) ≥2X ULN or international normalized ratio [INR] >1.5 (TBL ≥2X ULN exclusion did not apply for patients diagnosed with Gilbert’s syndrome); and serum ALT or AST ≥3X ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). These criteria could only be confirmed once the laboratory results were available; patients randomized into the trial who were later found to meet any of these criteria were withdrawn from the trial. |
| 16. Patient was female and of childbearing potential, or was male whose partner was of childbearing potential, unless willing to ensure that they or their partner use a highly effective method of birth control (eg, hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the study and for 3 months thereafter. |
| 17. Female patient who was pregnant (positive pregnancy test), lactating, or planning pregnancy during the course of the study and for 3 months thereafter. |
| 18. Patient had received a trial medication less than 12 weeks prior to the screening visit. |
| 19. Patient had any other significant disease or disorder which, in the opinion of the investigator, might either put the patient at risk because of participation in the study, might influence the result of the study, or might affect the patient’s ability to take part in the study. |
| 20. Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if they took part in the study. |
| 21. Patient had donated blood during the past 12 weeks and was unwilling to abstain from donation of blood during the study. |
| 22. Patient had been previously randomized into this study. |
| 23. Patient had any known or suspected history of alcohol or substance abuse. |
| 24. Patient had planned to travel outside the country and/or state of residence during the trial, unless the patient had confirmation that the trial medication was permitted in the destination country/state. |
Abbreviations: AEDs, antiepileptic drugs; ECG, electrocardiogram; IVRS, interactive voice-response system; mTOR, mechanistic target of rapamycin; TSC, tuberous sclerosis complex.
### eTable 2. Hierarchical Sequential Procedure – Type I Error Control by Gatekeeping

| Test | Outcome                  | Description                                      | Dosage Comparison Versus Placebo          |
|------|--------------------------|--------------------------------------------------|-------------------------------------------|
| 1    | Primary                  | Change in number of TSC-associated seizures      | Cannabidiol 25 mg/kg/day                 |
| 2    | First key secondary      | ≥50% responder rate for TSC-associated seizures  | Cannabidiol 25 mg/kg/day                 |
| 3    | Primary                  | Change in number of TSC-associated seizures      | Cannabidiol 50 mg/kg/day                 |
| 4    | First key secondary      | ≥50% responder rate for TSC-associated seizures  | Cannabidiol 50 mg/kg/day                 |
| 5    | Second key secondary     | Subject/caregiver global impression of change    | Cannabidiol 25 mg/kg/day                 |
| 6    | Third key secondary      | Change in total seizure                          | Cannabidiol 25 mg/kg/day                 |
| 7    | Second key secondary     | Subject/caregiver global impression of change    | Cannabidiol 50 mg/kg/day                 |
| 8    | Third key secondary      | Change in total seizure                          | Cannabidiol 50 mg/kg/day                 |

Abbreviation: TSC, tuberous sclerosis complex.
### eTable 3. Summary of Cannabidiol Dosage During the Treatment Period

|                                | CBD25 (n = 75) | CBD50 (n = 73) |
|--------------------------------|----------------|----------------|
| **Achieved target dosage, No. (%)** |                |                |
| Yes                            | 74 (99)        | 49 (67)        |
| No                             | 1 (1)          | 24 (33)        |
| **At target dosage at the end of treatment, No. (%)** |                |                |
| Yes                            | 65 (87)        | 39 (53)        |
| No                             | 10 (13)        | 34 (47)        |
| **Maximum dosage achieved, mean (SD), mg/kg/day** | 25 (1)         | 46 (7)         |
| **Dosage at the end of treatment, mean (SD), mg/kg/day** | 23 (4)         | 39 (14)        |
| **Modal dosage, mean (SD), mg/kg/day** | 24 (3)         | 36 (17)        |

Abbreviations: CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day; SD, standard deviation.
## eTable 4. Other Secondary Outcomes

| Outcome                                                                 | Placebo          | CBD25           | CBD50           | CBD25 Versus Placebo | CBD50 Versus Placebo |
|-------------------------------------------------------------------------|------------------|-----------------|-----------------|----------------------|----------------------|
| Percentage of patients with ≥25%, ≥75%, and 100% reduction from baseline in primary end point seizures<sup>a</sup> | n/N (%)          | n/N (%)         | n/N (%)         | Odds Ratio (95% CI)   | Odds Ratio (95% CI)   |
| ≥25% reduction                                                        | 33/76 (43)       | 43/75 (57)      | 43/73 (59)      | 1.75 (0.92 to 3.33)  | 1.87 (0.97 to 3.58)  |
| ≥75% reduction                                                        | 0                | 12/75 (16)      | 13/73 (18)      | NA                   | NA                   |
| 100% reduction                                                        | 0                | 1/75 (1)        | 0               | NA                   | NA                   |
| Percentage of patients experiencing worsening, no change, or improvements in primary end point seizures | n/N (%)          | n/N (%)         | n/N (%)         |                      |                      |
| >25% worsening                                                        | 6/76 (8)         | 6/75 (8)        | 8/73 (11)       |                      |                      |
| ≥0% to ≤25% worsening                                                 | 15/76 (20)       | 11/75 (15)      | 6/73 (8)        |                      |                      |
| >0% to <25% improvement                                               | 22/76 (29)       | 7/75 (9)        | 12/73 (16)      |                      |                      |
| ≥25% to 50% improvement                                               | 16/76 (21)       | 18/75 (24)      | 16/73 (22)      |                      |                      |
| ≥50% to 75% improvement                                               | 17/76 (22)       | 19/75 (25)      | 17/73 (23)      |                      |                      |
| ≥75% improvement                                                      | 0                | 14/75 (19)      | 14/73 (19)      |                      |                      |
| Change from baseline in seizure-free days<sup>b</sup>                 | LS mean (95% CI) | LS mean (95% CI) | LS mean (95% CI) | Treatment difference (95% CI) | Treatment difference (95% CI) |
| Treatment period per 28 days                                         | 3.41 (2.04 to 4.79)  | 6.23 (4.84 to 7.62) | 5.57 (4.16 to 6.97) | 2.82 (0.87 to 4.77)  | 2.16 (0.19 to 4.12)  |
| Change From Baseline in Seizure-Free Days<sup>b</sup> | LS Mean (95% CI) n = 76 | LS Mean (95% CI) n = 75 | LS Mean (95% CI) n = 73 | Treatment Difference (95% CI) | Treatment Difference (95% CI) |
|-----------------------------------------------|----------------------|----------------------|----------------------|-----------------------------|-----------------------------|
| Maintenance period per 28 days                | 3.89 (2.31 to 5.47)  | 7.32 (5.68 to 8.96)  | 6.69 (4.99 to 8.39)  | 3.43 (1.16 to 5.70)         | 2.80 (0.48 to 5.12)         |
| Percent change from baseline in other seizures frequency | | | | | |
| Median (LQ, UQ) [n]                           |                      |                      |                      |                             |                             |
| Absence                                       | -100 (-100 to -79.1) [7] | -25.66 (-100 to 14.1) [5] | -100 (-100 to -32.7) [14] |                             |                             |
| Myoclonic                                      | -56.71 (-88.9 to 18.7) [4] | -58.63 (-87.0 to -25.5) [3] | -83.56 (-100 to -53.7) [6] |                             |                             |
| Focal sensory                                  | -100 (-100 to -100) [3] | 12.35 (-100 to 124.7) [2] | -100 (-100 to -100) [1] |                             |                             |
| Infantile/epileptic spasms                    | -32.87 (-89.9 to -11.7) [3] | -100 (-100 to -53.7) [5] | -82.47 (-100 to -39.9) [7] |                             |                             |
| Growth and development (patients <18 years of age) | | | | | |
| Change from baseline in serum IGF-1 levels, median (min, max), nmol/L [n] | 0.2 (-13.6, 29) [50] | -1.6 (-28.9, 10.0) [51] | -2.9 (-26.9, 48.6) [51] |                             |                             |
| Tanner Stage over time (patients aged 10-17 years [inclusive]), n/N (%) Day 1 | | | | | |
| Stage 1                                       | 8/26 (31)            | 4/22 (18)            | 2/22 (9)             |                             |                             |
| Stage 2                                       |                       |                      |                      |                             |                             |
| Stage 3                                       |                       |                      |                      |                             |                             |

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| Stage 1 | Stage 2 | Stage 3 | Stage 4 | Stage 5 | End of treatment |
|--------|--------|--------|--------|--------|------------------|
| 5/26 (19) | 4/26 (15) | 3/26 (12) | 6/26 (23) | 4/26 (15) | 4/26 (15) |
| 3/26 (12) | 5/26 (23) | 6/26 (27) | 4/26 (18) | 4/26 (18) | 7/26 (32) |
| 5/23 (22) | 5/23 (22) | 4/23 (17) | 3/23 (13) | 6/23 (26) | 5/22 (23) |
| 2/20 (10) | 3/20 (15) | 3/20 (15) | 6/20 (30) | 6/20 (30) |

**Quality of life**

| Quality of life | LS mean (95% CI) [n] | LS mean (95% CI) [n] | LS mean (95% CI) [n] | Treatment difference (95% CI) | Treatment difference (95% CI) |
|----------------|----------------------|----------------------|----------------------|------------------------------|------------------------------|
| Change from baseline in overall QOLCE score (patients aged 2-18 years) | 2.4 (-1.6 to 6.4) [38] | 2.9 (-1.3 to 7.0) [35] | 2.2 (-1.8 to 6.3) [42] | 0.5 (-4.7 to 5.6) | -0.2 (-5.1 to 4.7) |
| Change from baseline in total QOLIE-31-P score (patients aged ≥19 years) | 1.7 (-7.6 to 11.1) [10] | -1.2 (-10.8 to 8.5) [10] | -8.6 (-18.9 to 1.7) [8] | -2.9 (-16.8 to 10.9) | -10.4 (-24.1 to 3.3) |

**Change from baseline in PGIC score**

| Change from baseline in PGIC score | n/N (%) | n/N (%) | n/N (%) | Odds ratio (95% CI) | Odds ratio (95% CI) |
|-----------------------------------|---------|---------|---------|---------------------|---------------------|
| Very much improved                | 1/76 (1) | 6/72 (8) | 5/69 (7) | 2.47 (1.35 to 4.52) | 2.33 (1.27 to 4.27) |
| Much improved                     | 9/76 (12) | 19/72 (26) | 17/69 (25) |                       |                     |
| Slightly improved                 | 17/76 (22) | 18/72 (25) | 20/69 (29) |                       |                     |
| No change                         | 45/76 (59) | 24/72 (33) | 21/69 (30) |                       |                     |
| Slightly worse                    | 4/76 (5) | 3/72 (4) | 4/69 (6) |                       |                     |
|                      | n/N (%) | n/N (%) | n/N (%) |
|----------------------|---------|---------|---------|
| **Much worse**       | 0       | 2/72 (3)| 2/69 (3)|
| **Change from baseline in PGIC score** | n/N (%) | n/N (%) | n/N (%) |
| **Very much worse**  | 0       | 0       | 0       |

Abbreviations: ANCOVA, analysis of covariance; CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day; CI, confidence interval; IGF-1, insulin-like growth factor-1; LQ, lower quartile; LS, least square; NA, not applicable; PGIC, Physician Global Impression of Change; QOLCE, Quality of Life in Childhood Epilepsy; QOLIE, Quality of Life in Epilepsy; UQ, upper quartile.

The primary end point seizures included all countable focal motor seizures without impairment of awareness, focal seizures with impairment of awareness, focal seizures evolving to bilateral motor seizures, and generalized seizures (tonic–clonic, tonic, clonic, or atonic).

The treatment period (day 1 to day 113) comprised the titration (day 1 to day 28) and maintenance (day 29 to day 113) phases.

*Patients who withdrew from the trial during the treatment period are considered nonresponders.

^The change from baseline in the primary end point seizure-free days was analyzed using an ANCOVA model with baseline number of primary end point seizure-free days and age group (1-6, 7-11, 12-17 and 18-65 years) as covariates and treatment group as a fixed factor.

^The change from baseline was analyzed using an ANCOVA model with baseline and age group (1-6, 7-11, 12-17 and 18-65 years) as covariates and treatment group as a fixed factor. The overall quality-of-life score was calculated by taking the mean of the subscale scores.

^The total score is calculated as (sum of all subscale weighted scores + sum of all subscale “distress” item converted scores) × 100. The change from baseline is analyzed using an ANCOVA model with baseline and age group (1-6, 7-11, 12-17 and 18-65 years) as covariates and treatment group as a fixed factor.
**eTable 5. Adverse Events of Special Interest in Patients Taking Cannabidiol With Clobazam**

| Adverse Event   | Without Clobazam | With Clobazam* |
|-----------------|------------------|----------------|
|                 | Placebo (n = 51) | CBD50 (n = 54) |
|                 | CBD25 (n = 58)   |                |
|                 |                  | CBD50 (n = 19) |
|                 |                  | Placebo (n = 25) |
| Somnolence      | 4 (8)            | 5 (9)          |
|                 | 9 (17)           | 3 (12)         |
|                 |                  | 5 (29)         |
|                 |                  | 10 (53)        |
| Rash            | 0                | 2 (3)          |
|                 | 6 (11)           | 2 (8)          |
|                 |                  | 2 (12)         |
|                 |                  | 1 (5)          |
| Pneumonia       | 1 (2)            | 0              |
|                 | 1 (2)            | 0              |
|                 |                  | 2 (12)         |
|                 |                  | 1 (5)          |

Abbreviations: CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day.

*One patient taking clobazam 45 mg daily in the 25-mg cannabidiol group reported an incidence of acute respiratory failure.
### Table 6. Adverse Events Leading to Treatment Discontinuation and Dose Reduction

| Adverse events leading to treatment discontinuation in ≥1 patient | Placebo (n = 76) | CBD25 (n = 75) | CBD50 (n = 73) |
|---------------------------------------------------------------|------------------|----------------|----------------|
| Rash                                                         | 0                | 2 (3)          | 2 (3)          |
| Alanine aminotransferase increased<sup>a</sup>               | 0                | 0              | 2 (3)          |
| Somnolence                                                   | 0                | 0              | 2 (3)          |
| Urticaria                                                    | 0                | 0              | 2 (3)          |
| Agitation                                                    | 1 (1)            | 0              | 0              |
| Angioedema                                                   | 0                | 0              | 1 (1)          |
| Aspartate aminotransferase increased<sup>a</sup>             | 0                | 0              | 1 (1)          |
| Ataxia                                                       | 1 (1)            | 0              | 0              |
| Blepharospasm                                                | 0                | 1 (1)          | 0              |
| Decubitus ulcer                                              | 0                | 1 (1)          | 0              |
| Diarrhea                                                     | 0                | 0              | 1 (1)          |
| Diet refusal                                                 | 0                | 0              | 1 (1)          |
| Electrocardiogram abnormal                                  | 0                | 1 (1)          | 0              |
| Eosinophil count increased                                   | 0                | 1 (1)          | 0              |
| Eye swelling                                                 | 0                | 0              | 1 (1)          |
| Hepatic enzyme increased<sup>a</sup>                        | 0                | 0              | 1 (1)          |
| Lip swelling                                                 | 0                | 0              | 1 (1)          |
| Liver injury                                                 | 0                | 1 (1)          | 0              |
| Musculoskeletal chest pain                                   | 0                | 0              | 1 (1)          |
| Rash erythematous                                            | 0                | 1 (1)          | 0              |
| Rash macular                                                 | 0                | 0              | 1 (1)          |
| Restlessness                                                 | 0                | 1 (1)          | 0              |
| Transaminase increased<sup>a</sup>                          | 0                | 0              | 1 (1)          |

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| Adverse event                                   | CBD25  | CBD50  | Overall |
|-----------------------------------------------|--------|--------|---------|
| **Type IV hypersensitivity reaction**         | 0      | 1 (1)  | 0       |
| Vomiting                                      | 0      | 1 (1)  | 0       |
| Weight decreased                              | 0      | 1 (1)  | 0       |

**Adverse events leading to permanent dose reduction in >1 patient**

| Adverse event                                   | CBD25  | CBD50  | Overall |
|-----------------------------------------------|--------|--------|---------|
| Diarrhea                                      | 1 (1)  | 2 (3)  | 7 (10)  |
| Somnolence                                    | 2 (3)  | 0      | 6 (8)   |
| Decreased appetite                            | 0      | 2 (3)  | 2 (3)   |
| Alanine aminotransferase increased\[a\]       | 0      | 0      | 3 (4)   |
| Irritability                                  | 0      | 0      | 3 (4)   |
| Aspartate aminotransferase increased\[a\]     | 0      | 0      | 2 (3)   |
| Abnormal behavior                             | 0      | 0      | 2 (3)   |

Abbreviations: CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day.

\[a\]Liver enzyme elevations include only those reported as an adverse event; see eTable 8 for all elevations regardless of adverse event status.
| Adverse Event, No. (%)                  | Placebo (n = 76) | CBD25 (n = 75) | CBD50 (n = 73) |
|----------------------------------------|------------------|----------------|---------------|
| Alanine aminotransferase increaseda    | 0                | 2 (3)          | 2 (3)         |
| Aspartate aminotransferase increaseda  | 0                | 2 (3)          | 2 (3)         |
| Status epilepticus                     | 1 (1)            | 2 (3)          | 0             |
| Gastroenteritis viral                  | 0                | 2 (3)          | 0             |
| Transaminases increaseda               | 0                | 0              | 2 (3)         |
| Vomiting                               | 0                | 2 (3)          | 0             |
| Abdominal pain                         | 0                | 0              | 1 (1)         |
| Acute respiratory failure              | 0                | 1 (1)          | 0             |
| Angioedema                             | 0                | 0              | 1 (1)         |
| Blood bilirubin increased              | 0                | 1 (1)          | 0             |
| Dehydration                            | 0                | 0              | 1 (1)         |
| Diarrhea                               | 0                | 0              | 1 (1)         |
| Electrolyte imbalance                  | 0                | 1 (1)          | 0             |
| Fatigue                                | 0                | 1 (1)          | 0             |
| Gastroenteritis                        | 0                | 0              | 1 (1)         |
| Generalized tonic−clonic seizure       | 0                | 0              | 1 (1)         |
| Hypophagia                             | 0                | 1 (1)          | 0             |
| Laceration                             | 0                | 0              | 1 (1)         |
| Liver injury                           | 0                | 1 (1)          | 0             |
| Malaise                                | 0                | 1 (1)          | 0             |
| Nausea                                 | 0                | 1 (1)          | 0             |
| Otitis media acute                     | 0                | 1 (1)          | 0             |
| Pneumonia                              | 1 (1)            | 1 (1)          | 0             |
| Pneumonia aspiration                   | 0                | 1 (1)          | 0             |
| Rash                                   | 0                | 1 (1)          | 0             |
| Rash erythematous                      | 0                | 1 (1)          | 0             |

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|                          | (n = 76) | (n = 75) | (n = 73) |
|--------------------------|----------|----------|----------|
| Rash macular             | 0        | 0        | 1 (1)    |
| Seizure                  | 0        | 1 (1)    | 1 (1)    |
| Toxicity to various agents | 0        | 0        | 1 (1)    |
| Type IV hypersensitivity reaction | 0        | 1 (1)    | 0        |
| Urticaria                | 0        | 0        | 1 (1)    |

Abbreviations: CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day.

*Liver enzyme elevations include only those reported as an adverse event; see eTable 8 for all elevations regardless of adverse event status.
Table 8. Treatment-Emergent ALT/AST Elevations\(^a\) in Patients by Valproate Use and ALT Levels at Baseline

|                                             | Placebo | CBD25  | CBD50  |
|--------------------------------------------|---------|--------|--------|
|                                            | n/N (%) |        |        |
| **ALT/AST >3 X ULN elevations**            |         |        |        |
| Overall                                    | 0/76    | 9/75 (12) | 19/73 (26) |
| On valproate                               | 0/35    | 7/29 (24) | 15/36 (42) |
| Off valproate                              | 0/40    | 3/46 (7)  | 3/37 (8)   |
| Baseline ALT \(\leq\) 1 X ULN             | 0/69    | 8/66 (12) | 13/62 (21) |
| Baseline ALT >1 X ULN                      | 0/6     | 1/9 (11)  | 5/11 (45)  |
| **ALT/AST >5 X ULN elevations**            |         |        |        |
| Overall                                    | 0/76    | 5/75 (7)  | 9/73 (12) |
| On valproate                               | 0/35    | 3/29 (10) | 8/36 (22) |
| Off valproate                              | 0/40    | 2/46 (4)  | 1/37 (3)  |
| Baseline ALT \(\leq\) 1 X ULN             | 0/69    | 4/66 (6)  | 5/62 (8)  |
| Baseline ALT >1 X ULN                      | 0/7     | 1/9 (11)  | 3/11 (27) |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day; ULN, upper limit of normal.

\(^a\)Includes all transaminase elevations, regardless of whether they were reported as adverse event.
### eTable 9. Onset and Resolution of ALT/AST Elevations*

|                  | ALT/AST >3X ULN | ALT/AST >5X ULN |
|------------------|-----------------|-----------------|
|                  | Placebo (n = 76) | CBD25 (n = 75)  | CBD50 (n = 73) | Placebo (n = 76) | CBD25 (n = 75) | CBD50 (n = 73) |
| n/N (%)          | 0               | 9/75 (12)       | 19/73 (26)     | 0               | 5/75 (7)        | 9/73 (12)       |
| **Time to Onset**|                 |                 |                 |                 |                 |                 |
| Within 30 days of treatment initiation | 0               | 6/9 (67)        | 14/19 (74)     | 0               | 4/5 (80)        | 6/9 (67)        |
| More than 30 days | 0               | 3/9 (33)        | 5/19 (26)      | 0               | 1/5 (20)        | 3/9 (33)        |
| **Resolution**   |                 |                 |                 |                 |                 |                 |
| Spontaneously    | 0               | 5/9 (56)        | 8/19 (42)      | 0               | 3/5 (60)        | 2/9 (22)        |
| Following cannabidiol discontinuation | 0               | 1/9 (11)        | 4/19 (21)      | 0               | 1/5 (20)        | 3/9 (33)        |
| After antiepileptic drug dose reduction | 0               | 3/9 (33)        | 7/19 (37)      | 0               | 1/5 (20)        | 4/9 (44)        |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day.

*Elevations in liver enzymes were determined by laboratory testing, regardless of whether they were reported as an adverse event or not.
Safety telephone calls were completed every 2 days during titration and 1 week after the end of titration.

For patients who did not enter the open-label extension trial or withdrew early and tapered trial medication. The visit occurred 10±3 days after the end-of-treatment visit for patients who completed the treatment but did not enter the open-label extension and 10±3 days after the withdrawal visit for patients who withdrew early from the trial and tapered medication. For patients who began tapering the trial medication but subsequently withdrew and did not complete the full tapering period, this visit occurred on the final day of dosing or as soon as possible after this date.

For patients who did not enter the open-label extension, the safety follow-up could be conducted over the phone.
Figure 2. Dosage Titration Schedule¹

Trial medications were taken daily in 2 equally divided doses. Total daily doses are shown.

¹Trial medications were taken daily in 2 equally divided doses. Total daily doses are shown.
Panel A shows the percent reduction in the frequency of primary end point and total seizures from baseline. Panel B shows the percent of patients who had a reduction of ≥50% and ≥75% in the number of primary end point seizures from baseline. Negative binomial regression was used to compare seizure frequency between the cannabidiol groups with placebo. Maintenance period was a 12-week period after the titration phase during which a steady trial medication dose was maintained. The estimated ratio of least squares means for treatment period to baseline period was used to evaluate the reduction in seizure frequency. *P values for the testing of the null hypothesis that the estimated ratio of each cannabidiol group to placebo was 1 are presented. The primary end point seizures are all countable focal motor seizures without impairment of awareness, focal seizures with impairment of awareness, focal seizures evolving to bilateral motor seizures, and generalized seizures (tonic–clonic, tonic, clonic, or atonic). Total seizures include all types combined, including focal sensory seizures and epileptic spasms. The odds ratio is presented for the comparisons in responder rates between the placebo group and the 25-mg and 50-mg cannabidiol groups. *P values were calculated from a Cochran–Mantel–Haenszel test stratified by age group (1-6, 7-11, 12-17, and 18-65 years).

*Nominal P values are reported.

Abbreviations: CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day.

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**eFigure 4. Sensitivity Analyses of Outcome**

| Model | Cannabidiol vs Placebo (n) | Treatment Ratio (95% CI) Favors | Favors |
|-------|---------------------------|-------------------------------|--------|
| NBR²  | 25 mg/kg/day 62 74  | 0.710 (0.572 to 0.882)  | 2 1 0.5 0.25 |
| (PP)  | 50 mg/kg/day 58 74  | 0.618 (0.496 to 0.770)  |        |
| WRST³ | 25 mg/kg/day 75 76  | -16.77 (-31.32 to -6.28) | 25 0 -25 -50 |
| (ITT) | 50 mg/kg/day 73 76  | -16.95 (-29.51 to -4.45) |        |
| Rank ANCOVA⁴ | 25 mg/kg/day 75 76 | -30.4 (-50.8 to -10.0)  | 25 0 -25 -50 |
| (ITT) | 50 mg/kg/day 73 76  | -27.2 (-47.8 to -6.6)   |        |
| Log ANCOVA⁴ | 25 mg/kg/day 75 76 | 0.675 (0.531 to 0.858)  | 2 1 0.5 0.25 |
| (ITT) | 50 mg/kg/day 73 76  | 0.674 (0.530 to 0.859)  |        |
| ANCOVA⁵ | 25 mg/kg/day 75 76 | -15.13 (-28.38 to -1.88) | 25 0 -25 -50 |
| (ITT) | 50 mg/kg/day 73 76  | -14.73 (-28.08 to -1.40) |        |

**NBR² (Maintenance ITT)**

| Maintenance Period | Cannabidiol vs Placebo (n) | Treatment Ratio (95% CI) Favors | Favors |
|--------------------|---------------------------|-------------------------------|--------|
| 25 mg/kg/day 75 76  | 0.631 (0.490 to 0.812)  | 2 1 0.5 0.25 |
| 50 mg/kg/day 73 76  | 0.631 (0.489 to 0.815)  |        |
| Weeks 1-4 | 25 mg/kg/day 75 76  | 0.697 (0.551 to 0.882)  |        |
| 50 mg/kg/day 73 76  | 0.656 (0.517 to 0.832)  |        |
| Weeks 5-8 | 25 mg/kg/day 75 76  | 0.619 (0.471 to 0.812)  |        |
| 50 mg/kg/day 73 76  | 0.620 (0.471 to 0.815)  |        |
| Weeks 9-12 | 25 mg/kg/day 75 76  | 0.666 (0.498 to 0.889)  |        |
| 50 mg/kg/day 73 76  | 0.808 (0.455 to 0.813)  |        |

**NBR² (ITT, unreported days in IVRS)**

| Cannabidiol vs Placebo (n) | Treatment Ratio (95% CI) Favors | Favors |
|---------------------------|-------------------------------|--------|
| 25 mg/kg/day 75 76  | 0.704 (0.576 to 0.886)  | 2 1 0.5 0.25 |
| 50 mg/kg/day 73 76  | 0.723 (0.592 to 0.884)  |        |

**NBR² (ITT, After MI for values MNAR)**

| Sensitivity parameter | Cannabidiol vs Placebo (n) | Treatment Ratio (95% CI) Favors | Favors |
|----------------------|---------------------------|-------------------------------|--------|
| K = 0.9² | 25 mg/kg/day 75 76  | 0.690 (0.561 to 0.849)  |        |
| 50 mg/kg/day 73 76  | 0.687 (0.558 to 0.846)  |        |
| K = 5.9² | 25 mg/kg/day 75 76  | 0.805 (0.649 to 0.999)  |        |
| 50 mg/kg/day 73 76  | 0.769 (0.619 to 0.956)  |        |
| K = 8.9² | 25 mg/kg/day 75 76  | 0.797 (0.637 to 0.997)  |        |
| 50 mg/kg/day 73 76  | 0.797 (0.637 to 0.997)  |        |

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Change from baseline in the primary end point TSC-associated seizures during the treatment period was analyzed in the per-protocol analysis set using negative binomial regression analysis.

Percentage change from baseline in TSC-associated seizures during the treatment period was analyzed using Wilcoxon rank-sum test. An estimate of the median differences between each cannabidiol group and placebo with approximate 95% CIs were calculated using the Hodges–Lehmann approach.

The ranks of the percentage change from baseline and the baseline TSC-associated seizure frequency during the treatment period were calculated. The ranks of the percentage change from baseline were then analyzed using an ANCOVA model with the rank of the baseline TSC-associated seizure frequency and stratified age group as covariates and treatment arm as a fixed factor.

The TSC-associated seizure frequency during the treatment period and the baseline TSC-associated seizure frequency were log transformed and then analyzed using an ANCOVA model with the log-transformed baseline TSC-associated seizure frequency and stratified age group as covariates and treatment arm as a fixed factor. If any patients had no TSC-associated seizures during the baseline or treatment periods, 1 was added to the TSC-associated seizure frequency for all patients prior to log transformation. The back-transformed estimated treatment ratios and the 95% CIs are presented.

Percentage change from baseline in TSC-associated seizure frequency during the treatment period was analyzed using ANCOVA, including baseline and stratified age group as covariates and treatment arm as a fixed factor. Treatment differences in the estimated least squares means and the 95% CIs are presented.

Change from baseline in the primary end point TSC-associated seizures during the full maintenance period and 4-week treatment windows during the maintenance period was analyzed using negative binomial regression.

Missing data from the treatment period arising from unreported days in IVRS were imputed for each patient using the worst (highest number of seizures) value of the following: last observation carried forward, next observation carried backward and the mean daily number of seizures during the treatment period (using the non-missing data). The model included total number of seizures as a response variable and age group, time (baseline and treatment period), treatment and treatment by time interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period was included as an offset.

Primary end point analysis was repeated after MI for values MNAR from discontinuation due to any reason or other monotone missing data.

Sensitivity parameter represents the degree of decrease or increase (positive values of K represent decrease and negative values represent increase) in efficacy. The increment in the positive value of K continued until the overall P value was >0.05. The decrease in the negative values of K continued until the overall P value became smaller than the P value from the primary analysis.
eFigure 5. Reduction From Baseline in the Primary End Point Seizures During the Titration Period and the 4-Week Treatment Windows During the Maintenance Period

All *P* values are nominal. The titration period comprised day 1 to day 28 and the maintenance period comprised day 29 to day 113. Patients with at least 7 days of seizure data within the period were included in the analysis. Primary end point seizures included all countable focal motor seizures without impairment of awareness, focal seizures with impairment of awareness, focal seizures evolving to bilateral motor seizures, and generalized seizures (tonic–clonic, tonic, clonic, or atonic); they excluded absence, myoclonic, focal sensory, and infantile/epileptic spasms.

Abbreviations: CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day.
Figure 6. Combined Subject/Caregiver Global Impression of Change in Overall Condition

Global impression of change was assessed on a 7-point Likert scale with 3 categories for improvement in overall condition (slightly, much, and very much improved), 3 categories for worsening of condition (slightly, much, and very much worse), and an option to indicate no change in condition. The combined subject and caregiver impression of global change used either the caregiver’s or the subject’s version if only one version was completed or the caregiver’s version if both versions were completed.

Abbreviations: CBD25, cannabidiol 25 mg/kg/day; CBD50, cannabidiol 50 mg/kg/day.