1.382 Cannabidiol Efficacy in Patients With Lennox-Gastaut Syndrome With Developmental and Epileptic Encephalopathy-Associated Genetic Variants: A Subgroup Analysis

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Introduction

- Lennox-Gastaut syndrome (LGS) is a severe developmental and epileptic encephalopathy (DEE) characterized by hallmark electroclinical features[1]
  - LGS may overlap with DEEs of genetic etiologies[1–3]
- Plant-derived, highly purified cannabidiol (CBD; Epidiolex®, 100 mg/mL oral solution) is approved in the US for the treatment of seizures associated with LGS, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age[4]
  - CBD safety and efficacy in patients with LGS were demonstrated in 2 placebo-controlled randomized clinical trials (RCTs), GWPCARE3 (NCT02224560) and GWPCARE4 (NCT02224690), and an open-label extension trial GWPCARE5 (NCT02224573)[5–7]
- Numerous genetic variants associated with rare genetic DEEs have been identified, and there have been advancements in understanding of the genetic landscape of DEEs since the original CBD RCTs were conducted[1–3]
- Given the recent advances in the field and limited availability of RCT data in individuals with genetic DEEs, this post hoc analysis examined data from the CBD RCTs in a subgroup of participants with a genetic DEE in addition to LGS

Objective

- To evaluate the efficacy of CBD in a subgroup of RCT participants who had LGS and a genetic DEE

Methods

Study selection criteria and study design

- RCT participants received CBD (GWPCARE3, 10 or 20 mg/kg/day; GWPCARE4, 20 mg/kg/day) or placebo over a 4-week baseline and 14-week treatment period (including 2-week titration and 12-week maintenance periods) in addition to existing treatments
- All participants met clinical diagnostic criteria for LGS including documented history of a slow (<3.0 Hz) spike-and-wave electroencephalogram and evidence of ≥2 types of generalized seizures, including drop seizures, for ≥6 months
- RCT participants with documented genetic variants in their clinical histories were identified; all identified variants were searched in the Genes4Epilepsy database[3]
- For variants linked in the Genes4Epilepsy database to a DEE or progressive myoclonic epilepsy phenotype, manual literature searches were performed to identify those associated with named syndromes
- Participants with genetic variants associated with named syndromes were classified as having a genetic DEE
- Results obtained from the searches were reviewed to ensure the reliability of DEE classifications and confirm the accuracy of diagnoses in clinical notes

Study outcomes

- Efficacy endpoints included change in drop seizure frequency from baseline, proportion of participants with ≥50% or ≥75% reduction in drop seizures, and Subject/Caregiver Global Impression of Change (S/CareGI-C) at 14 weeks
- Safety assessments included treatment-emergent adverse events (TEAEs), treatment-related (TR)-TEAEs, serious TEAEs and TR-TEAEs, and withdrawals

Statistical analysis

- Descriptive statistics were used to summarize participant characteristics
- In the genetic DEE subgroup, CBD 10 mg/kg/day and 20 mg/kg/day groups were pooled for analyses to increase the sample size
- This study used data on Epidiolex®, and the results of this post hoc analysis do not apply to other CBD-containing products

Results

Baseline demographics

Table 1. Baseline demographics and clinical characteristics

	Genetic DEE Subgroup (GWPCARE3 + GWPCARE4)				All participants[a]				
					GWPCARE3			GWPCARE4	
	CBD10 (n=6)	CBD20 (n=25)	All CBD (CBD10 + CBD20)[b] (n=31)	Placebo (n=22)	CBD10 (n=73)	CBD20 (n=76)	Placebo (n=76)	CBD20 (n=86)	Placebo (n=85)
Baseline demographics, n (%)									
Male	3 (50.0)	10 (40.0)	13 (41.9)	13 (59.1)	40 (54.8)	45 (59.2)	44 (57.9)	45 (52.3)	43 (50.6)
Country: USA	5 (83.3)	23 (92.0)	28 (90.3)	20 (90.9)	60 (82.2)	59 (77.6)	62 (81.6)	62 (72.1)	66 (77.6)
Taking clobazam	2 (33.3)	14 (56.0)	16 (51.6)	13 (59.1)	37 (50.7)	36 (47.4)	37 (48.7)	42 (48.8)	42 (49.4)
Age 2–17 years	5 (83.3)	19 (76.0)	24 (77.4)	16 (72.7)	51 (69.9)	54 (71.1)	53 (69.7)	56 (65.1)	57 (67.1)
Age 18–55 years	1 (16.7)	6 (24.0)	7 (22.6)	6 (27.3)	22 (30.1)	22 (28.9)	23 (30.3)	30 (34.9)	28 (32.9)
Baseline drop seizure frequency[c]									
Median (Q1, Q3)	64.3 (24.0, 93.9)	87.0 (39.0, 156.8)	87.0 (37.3, 156.8)	81.7 (47.9, 153.1)	86.9 (40.6, 190.0)	85.5 (38.3, 161.5)	80.3 (47.8, 148.0)	71.4 (27.0, 156.0)	74.7 (47.3, 144.0)

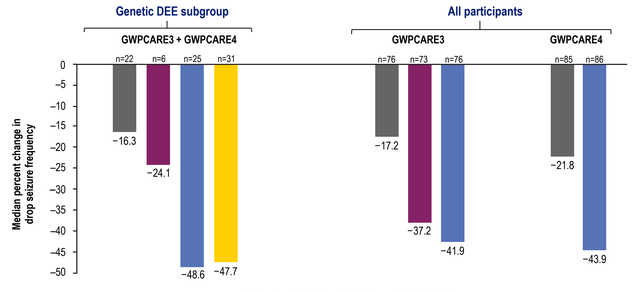
[a]Includes participants with genetic variants. [b]All CBD group includes participants with genetic variants randomized to receive CBD 10 mg/kg/day (n=6) or 20 mg/kg/day (n=25). [c]Baseline drop seizure frequency calculated as the number of seizures during the 28-day baseline period.
CBD, cannabidiol; CBD10, CBD 10 mg/kg/day; CBD20, CBD 20 mg/kg/day; DEE, developmental and epileptic encephalopathy; Q1, first quartile; Q3, third quartile.

- A total of 53 participants aged 2–55 years were identified who had a genetic DEE in addition to LGS (n=6 randomized to CBD 10 mg/kg/day; n=25, CBD 20 mg/kg/day; n=22, placebo)
  - Approximately half of the participants in the genetic DEE subgroup were receiving clobazam as part of their treatment regimen; approximately three-fourths were between ages 2 and 17 years
- The genetic DEE subgroup had broadly similar demographic characteristics and baseline seizure frequency compared with the overall trial populations (**Table 1**)
  - The median baseline drop seizure frequency for participants randomized to CBD 20 mg/kg/day was 87.0 among participants in the genetic DEE subgroup and 85.5 (GWPCARE3) and 71.4 (GWPCARE4) among participants in the overall trial populations
- Genetic variants associated with DEEs are detailed in **Table S1** (available via the QR code)

Efficacy results

Drop seizure frequency

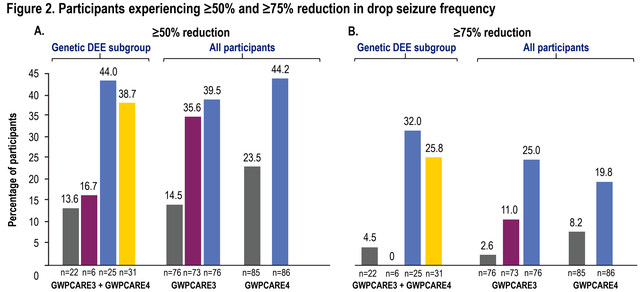
Figure 1. Change in monthly drop seizure frequency at 14 weeks after CBD initiation



CBD, cannabidiol; CBD10, CBD 10 mg/kg/day; CBD20, CBD 20 mg/kg/day; DEE, developmental and epileptic encephalopathy.

- Among participants in the genetic DEE subgroup randomized to CBD 20 mg/kg/day, drop seizure frequency decreased from baseline by a median percent change of −48.6% (Q1, Q3: −86.8, −25.5), compared with −16.3% (−44.2, 1.7) in the placebo group (**Figure 1**)
- The results were consistent with the RCTs overall (GWPCARE3: CBD20 −41.9% vs placebo −17.2%; GWPCARE4: CBD20 −43.9% vs placebo −21.8%)

Figure 2. Participants experiencing ≥50% and ≥75% reduction in drop seizure frequency

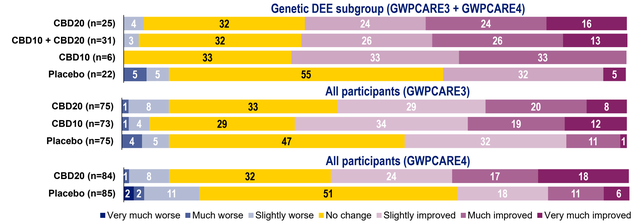


CBD, cannabidiol; CBD10, CBD 10 mg/kg/day; CBD20, CBD 20 mg/kg/day; DEE, developmental and epileptic encephalopathy.

- The proportions of participants in the CBD20 category achieving ≥50% and ≥75% median reductions in drop seizure frequency were largely similar in the genetic DEE subgroup (≥50%: 44.0% and ≥75%: 32.0%) and the overall RCT populations (GWPCARE3: 39.5% and 25%; GWPCARE4: 44.2% and 19.8%) (**Figure 2A and 2B**)

Change in Overall Condition

Figure 3. Proportion of participants/caregivers reporting improvement on the S/CareGI-C scale[a]



[a]Values may not total to 100% due to rounding. CBD, cannabidiol; CBD10, CBD 10 mg/kg/day; CBD20, CBD 20 mg/kg/day; DEE, developmental and epileptic encephalopathy; S/CareGI-C, Subject/Caregiver Global Impression of Change.

- The percentages of participants with improvement reported on the S/CareGI-C scale in the CBD20 category were also largely similar in those with genetic DEEs (64%) and the overall RCT populations (GWPCARE3: 57%, GWPCARE4: 58%)[5,6] (**Figure 3**)

Safety results

Table 2. Summary of TEAEs reported by participants in the genetic DEE subgroup

	Genetic DEE Subgroup (pooled GWPCARE3 + GWPCARE4), n (%)			
	CBD10 (n=5)	CBD20 (n=26)[a]	CBD10 + CBD20 (n=31)[b]	Placebo (n=22)
Any TEAEs	4 (80)	24 (92.3)	28 (90.3)	20 (90.9)
Any TR-TEAEs	0	16 (61.5)	16 (51.6)	10 (45.5)
Any TEAEs leading to withdrawal	0	1 (3.8)	1 (3.2)	0
Any TR-TEAEs leading to withdrawal	0	1 (3.8)	1 (3.2)	0
Any serious TEAEs	0	1 (3.8)	1 (3.2)	2 (9.1)
Any serious TR-TEAEs	0	1 (3.8)	1 (3.2)	0

[a]One participant randomized to the CBD 10 mg/kg/day arm received >10 mg/kg/day CBD and was assigned to the CBD 20 mg/kg/day arm for safety analysis but was included in the CBD 10 mg/kg/day arm for efficacy analysis. [b]Includes participants with genetic variants who received CBD 10 mg/kg/day (n=5) or 20 mg/kg/day (n=26). CBD, cannabidiol; CBD10, CBD 10 mg/kg/day; CBD20, CBD 20 mg/kg/day; DEE, developmental and epileptic encephalopathy; TEAE, treatment-emergent adverse event; TR, treatment-related.

- TEAE incidence in the genetic DEE subgroup was 90.3% among those receiving CBD vs 90.9% in the placebo group; common TEAEs included diarrhea, upper respiratory tract infection, decreased appetite, and somnolence (**Table 2**)
- One participant randomized to CBD 20 mg/kg/day experienced serious TEAEs of liver enzyme elevation and somnolence
- The overall safety profile in the genetic DEE subgroup was consistent with individual RCTs[5,6]

Conclusions

- CBD RCTs included participants who had genetic DEEs in addition to meeting clinical diagnostic criteria for LGS, and understanding of genetic DEEs has advanced since the RCTs were conducted
- Given the shared features of developmental delay, seizures, and underlying genetic or structural etiologies, these syndromes may represent different phenotypic expressions of a common epileptogenic pathway[8]
- In participants with LGS secondary to a genetic DEE, CBD efficacy and safety appeared consistent with the overall LGS RCT populations

References: 1. Cross JH, et al. *Front Neurol.* 2017;8:505. **2.** Happ HC, et al. *Epilepsy Curr.* 2020;20(S2):90–96. **3.** Oliver KL, et al. *Epilepsia.* 2023;64(5):1368–1375. **4.** US Food and Drug Administration. Epidiolex® Prescribing Information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210365s023lbl.pdf. (Accessed September 25, 2025.) **5.** Devinsky O, et al. *N Engl J Med.* 2018;378(20):1888–1897. **6.** Thiele EA, et al. *Lancet.* 2018;391(10125):1085–1096. **7.** Patel A, et al. *Epilepsia.* 2021;62(9):2228–2239. **8.** Guerrini R, et al. *Neurotherapeutics.* 2014;11(2):269–285.

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Epidiolex® is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.

Poster presented at American Epilepsy Society Annual Meeting, December 5–9, 2025; Atlanta, GA, USA

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Supplementary Material

Table S1. Genes with genetic variants associated with genetic DEEs

Affected gene or chromosome	Number of participants with genetic variant[a]
AFG3L2	1
ALDH7A1	1
ALG14	1
ALG13	1
ARFGEF2	1
ARX	2
ASPM	1
CDKL5	4
CNTNAP2	1
DCX	4
FKRP	1
GAMT	1
GLDC	1
JMJD1C	1
KANSL1	2
KCNQ2	1
KCNT1	2
KCTD7	1
MBD5	2
MECP2	1
MED17	1
MEF2C	1
NPC2	1
PCDH19	3
PLCB1	1
PNKP	1
POLG	2
PURA	1
SCN1A	2
SCN2A	1
STX1A	1
TCF4	1
TSC1	1
TSC2	3
UBE3A	1
VPS13B	1
Chromosome 14[b]	1
Chromosome 15[c]	5
Chromosome 21[b]	5

[a]Of the 53 participants in the genetic DEE cohort, more than 1 genetic variant was identified for some individuals. [b]Trisomy. [c]Mutation/duplication/isodicentric.
DEE, developmental and epileptic encephalopathy.

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