SUPPORTING INFORMATION

TABLE S1 Demographics and baseline characteristics for LGS populations by trial, overall and on clobazam (intention-to-treat population)

	GWPCARE3						GWPCARE4			
	Overall			On clobazam			Overall		On clobazam	
	Placebo (n = 76)	CBD10 (n = 73)	CBD20 (n = 76)	Placebo (n = 37)	CBD10 (n = 37)	CBD20 (n = 36)	Placebo (n = 85)	CBD20 (n = 86)	Placebo (n = 42)	CBD20 (n = 42)
Age, years										
Mean	15.3	15.4	16.0	13.0	14.7	16.1	15.3	15.5	12.1	14.4
SD	9.3	9.5	10.8	7.5	7.8	10.8	9.8	8.7	7.5	7.9
Sex, n (%)										
Male	44 (58)	40 (55)	45 (59)	21 (57)	16 (43)	21 (58)	43 (51)	45 (52)	21 (50)	22 (52)
Region, n (%)										
USA	62 (82)	60 (82)	59 (78)	33 (89)	36 (97)	31 (86)	66 (78)	62 (72)	38 (91)	39 (93)
Rest of world	14 (18)	13 (18)	17 (22)	4 (11)	1 (3)	5 (14)	19 (22)	24 (28)	4 (10)	3 (7)
Weight at baseline, kg										
Mean	45.7	44.3	41.0	41.7	42.0	43.6	43.0	42.7	39.6	41.6
SD	23.2	26.2	20.6	21.0	21.0	21.6	23.0	22.6	23.0	21.5
Body mass index at baseline, kg/m^2										
Mean	21.4	20.9	19.0	20.2	20.1	20.2	19.8	21.0	19.6	22.0
SD	6.9	7.6	5.7	5.4	5.6	5.4	5.7	10.0	5.3	12.6
Baseline primary seizure frequency, per 28 days*										
Median	80.3	86.9	85.5	76.3	87.0	69.0	74.7	71.4	83.5	59.0
Range	8.7, 1278.3	14.0, 7494.0	13.0, 1092.0	8.7, 1278.3	14.0, 7494.0	13.5, 682.3	11.2, 3174.6	10.3, 855.9	22.0, 3174.6	10.3, 551.0
Number of AEDs, median (range)										
Previous AEDs	6 (1, 22)	6 (0, 21)	6 (1, 18)	5 (1, 16)	6 (1, 19)	5 (1,18)	6 (0, 28)	6 (1, 18)	5 (0, 14)	5 (1, 16)
Current AEDs	3 (1, 5)	3 (1, 5)	3 (0, 5)	3 (1, 5)	3 (1, 5)	3 (1, 5)	3 (1, 4)	3 (1, 5)	3 (2, 4)	3 (2, 5)
Most common (>25% in any group) AEDs currently being taken, n (%)										

Clobazam	37 (49)	37 (51)	36 (47)	37 (100)	37 (100)	36 (100)	42 (49)	42 (49)	42 (100)	42 (100)
Valproate[†]	30 (40)	27 (37)	28 (37)	12 (32)	7 (19)	10 (28)	33 (39)	36 (42)	12 (29)	12 (29)
Levetiracetam	23 (30)	22 (30)	24 (32)	14 (38)	9 (24)	12 (33)	35 (41)	23 (27)	18 (43)	14 (33)
Lamotrigine	25 (33)	22 (30)	20 (26)	8 (22)	10 (27)	12 (33)	31 (37)	33 (38)	14 (33)	17 (41)
Rufinamide	20 (26)	19 (26)	26 (34)	8 (22)	12 (32)	9 (25)	21 (25)	25 (29)	11 (26)	13 (31)

Abbreviations: AED, antiepileptic drug; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; LGS, Lennox-Gastaut syndrome; SD, standard deviation.

*Baseline period included all seizure data prior to day 1.

[†]Valproate includes ergenyl chrono for all trials.

TABLE S2 Demographics and baseline characteristics for DS populations by trial, overall and on clobazam (intention-to-treat population)

	GWPCARE2					GWPCARE1B				
	Overall			On clobazam		Overall			On clobazam	
	Placebo (n = 65)	CBD10 (n = 66)*	CBD20 (n = 67)	Placebo (n = 41)	CBD10 (n = 45)	CBD20 (n = 40)	Placebo (n = 59)	CBD20 (n = 61)	Placebo (n = 38)	CBD20 (n = 40)
Age, years										
Mean	9.6	9.2	9.3	9.2	9.1	9.6	9.8	9.7	10.3	9.0
SD	4.6	4.3	4.3	4.9	4.1	4.0	4.9	4.7	5.1	4.6
Sex, n (%)										
Male	31 (48)	27 (41)	36 (54)	19 (46)	23 (51)	23 (58)	27 (46)	35 (57)	16 (42)	22 (55)
Region, n (%)										
USA	32 (49)	30 (46)	31 (46)	23 (56)	22 (49)	21 (53)	37 (63)	35 (57)	29 (76)	23 (58)
Rest of world	33 (51)	36 (55)	36 (54)	18 (44)	23 (51)	19 (48)	22 (37)	26 (43)	9 (24)	17 (43)
Weight at baseline, kg										
Mean	34.0	32.8	34.2	33.4	33.5	36.6	35.1	33.8	36.5	33.1
SD	14.9	16.6	19.2	16.1	17.3	21.9	18.3	16.6	18.9	17.9
Body mass index at baseline, kg/m^2										
Mean	18.8	18.5	18.9	18.8	18.9	19.4	19.1	18.3	19.3	18.6
SD	3.9	4.5	4.6	3.4	5.0	5.4	4.7	4.5	4.3	4.5
Baseline primary seizure frequency, per 28 days†										
Median	16.6	13.5	9.0	17.7	13.1	9.6	14.9	12.4	15.9	10.8
Range	3.0, 770.5	0.0, 467.0	3.9, 661.2	3.0, 401.0	4.0, 238.4	3.9, 661.2	3.7, 718.0	3.9, 1716.7	3.7, 448.9	3.9, 553.5
Number of AEDs, median (range)										
Previous AEDs	4 (0, 11)	4 (0, 19)	4 (0, 11)	4 (0, 9)	4 (0, 12)	4 (1, 11)	4 (0, 14)	4 (0, 26)	4 (1, 14)	3 (0, 20)
Current AEDs	3 (1, 5)	3 (1, 5)	3 (1, 4)	3 (1, 5)	3 (1, 5)	3 (2, 4)	3 (1, 5)	3 (1, 5)	3 (2, 5)	3 (1, 5)
Most common (>25% in any group) AEDs currently being taken, n (%)										
Clobazam	41 (63)	45 (68)	40 (60)	41 (100)	45 (100)	40 (100)	38 (64)	40 (66)	38 (100)	40 (100)
Valproate‡	48 (74)	44 (67)	47 (70)	29 (71)	30 (67)	30 (75)	32 (54)	36 (59)	21 (55)	26 (65)

Stiripentol	24 (37)	25 (38)	22 (33)	17 (41)	17 (38)	18 (45)	21 (36)	30 (49)	14 (37)	23 (58)
Levetiracetam	14 (22)	19 (29)	21 (31)	8 (20)	11 (24)	9 (23)	17 (29)	16 (26)	9 (24)	6 (15)
Topiramate	17 (26)	11 (17)	18 (27)	11 (27)	8 (18)	10 (25)	15 (25)	16 (26)	7 (18)	8 (20)

Abbreviations: AED, antiepileptic drug; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; SD, standard deviation.

*One patient randomized to 10 mg/kg/day CBD was not treated and was withdrawn by the principal investigator.

†Baseline period included all seizure data prior to day 1.

‡Valproate includes ergenyl chrono for all trials.

TABLE S3 Reduction from baseline in primary seizures and ≥50% responder rates for by-trial LGS populations, overall and on clobazam (intention-to-treat population)

		LGS overall			LGS on clobazam		
Trial	**Treatment**	**N**	**% reduction from baseline***	**Difference or % reduction compared with placebo (95% CI)†**	**N**	**% reduction from baseline***	**Difference or % reduction compared with placebo (95% CI)†**
GWPCARE3	Placebo	76	17.2		37	22.7	
	CBD10	73	37.2	19.2 (7.7-31.2) *P* = .0016	37	45.6	29.6% (2.4-49.2%) *P* = .0355‡
	CBD20	76	41.9	21.6 (6.7-34.8) *P* = .0047	36	64.3	53.8% (35.7-66.8%) *P* < .0001‡
GWPCARE4	Placebo	85	21.8		42	30.7	
	CBD20	86	43.9	17.2 (4.1-30.3) *P* = .0135	42	62.4	45.7% (27.0-59.6%) *P* < .0001‡
			≥50% responder rate (%)§		**N**	**≥50% responder rate (%)§**	
GWPCARE3	Placebo	76	14.5		37	21.6	
	CBD10	73	35.6 *P* = .0030		37	40.5 *P* = .0584‡	
	CBD20	76	39.5 *P* = .0006		36	55.6 *P* = .0021‡	
GWPCARE4	Placebo	85	23.5		42	28.6	
	CBD20	86	44.2 *P* = .0043		42	54.8 *P* = .0140‡	

Abbreviations: CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; CI, confidence interval; LGS, Lennox-Gastaut syndrome.

*Data for the overall population are presented as median percent reduction from baseline; data for the on-clobazam subgroup are presented as percent reduction from baseline estimated from a negative binomial regression analysis.

[†]Overall data are presented as estimated median difference and *P*-value from a Wilcoxon rank-sum test. Data for the on-clobazam subgroup are estimated from a negative binomial regression analysis.

[‡]Nominal *P*-value.

[§]The overall *P*-value is based on a Cochran-Mantel-Haenszel test; the nominal *P*-values for the on-clobazam subgroup are based on logistic regression analysis.

TABLE S4 Other secondary endpoints for by-trial LGS populations, overall and on clobazam (intention-to-treat population)

		Overall population			Patients on clobazam		
		N	**Value**	***P*-value**	**N**	**Value**	***P*-value**
Percentage reduction in total seizures per 28 days over treatment period*							
GWPCARE3	Placebo	76	19		37	25	
	CBD10	73	36	.0015	37	53	.0025†
	CBD20	76	38	.0091	36	64	<.0001†
GWPCARE4	Placebo	85	14		42	25	
	CBD20	86	41	.0005	42	66	<.0001†
Improvement in S/CGIC, % of patients*							
GWPCARE3	Placebo	75	44		37	46	
	CBD10	73	66	.0020†	37	76	.0005†
	CBD20	75	57	.0439†	35	80	.0003†
GWPCARE4	Placebo	85	34		42	31	
	CBD20	84	58	.0012†	41	81	<.0001†
≥75% responder rate, %							
GWPCARE3	Placebo	76	3		37	3	
	CBD10	73	11	.0603†	37	11	.1836†
	CBD20	76	25	.0010†	36	36	.0044†
GWPCARE4	Placebo	85	8		42	7	
	CBD20	86	20	.0297†	42	31	.0051†
Drop seizure-free days per 28 days, change from baseline							
GWPCARE3	Placebo	76	2.3		37	3.4	
	CBD10	73	5.6	.0030†	37	6.7	.0259†

	CBD20	76	6.9	<.0001†	36	11.0	<.0001†
GWPCARE4	Placebo	85	3.4		42	3.4	
	CBD20	86	6.1	.0075†	42	8.9	<.0001†

Note: For median percentage reduction in total seizures per 28 days over treatment period, overall data are analyzed using a Wilcoxon rank-sum test. Onclobazam *P*-values are percentage reduction from baseline estimated from a negative binomial regression analysis. The S/CGIC and ≥75% responder rate data were analyzed using a logistic regression model with treatment, factor, and factor by treatment interaction as covariates. The change from baseline in seizure-free days is analyzed using an ANCOVA model with baseline number of drop seizure-free days, age group, treatment, factor, and factor by treatment interaction as covariates. All statistical analyses are based on difference or percentage reduction compared with placebo.

Abbreviations: ANCOVA, analysis of covariance; CBD10, cannabidiol 10 mg/kg/day; CBD 20, cannabidiol 20 mg/kg/day; LGS, Lennox-Gastaut syndrome; S/CGIC, Subject/Caregiver Global Impression of Change.

*Key secondary endpoint.

†Nominal *P*-value.

TABLE S5 Percentage reduction from baseline in primary seizures and ≥50% responder rates for DS by trial

		DS overall			DS on clobazam		
Trial	**Treatment**	**N**	**% reduction from baseline***	**Difference or % reduction compared with placebo (95% CI)†**	**N**	**% reduction from baseline***	**Difference or % reduction compared with placebo (95% CI)†**
GWPCARE2	Placebo	65	26.9		41	37.6	
	CBD10	66	48.7	29.8% (8.4-46.2%)	45	60.9	37.4% (13.9-54.5%)
				P = .0095			*P* = .0042‡
	CBD20	67	45.7	25.7% (2.9-43.2%)	40	56.8	30.8% (3.6-50.4%)
				P = .0299			*P* = .0297‡
GWPCARE1	Placebo	59	13.3		38	18.9	
	CBD20	61	38.9	22.8 (5.4-41.1)	40	53.6	42.8% (17.4-60.4%)
				P = .0123			*P* = .0032‡
			≥50% responder rate (%)§		**N**	**≥50% responder rate (%)§**	
GWPCARE2	Placebo	65	26.2		41	36.6	
	CBD10	66	43.9		45	55.6	
			P = .0332			*P* = .0623‡	
	CBD20	67	49.3		40	62.5	
			P = .0069			*P* = .0130‡	
GWPCARE1	Placebo	59	27.1		38	23.7	
	CBD20	61	42.6		40	47.5	
			P = .0784			*P* = .0382‡	

Abbreviations: CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; CI, confidence interval; DS, Dravet syndrome.

*For trial GWPCARE1, overall data are presented as median percent reduction from baseline. Data for trial GWPCARE2 and the on-clobazam subgroup are presented as percent reduction from baseline estimated from a negative binomial regression analysis.

†For trial GWPCARE1, overall data are presented as estimated median difference and *P*-value from a Wilcoxon rank-sum test. Data for trial GWPCARE2 and the on-clobazam subgroup are estimated from a negative binomial regression analysis.

‡Nominal *P*-value.

§The overall *P*-value is based on a Cochran-Mantel-Haenszel test; the nominal *P*-value for the on-clobazam subgroup is based on logistic regression analysis.

TABLE S6 Other secondary endpoints for DS populations by trial, overall and on clobazam (intention-to-treat population)

		Overall population			Patients on clobazam		
		N	**Value**	***P*-value**	**N**	**Value**	***P*-value**
Median percentage reduction in total seizures per 28 days over treatment period*							
GWPCARE2	Placebo	65	30		41	41	
	CBD10	66	56	.0003†	45	66	.0003†
	CBD20	67	47	.0255†	40	58	.0341†
GWPCARE1	Placebo	59	9		38	27	
	CBD20	61	29	.0335†	40	54	.0211†
Improvement in S/CGIC, % of patients*							
GWPCARE2	Placebo	65	42		41	42	
	CBD10	66	68	.0009†	45	73	.0009†
	CBD20	66	61	.0279†	39	77	.0018†
GWPCARE1	Placebo	58	35		37	30	
	CBD20	60	62	.0155†	39	62	.0136†
≥75% responder rate, %							
GWPCARE2	Placebo	65	6		41	10	
	CBD10	66	30	.0012†	45	36	.0075†
	CBD20	67	18	.0507†	40	25	.0731†
GWPCARE1	Placebo	59	12		38	13	
	CBD20	61	23	.1131†	40	25	.2311†
Convulsive seizure-free days per 28 days, change from baseline							
GWPCARE2	Placebo	65	1.6		41	2.6	
	CBD10	66	4.0	.0009†	45	5.3	.0015†
	CBD20	67	2.9	.0683†	40	3.9	.1348†
GWPCARE1	Placebo	59	1.7		38	1.2	

	CBD20	61	3.1	.0396†	40	3.4	.0114†

Note: For median percentage reduction in total seizures per 28 days over treatment period, overall data are analyzed using a Wilcoxon rank-sum test. Onclobazam *P*-values are percentage reduction from baseline estimated from a negative binomial regression analysis. The S/CGIC and ≥75% responder rate was analyzed using a logistic regression model with treatment, factor, and factor by treatment interaction as covariates. The change from baseline in seizure-free days is analyzed using an ANCOVA model with baseline number of convulsive seizure-free days, age group, treatment, factor, and factor by treatment interaction as covariates. All statistical analyses are based on difference or percentage reduction compared with placebo.

Abbreviations: ANCOVA, analysis of covariance; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; S/CGIC, Subject/Caregiver Global Impression of Change.

*Key secondary endpoint.

†Nominal *P*-value.