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Introduction

- Plant-derived highly purified cannabidiol oral solution (CBD) is approved in the EU and UK for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), in conjunction with clobazam, based on data from a large clinical programme of randomised controlled trials (RCTs).¹⁻⁶
- In pharmacokinetic studies, CBD bioavailability has previously been shown to increase with a high-fat meal versus fasting.^{7,8}
- Real-world studies and case reports suggest that coadministration of a ketogenic (high fat, low carbohydrate) diet with CBD influences CBD plasma levels and seizure reduction.⁹⁻¹¹
 - However, in patients with LGS or DS receiving CBD, the relationship between a ketogenic diet and CBD bioavailability or seizure response remains unclear
- This post-hoc analysis of the CBD RCTs explored this relationship.

Objective

- To gain a better understanding of the effect of a ketogenic diet on CBD plasma concentration and seizure reduction in patients with LGS or DS treated with CBD in the RCTs.

Methods

- A post-hoc analysis of pooled RCT data in patients with LGS (NCT02224560, NCT02224690) or DS (NCT02224703) who were, or were not, on a ketogenic diet alongside CBD treatment.
- Data were also pooled from another RCT in patients with DS (NCT02091375) for the seizure frequency analysis.
- Patient data were from those enrolled in the RCTs who had received 10 (CBD10) or 20 (CBD20) mg/kg/day plant-derived, highly purified CBD (Epidyolex® [EU]/Epidiolex® [US]; 100 mg/mL oral solution) and who had available dietary records.
- Outcomes included:
 - CBD plasma concentration over time (assessed using liquid chromatography with tandem mass spectrometry)
 - Change in blood plasma levels of CBD over time
 - Change in total seizure frequency over time
- The RCTs were conducted with Epidyolex®/Epidiolex®, and the results do not apply to other CBD-containing products.

Results

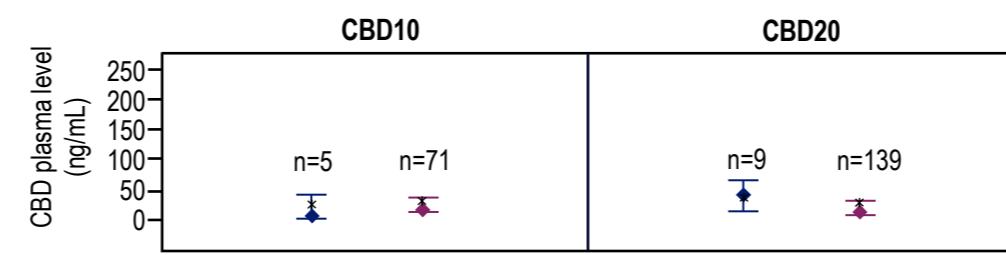
Patient baseline characteristics^a

	Patients on a ketogenic diet (N=18)		Patients not on a ketogenic diet (N=244)	
	CBD10 (n=7)	CBD20 (n=11)	CBD10 (n=82)	CBD20 (n=162)
Mean age, y (min, max)	9.2 (4.5, 17.7)	10.0 (3.0, 17.1)	13.5 (2.6, 38.2)	16.2 (2.6, 48.0)
Sex, n (%)				
Female	5 (71.4)	2 (18.2)	40 (48.8)	77 (47.5)
Number of prior ASMs, n (%)				
0	0 (0)	0 (0)	3 (3.7)	0 (0)
1	0 (0)	1 (9.1)	3 (3.7)	6 (3.7)
2	0 (0)	1 (9.1)	10 (12.2)	5 (3.1)
3	2 (28.6)	0 (0)	10 (12.2)	18 (11.1)
≥4	5 (71.4)	9 (81.8)	56 (68.3)	133 (82.1)
Number of ASMs during the RCT, n (%)				
1	0 (0)	1 (9.1)	5 (6.1)	10 (6.2)
2	0 (0)	1 (9.1)	25 (30.5)	40 (24.7)
3	4 (57.1)	5 (45.5)	25 (30.5)	57 (35.2)
≥4	3 (42.9)	4 (36.4)	27 (32.9)	55 (34.0)
Baseline seizure frequency per 28 days, mean (min, max)				
Total	1385.2 (44.8, 7494.0)	513.3 (19.4, 2671.0)	469.7 (3.7, 13607)	379.0 (3.9, 4591.0)

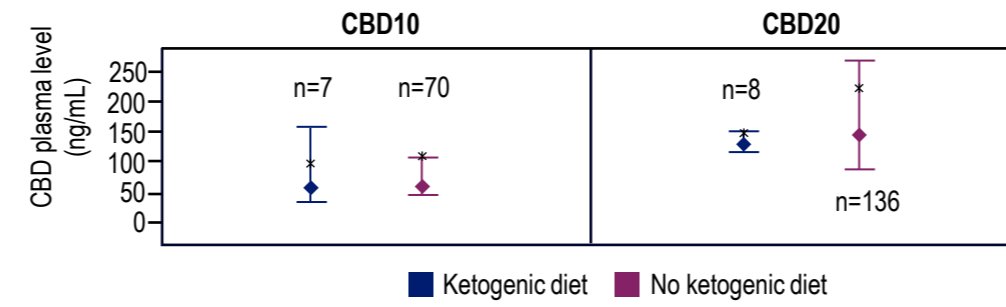
^aPatients with available plasma samples only. ASMs, antiseizure medications; CBD, cannabidiol; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; RCT, randomised controlled trial; y, year.

Median CBD blood plasma level by ketogenic diet over time

Day 1^a

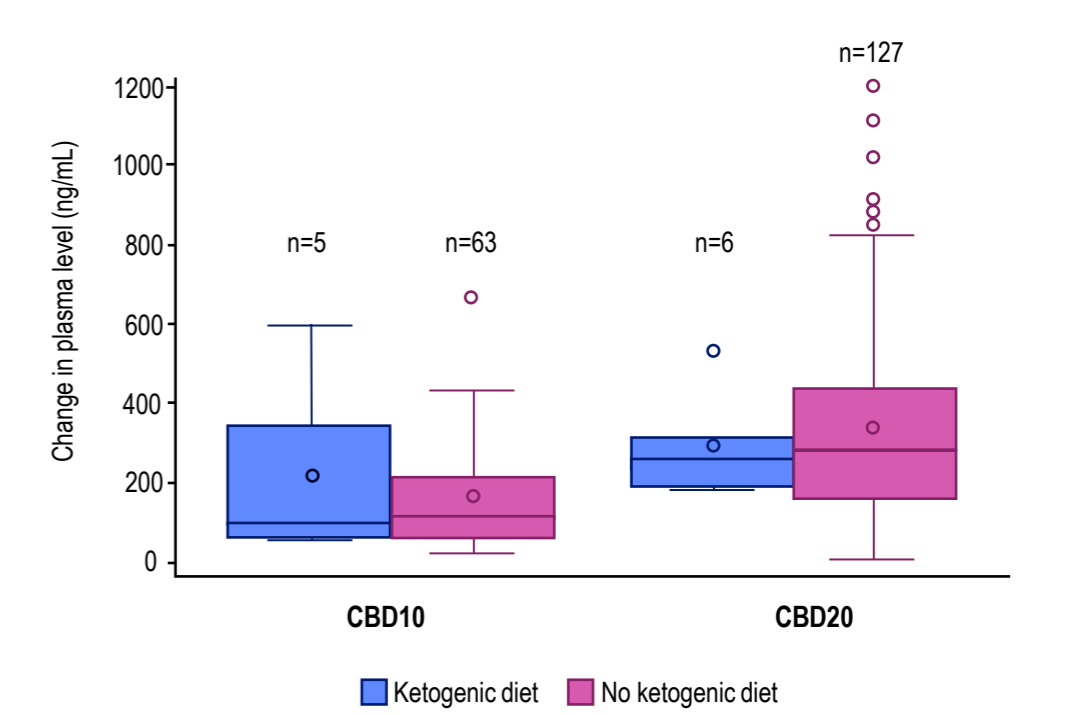


End of treatment^b



^a14 patients on a ketogenic diet and 210 patients not on a ketogenic diet had Day 1 plasma samples available; ^b15 patients on a ketogenic diet and 206 patients not on a ketogenic diet had end-of-treatment plasma samples available. Upper bar = Q1; lower bar = Q3; diamond = median; asterisk = mean. CBD, cannabidiol; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; Q1, first quartile; Q3, third quartile.

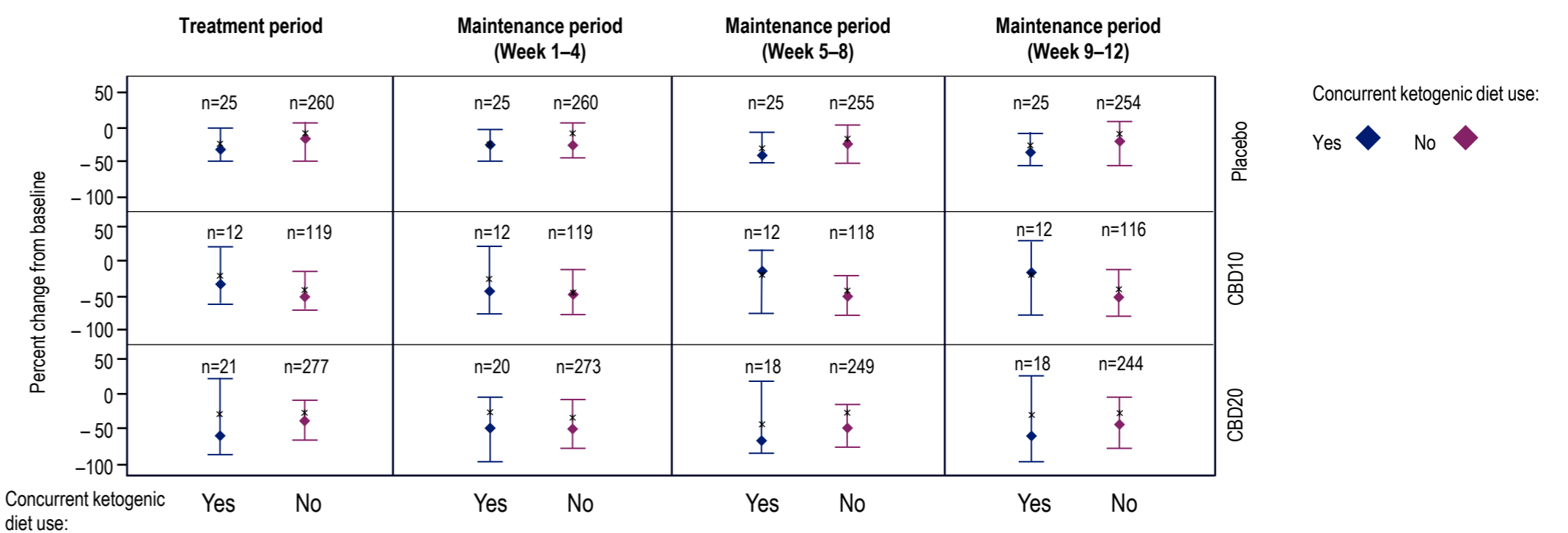
Median change in CBD blood plasma level from Day 1 to End of Treatment by ketogenic diet



Upper and lower bounds of the box = Q1 and Q3; central line inside box = median; circle = mean, error bars = minimum and maximum; circles outside the boxes = outliers. CBD, cannabidiol; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; Q1, first quartile; Q3, third quartile.

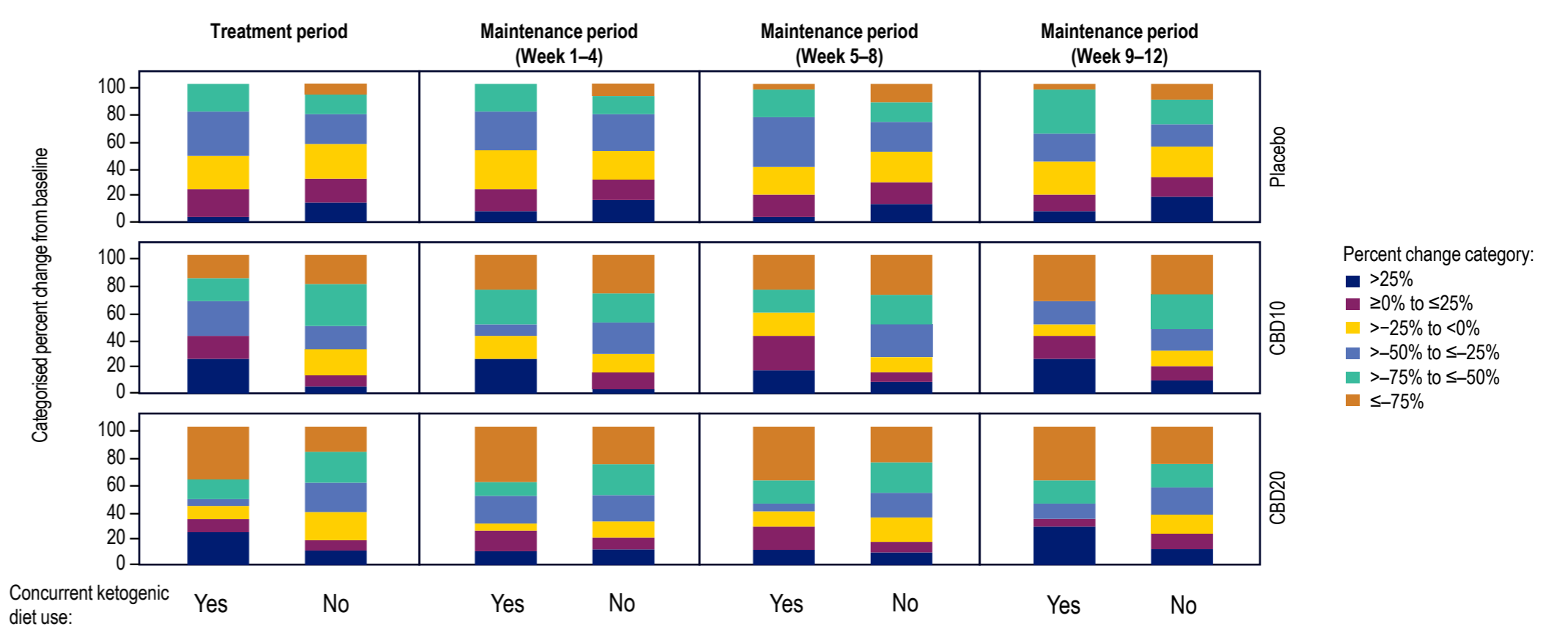
- Median CBD plasma levels were not substantially different between the ketogenic diet and non-ketogenic diet groups in patients receiving 10 or 20 mg/kg/day CBD at the start and end of CBD treatment.

Percentage change in total seizure frequency over time^a



^aIncludes patients from the RCTs: NCT02224560 (LGS), NCT02224690 (LGS), NCT02224703 (DS), and NCT02091375 (DS); patient characteristics are provided in the supplementary material available via the QR code. Upper bar = Q1; lower bar = Q3; diamond = median; asterisk = mean. CBD, cannabidiol; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; RCTs, randomised controlled trials.

Total seizure responder rates over time^a



^aIncludes patients from the RCTs: NCT02224560 (LGS), NCT02224690 (LGS), NCT02224703 (DS) and NCT02091375 (DS); patient characteristics are provided in the supplementary material available via the QR code. CBD, cannabidiol; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; RCTs, randomised controlled trials.

- Percentage change from baseline in total seizure frequency and total seizure responder rates were not substantially different between the ketogenic diet and non-ketogenic diet groups.
- Findings were consistent across individual seizure types (see supplementary material via the QR code).

Limitations

- The RCTs were not designed to investigate the effect of a ketogenic diet on CBD exposure/effectiveness:
 - Data may be impacted by differences in the timing of meals in relation to CBD dosing and collection of blood plasma
 - High CBD outliers may represent patients taking CBD with a meal
 - Diet composition in the ketogenic and non-ketogenic diet groups was unknown
 - The lack of statistical testing and low sample size further limits the reliability and generalisability of the findings

Conclusions

- In this post-hoc analysis of the CBD LGS and DS RCTs, no substantial differences were observed in CBD plasma concentration or seizure responses in patients on a ketogenic diet versus those who were not.
- Further research is needed using studies specifically designed to assess the impact of a ketogenic diet and its timing on CBD plasma levels and seizure reduction.

References: 1. Kuhne F, et al. *Epilepsia Open*. 2023;8(2):360-370. 2. Tzadok M, et al. *Pediatr Neurol*. 2024;150:91-96. 3. Devinsky O, et al. *N Engl J Med*. 2018;378(20):1888-1897. 4. Thiele EA, et al. *Lancet*. 2018;391(10125):1085-1096. 5. Devinsky O, et al. *N Engl J Med*. 2017;376(21):2011-2020. 6. Miller I, et al. *JAMA Neurol*. 2020;77(5):613-621. 7. Crockett J, et al. *Epilepsia*. 2020;61(2):267-277. 8. Taylor L, et al. *CNS Drugs*. 2018;32(11):1053-1067. 9. Coskun Y, Yildirim C. *Int J Neurosci*. 2022;133(3):322-326. 10. Gupta S, et al. *Eur J Med Genet*. 2020;63(9):103970. 11. Bristol L, et al. *Pharmaceutics*. 2023;15(8):2120.

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Disclosures: All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. CJL has received speaker/expert group honoraria from Angelini, Eisai, Jazz Pharmaceuticals, and UCB Pharma; MMC is an employee of Jazz Pharmaceuticals, Inc.; HM and KV are employees of Jazz Pharmaceuticals, UK Ltd. Epidyolex® is approved in the UK and EU for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, in patients ≥2 years of age; it is additionally approved in the UK and EU for the adjunctive treatment of seizures associated with tuberous sclerosis complex in patients ≥2 years of age.



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Supplementary materials

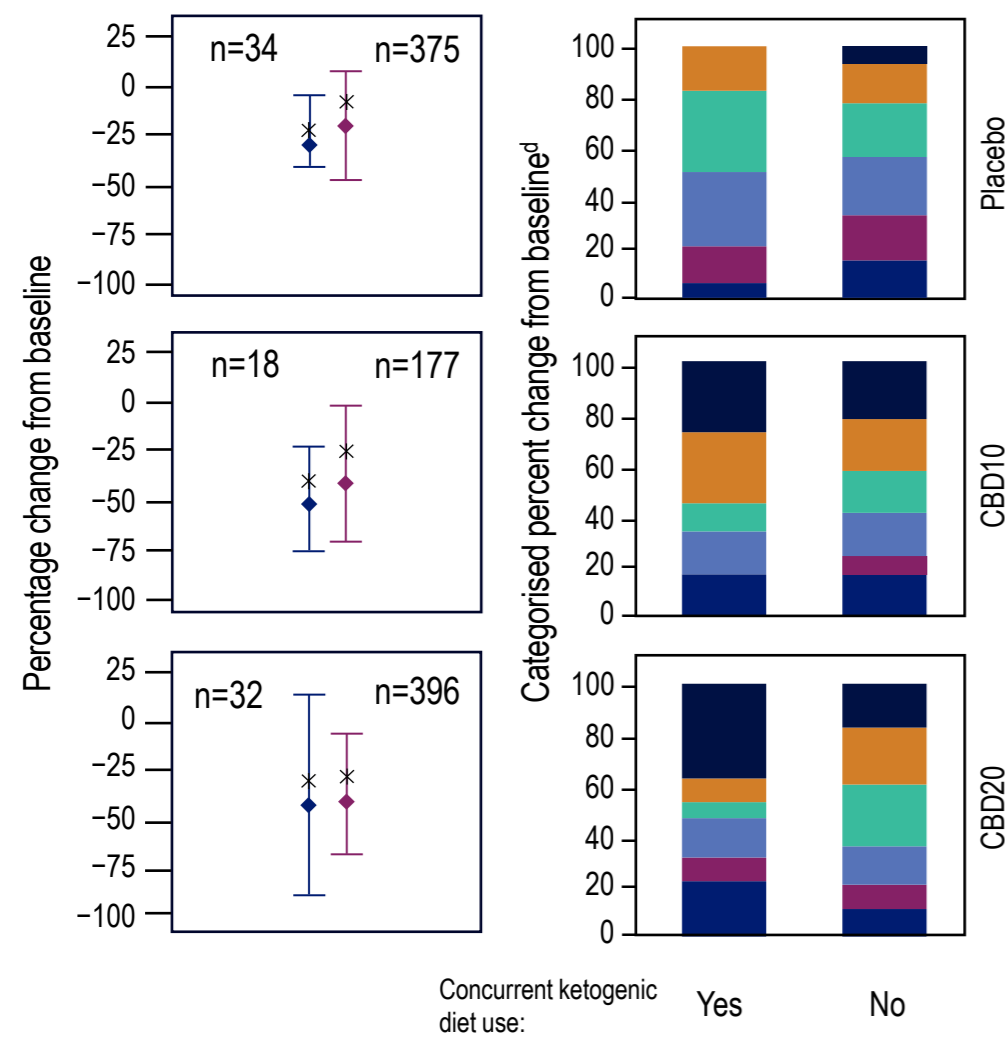
Baseline characteristics of patients with baseline total seizure data available^a

	Patients on a ketogenic diet (N=58)			Patients not on a ketogenic diet (N=655)		
	Placebo (n=25)	CBD10 (n=12)	CBD20 (n=21)	Placebo (n=260)	CBD10 (n=118)	CBD20 (n=277)
Mean age, y (min, max)	10.6 (3.0, 20.5)	7.0 (2.8, 17.7)	7.6 (2.6, 17.1)	13.1 (2.2, 45.1)	12.6 (2.3, 38.2)	13.6 (2.2, 48.0)
Sex, n (%)						
Female	6 (24.0)	8 (66.7)	6 (28.6)	134 (51.5)	61 (51.7)	126 (45.5)
Number of prior ASMs, n (%)						
0	0 (0)	1 (8.3)	1 (4.8)	6 (2.3)	4 (3.4)	6 (2.2)
1	2 (8.0)	1 (8.3)	1 (4.8)	16 (6.2)	8 (6.8)	17 (6.1)
2	3 (12.0)	1 (8.3)	2 (9.5)	30 (11.5)	12 (10.2)	21 (7.6)
3	4 (16.0)	3 (25.0)	5 (23.8)	28 (10.8)	14 (11.9)	32 (11.6)
≥4	16 (64.0)	6 (50.0)	12 (57.1)	180 (69.2)	80 (67.8)	201 (72.6)
Number of ASMs during the RCT, n (%)						
1	1 (4.0)	0 (0)	2 (9.5)	10 (3.8)	7 (5.9)	15 (5.4)
2	10 (40.0)	2 (16.7)	7 (33.3)	54 (20.8)	34 (28.8)	56 (20.2)
3	7 (28.0)	5 (41.7)	7 (33.3)	101 (38.8)	40 (33.9)	112 (40.4)
≥4	7 (28.0)	5 (41.7)	5 (23.8)	95 (36.5)	37 (31.4)	94 (33.9)
Baseline seizure frequency per 28 days, mean (min, max)						
Total	705.4 (39.4, 3207.0)	863.3 (6.0, 7494.0)	466.7 (4.8, 2671.0)	339.6 (4.0, 4357.4)	374.0 (3.7, 13607.0)	339.8 (3.9, 4591.0)

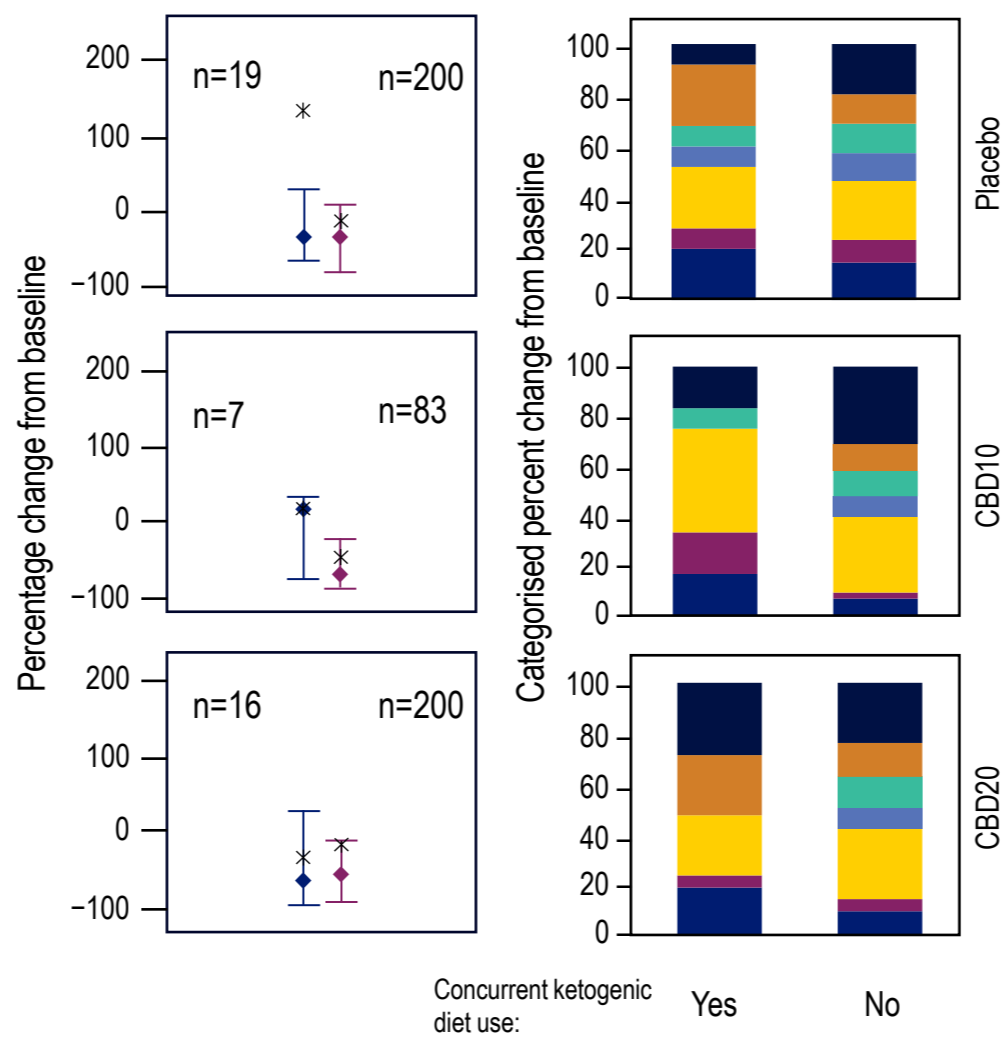
^aIncludes patients from the RCTs: NCT02224560 (LGS), NCT02224690 (LGS), NCT02224703 (DS) and NCT02091375 (DS). ASMs, antiseizure medications; CBD, cannabidiol; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; RCT, randomised controlled trial.

Percentage change in total seizure frequency and responder rates, by seizure type^a

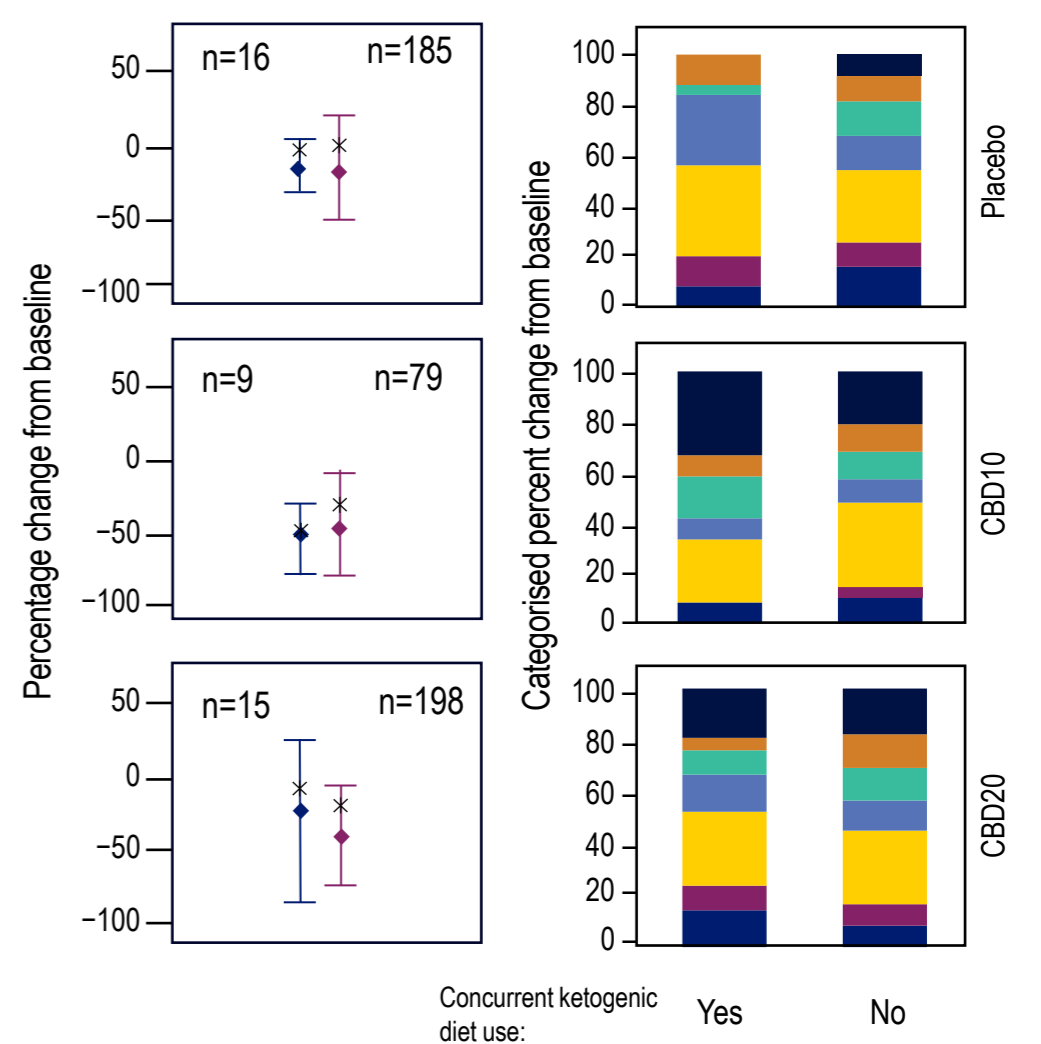
Convulsive seizures^{b,c}



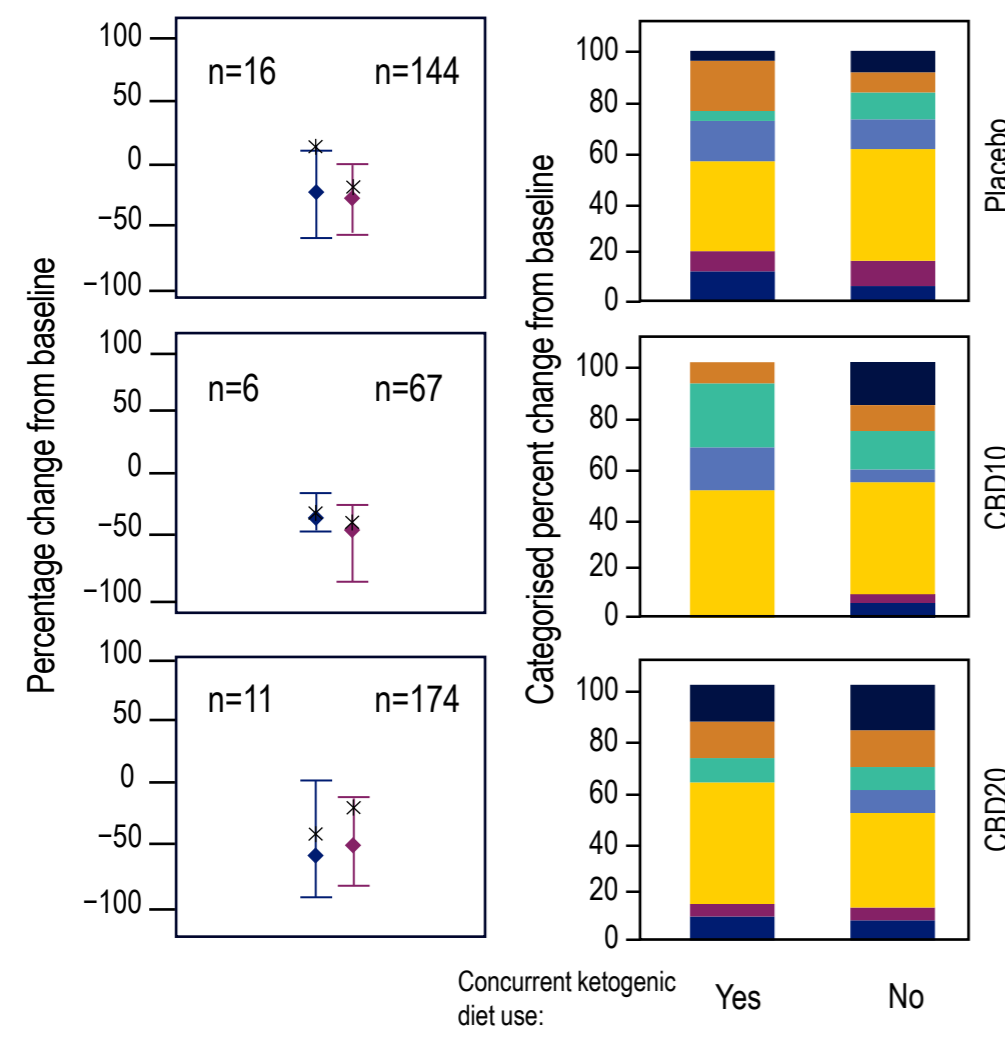
Non-convulsive seizures



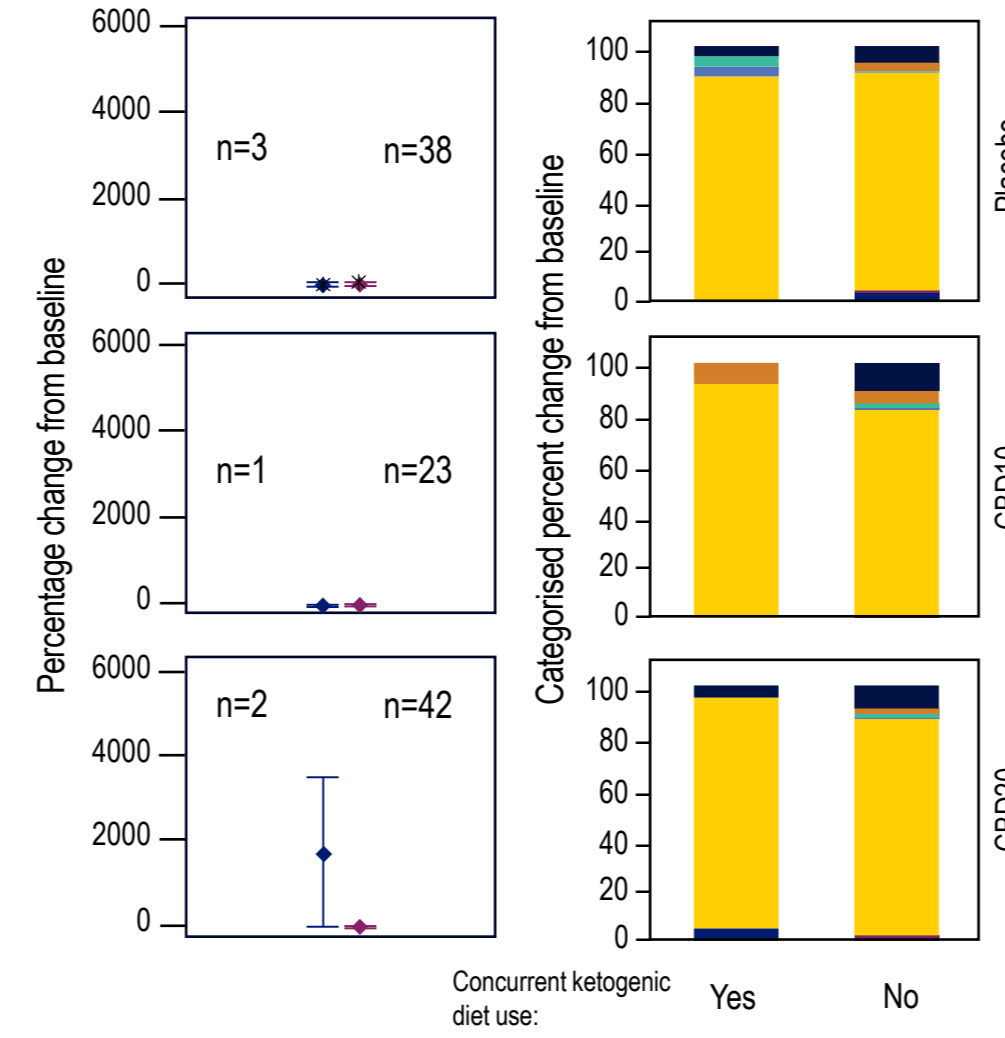
Tonic-clonic seizures^b



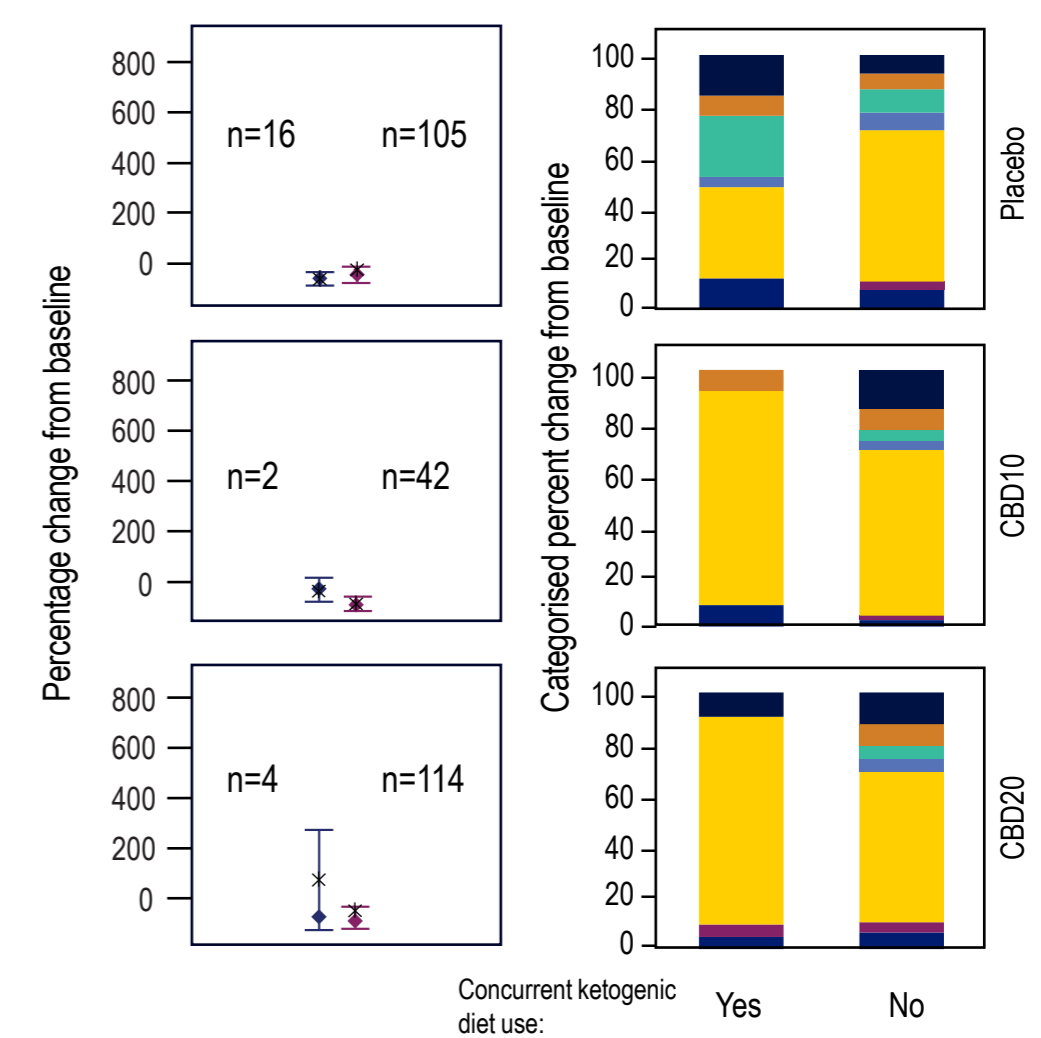
Tonic seizures^b



Clonic seizures^a



Atonic seizures^b



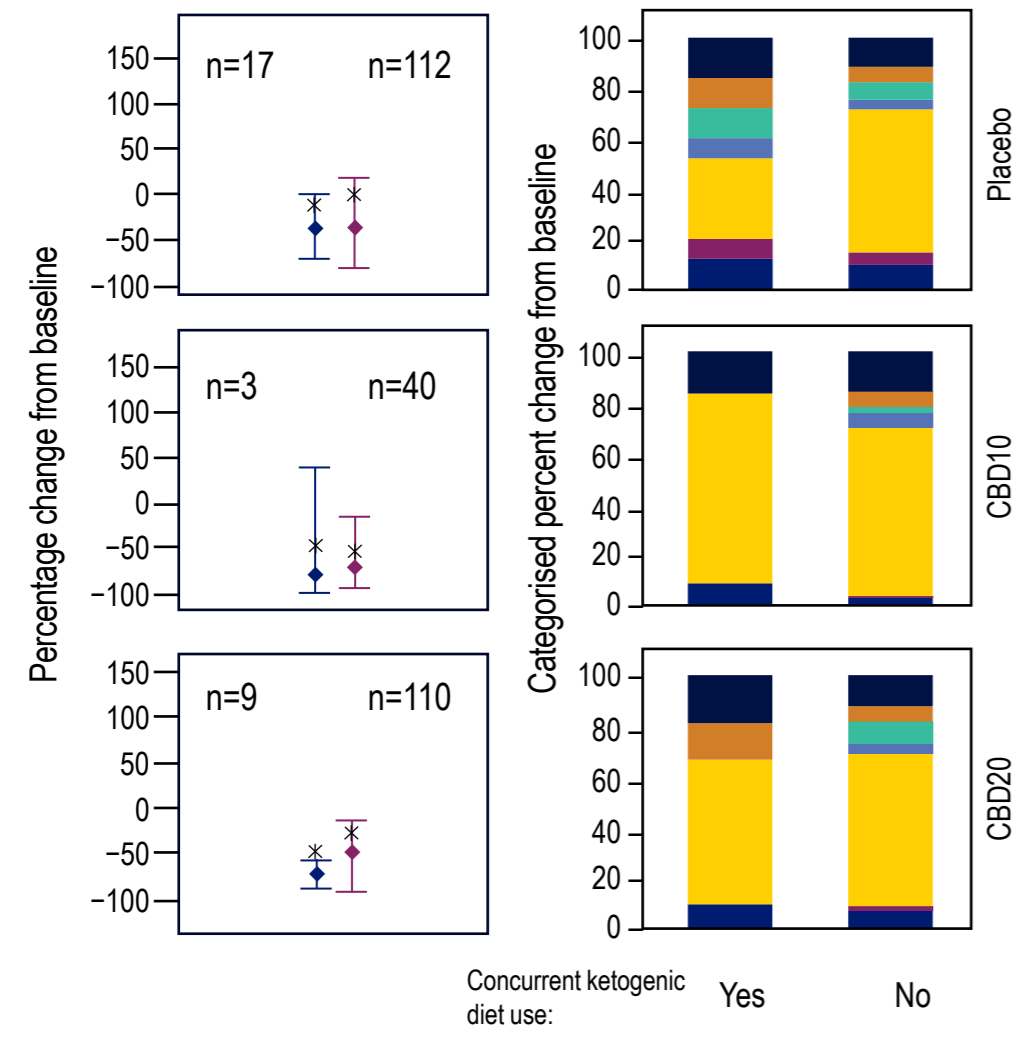
Figures include patients from the RCTs: NCT02224560 (LGS), NCT02224690 (LGS), NCT02224703 (DS) and NCT02091375 (DS).
^aData shown for RCT Treatment Period only. ^bConvulsive (total motor) seizures. ^cDefined as primary seizures in DS (convulsive) and LGS (drop seizures). *0% category not included for this dataset.
 Upper bar = Q1; lower bar = Q3; diamond = median; asterisk = mean. CBD, cannabidiol; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; RCT, randomised controlled trial.



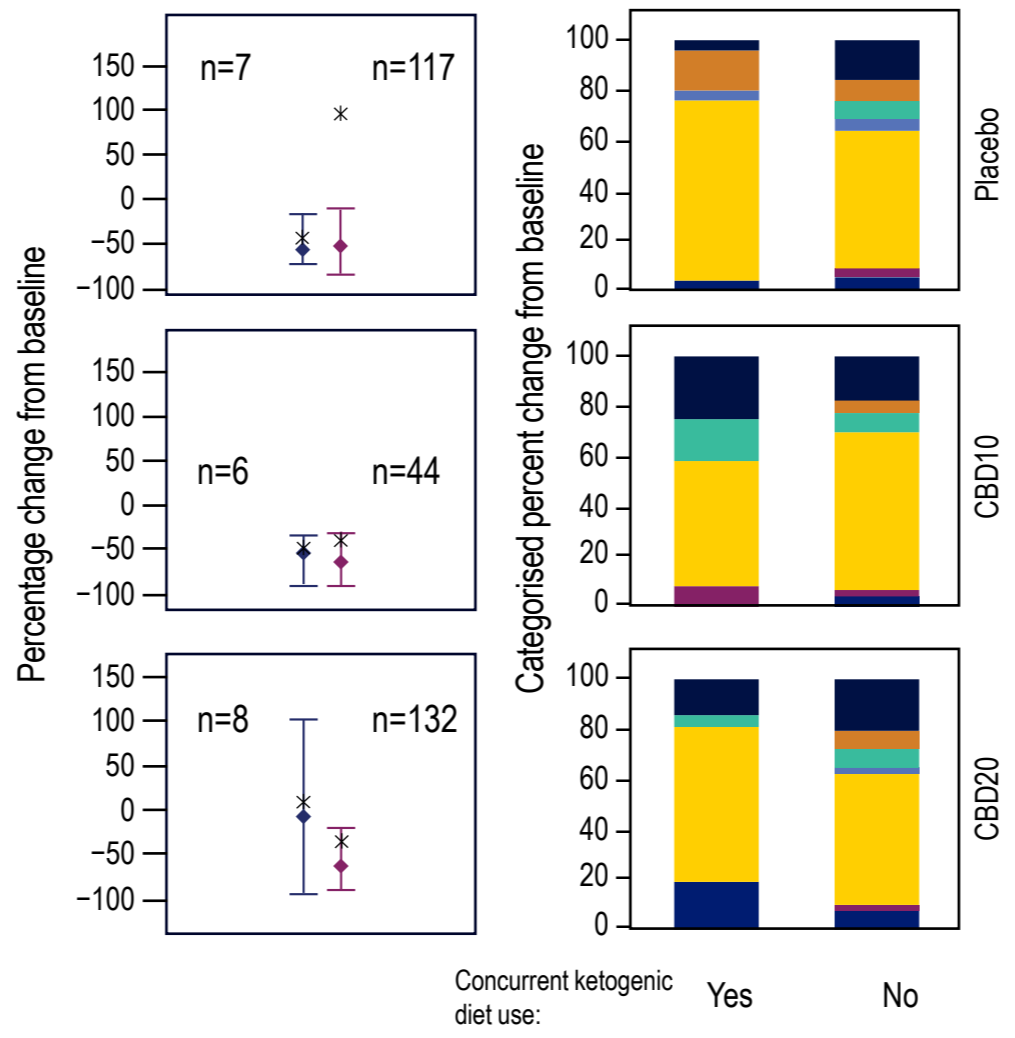
Supplementary materials

Percentage change in total seizure frequency and responder rates, by seizure type^a (continued)

Myoclonic seizures



Absence seizures



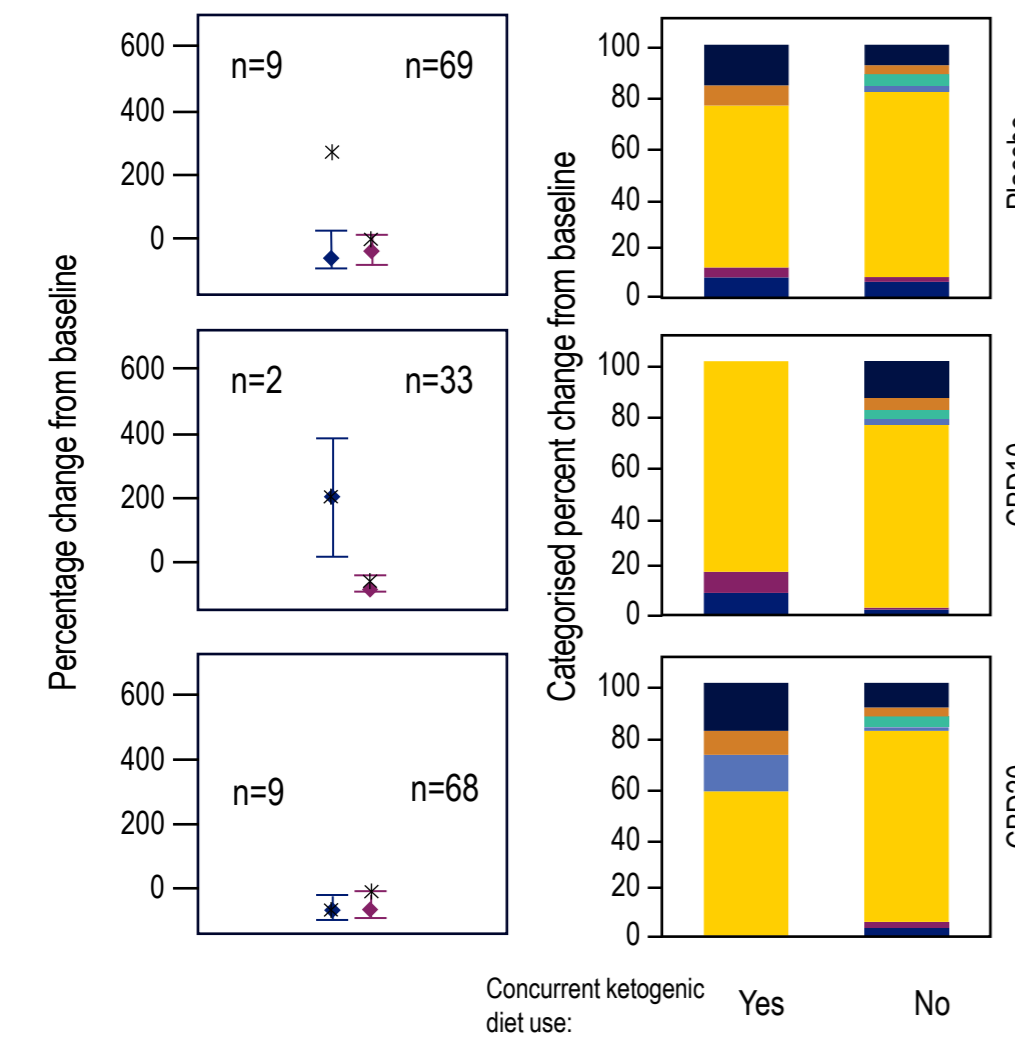
Concurrent ketogenic diet use: ◆ Yes ◆ No

Percent change category:

- >25%
- ≥0% to ≤25%
- 0%
- >-25% to <0%
- >-50% to ≤-25%
- >-75% to ≤-50%
- ≤-75%

Figures include patients from the RCTs: NCT02224560 (LGS), NCT02224690 (LGS), NCT02224703 (DS) and NCT02091375 (DS).
^aData shown for RCT Treatment Period only.
 Upper bar = Q1; lower bar = Q3; diamond = median; asterisk = mean. CBD, cannabidiol; CBD10, cannabidiol 10 mg/kg/day; CBD20, cannabidiol 20 mg/kg/day; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; RCT, randomised controlled trial.

Countable partial seizures



Other partial seizures

