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Clinically Meaningful Reduction in Seizure Frequency in Patients with Tuberous Sclerosis Complex Treated with Cannabidiol

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Introduction

- Tuberous sclerosis complex (TSC), a rare genetic syndrome, is often associated with a broad spectrum of treatment-resistant seizures[1,2]
- Seizures interfere with social, neuropsychiatric, and cognitive development;[3] therefore, even the smallest reductions in seizure frequency correlate with meaningful improvements in caregiver-reported nonseizure outcomes[4,5]
- In clinical trials, a ≥50% reduction in seizure frequency is often accepted as a primary endpoint for treatment efficacy,[6] but the real-world threshold for a clinically important response for patients with TSC is largely untested
- Plant-derived, highly purified cannabidiol (CBD; Epidyolex® [EU]/Epidiolex® [US], 100 mg/mL oral solution) is approved for use in patients with seizures associated with LGS, DS, and TSC[7–9]

Objective

- To investigate the threshold for a clinically important response in terms of reduction in TSC-associated seizure frequency that is associated with an improvement in Caregiver Global Impression of Change (CGIC) in patients with TSC from a randomised controlled trial of CBD (NCT02544763)

Methods

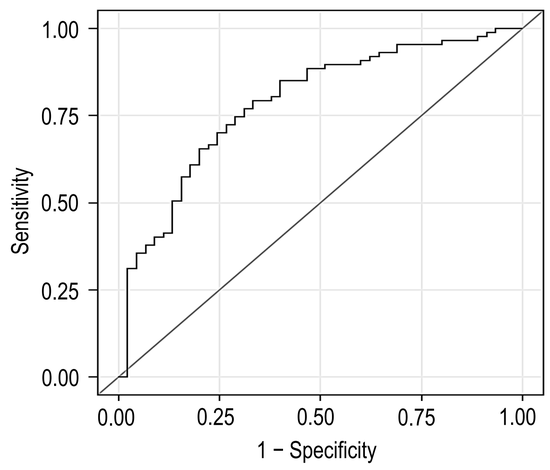
- This *post hoc* analysis used receiver operating characteristics (ROC) to quantify thresholds at which monthly seizure frequency reduction is clinically important, based on data from patients receiving 25 or 50 mg/kg/day CBD (n=132) for 16 weeks[10]
- For clinically important response or minimal clinically important difference (MCID), reduction in TSC-associated seizure frequency was anchored to CGIC ratings of 'slightly improved' or better (scores 1–3 versus 4–7), or 'much improved' or better (scores 1, 2 versus 3–7)
- The thresholds were defined as a 'relevant treatment benefit' for clinically important response and 'the smallest change detected beyond random error' for MCID
- Anchor-based methods (ROC curves) and distribution-based methods (with half standard deviation [SD] and standard error of the mean [SEM]) were applied to determine the thresholds for clinically important response and MCID, respectively
- The phase 3 trial was conducted with Epidyolex®/Epidiolex®, and the results of this *post hoc* analysis do not apply to other CBD-containing products

Results

- Caregivers of 132 patients with TSC treated with CBD reported that the patient's overall condition was 'slightly improved' or better in 87 (66%) patients, and 'much improved' or better in 43 (33%) patients
- Spearman's correlation between CGIC scores and TSC-associated seizure reduction rate was 0.54, 0.57, and 0.37 in the overall (n=132), paediatric (n=103), and adult (n=29) populations, respectively (values ≥0.30 are recommended to demonstrate suitable anchors[11])
- Details of baseline characteristics by anchoring variables can be viewed in the **Supplementary Material** via the QR code

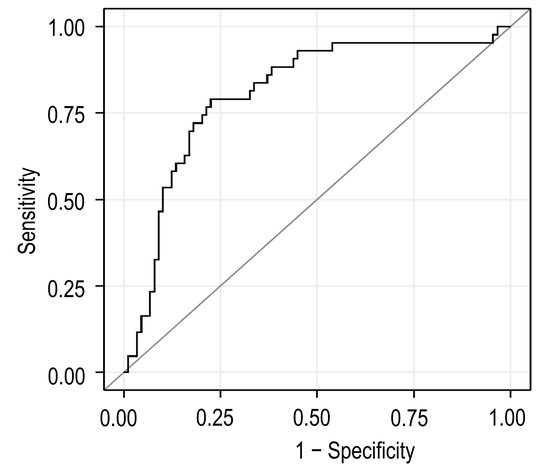
Figure 1. ROC curves to determine thresholds in the overall population (n=132)

CGIC: 'slightly improved' or better



Area under the curve	0.7867
Best-fit % TSC-associated seizure reduction for clinically important response	33%
Accuracy	**73%**
Sensitivity	72%
Specificity	73%

CGIC: 'much improved' or better



Area under the curve	0.8093
Best-fit % TSC-associated seizure reduction for clinically important response	52%
Accuracy	**78%**
Sensitivity	79%
Specificity	78%

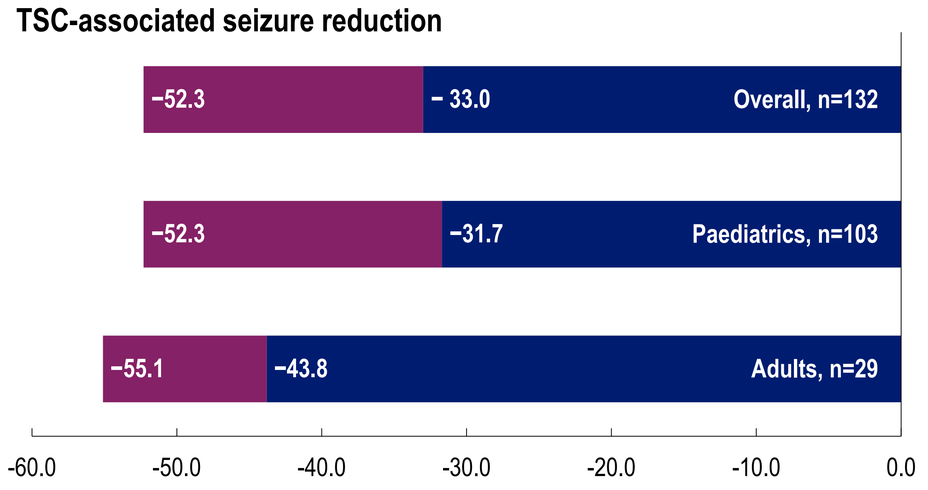
CGIC, Caregiver Global Impression of Change; ROC, receiver operating characteristic; TSC, tuberous sclerosis complex.

- The threshold for a clinically important response in seizure reduction associated with CGIC of 'slightly improved' or better was less than 50%, in all populations (**Figure 2**)
- Applying these thresholds to identify the proportion of patients overall (%) with a clinically important response in terms of TSC-associated seizure reduction:
  - Using 'slightly improved', 75 (57%) patients had a clinically important response
  - Using 'much improved', 54 (41%) patients had a clinically important response

CGIC anchor: ■ Slightly improved or better ■ Much improved or better

CGIC, Caregiver Global Impression of Change; TSC, tuberous sclerosis complex.

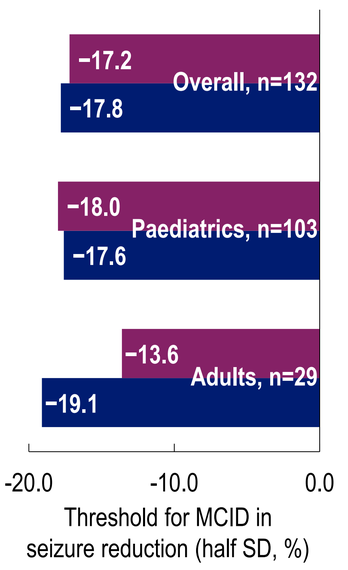
Figure 2. Thresholds for a clinically important response in TSC-associated seizure reduction



- Thresholds for MCID by half SD were −17.8% for a CGIC of 'slightly improved' or better, and −17.2% for 'much improved' or better (**Figure 3**)
  - Similarly, thresholds for MCID by SEM, for CGIC of 'slightly improved' or better and 'much improved' or better, were −19.5% and −18.9% overall, −21.0% and −14.9% for adults, and −19.3% and −19.7% for paediatric patients, respectively
- No substantial differences in MCID thresholds were observed between the 'slightly improved' and 'much improved' CGIC anchors, reflecting that these values for a minimum improvement level are similar regardless of where the threshold for a clinically important response is determined to be

CGIC, Caregiver Global Impression of Change; MCID, minimal clinically important difference; SD, standard deviation; TSC, tuberous sclerosis complex.

Figure 3. Thresholds for minimal clinically important difference in TSC-associated seizure reduction



Conclusions

- Anchoring to CGIC of 'slightly improved' or better, the threshold for a clinically important response in reduction of TSC-associated seizures was 33%, suggesting that a cut-off of a 50% reduction in seizures may overlook patients who are achieving meaningful improvements in their overall condition, as perceived by their caregivers
  - Anchoring between reduction in TSC-associated seizures and CGIC seems appropriate (Spearman's correlation >0.30)
- The threshold for MCID in reduction of TSC-associated seizures was ~20%
- A potential limitation of this approach is that changes in nonseizure outcomes might impact CGIC independently of seizure reduction and are not captured within this analysis
- The findings of this *post hoc* analysis may give insight as to what constitutes a meaningful reduction in seizure frequency for patients with TSC

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and holds stock and/or stock options in the company; **CN** is an employee of Jazz Pharmaceuticals, Switzerland GmbH, and holds stock and/or stock options in the company; **KV** is an employee of Jazz Pharmaceuticals, UK Ltd., and holds stock and/or stock options in the company. Epidyolex® is approved in the EU and UK 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 EU and UK for the adjunctive treatment of seizures associated with tuberous sclerosis complex in patients ≥2 years of age.
Clinical trial ID: NCT02544763 (GWPCARE6).

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Supplementary Material

Table S1. Baseline characteristics by anchoring variables

	CGIC slightly improved or better [Yes] (N=87)	CGIC slightly improved or better [No] (N=45)	CGIC much improved or better [Yes] (N=43)	CGIC much improved or better [No] (N=89)
Age, years				
n	87	45	43	89
Mean (SD)	13.6 (10.59)	11.6 (7.74)	12.2 (10.16)	13.2 (9.55)
Median (Q1–Q3)	11.0 (5.6–17.6)	8.5 (5.8–17.1)	9.5 (4.0–17.6)	11.3 (7.0–17.7)
Sex, n (%)				
Male	53 (60.9)	25 (55.6)	30 (69.8)	48 (53.9)
Female	34 (39.1)	20 (44.4)	13 (30.2)	41 (46.1)
Age group, n (%)				
1–17 years	68 (78.2)	35 (77.8)	35 (81.4)	68 (76.4)
≥18 years	19 (21.8)	10 (22.2)	8 (18.6)	21 (23.6)
Number of ASMs patient taking at the time of study				
n	87	44	43	88
Mean (SD)	2.6 (0.99)	2.8 (0.96)	2.7 (1.03)	2.7 (0.97)
Median (Q1–Q3)	3 (2–3)	3 (2–3)	3 (2–4)	3 (2–3)
Patients taking clobazam				
n (%)	23 (26.4)	7 (15.6)	12 (27.9)	18 (20.2)

ASM, antiseizure medication; CGIC, Caregiver Global Impression of Change; Q1–Q3, interquartile range; SD, standard deviation.