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Tuberous Sclerosis Complex–Associated Neuropsychiatric Disorders Outcomes Following Add-on Cannabidiol Treatment: 3-Month Analysis of the Open-Label Phase 3b/4 Trial EpiCom

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Introduction

- 90% of people with tuberous sclerosis complex (TSC) also have TSC-associated neuropsychiatric disorders (TANDs), yet there are limited treatment options and few studies that evaluate pharmacotherapies, despite the significant impact on patients' quality of life[1,2]
- Measuring neuropsychiatric outcomes in individuals with TSC is challenging due to limited validation, acceptance, and relevance of the available tools[1,2]
- A plant-derived, highly purified pharmaceutical formulation of cannabidiol (CBD; Epidyolex® [EU]/Epidiolex® [US]) is approved for the treatment of seizures associated with TSC[3–5]
- Anecdotal reports from the TSC community of patients, caregivers, and healthcare professionals have suggested benefits with CBD treatment in behavioural (eg, calm or relaxed behaviour) and neuropsychological symptoms (eg, increased attention span, awareness, and concentration)[6]
- EpiCom (**Epi**lepsy **Com**orbidities; NCT05864846) is an interventional, multicentre, open-label, single-arm, phase 3b/4 study designed to evaluate behavioural and other co-occurring outcomes following add-on CBD treatment in participants with TSC-associated seizures[7]
- Here we present the prespecified 3-month intermediate analysis of EpiCom

Objective

- To investigate the behavioural and other co-occurring outcomes after initiation of treatment with add-on CBD in patients with TSC who experience seizures

Methods

- Eligible participants aged 1 to 65 years with TSC and moderate/severe behavioural challenges on the Caregiver Global Impression of Severity (CareGI-S) scale were enrolled (**Table 1**)
- Participants received CBD (Epidyolex® [EU]/Epidiolex® [US], 100 mg/mL oral solution) ≤25 mg/kg/day (based on response and tolerability) in addition to the standard of care (SOC) for 26 weeks (**Figure 1**)
  - Participants could then choose to continue CBD with SOC, or SOC alone, for up to 52 weeks
- Key efficacy endpoints evaluated at the 13-week intermediate analysis included the following:
  - Behavioural outcomes evaluated as change from baseline in the most problematic behavior (MPB) on TAND Self-Report, Quantified Checklist (TAND-SQ), and the Aberrant Behavior Checklist (ABC) at Week 13
  - Symptom severity as evaluated by change from baseline in CareGI-S and Clinician Global Impression of Severity (CGI-S) scales at Weeks 4 and 13
  - Safety of CBD as evaluated by the severity of adverse events (AEs) and discontinuations due to AEs
- This study was conducted with Epidyolex®/Epidiolex®, and results do not apply to other CBD-containing products

Table 1. Key inclusion and exclusion criteria

Inclusions

- **Confirmed diagnosis of TSC** with history of seizures
- **Moderate/severe behavioural challenges** (eg, aggression, impulsivity, temper tantrums, self-injury, and hyperactivity), with a most problematic behavior score of ≥6 on the TAND-SQ at baseline[a]
- On **≥1 antiseizure medication**
- **Naive to CBD** or has been off CBD for ≥3 months before screening

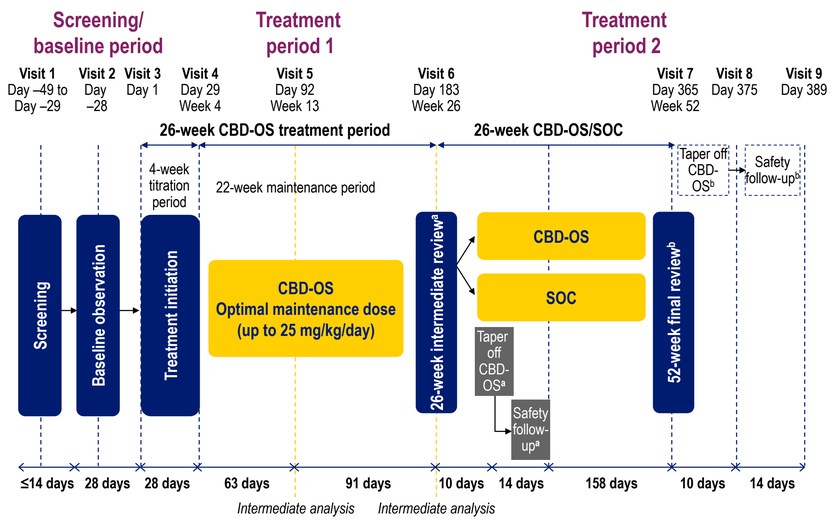
Exclusions

- Any medical condition that could affect study outcomes
- Felbamate initiation within the year before screening
- Recreational or medical cannabis use within the 3 months before screening
- Significant hepatic impairment and any history of suicidal behaviour or ideation of type 4 or 5 as evaluated by the Columbia-Suicide Severity Rating Scale

[a]Based on the Likert scale: 1 = Very unimportant; 5 = Neither important nor unimportant; and 10 = Extremely important.
CBD, cannabidiol; TAND, TSC-associated neuropsychiatric disorder; TAND-SQ, TAND Self-Report, Quantified Checklist; TSC, tuberous sclerosis complex.

Methods (cont.)

Figure 1. Study design



[a]Participants who decide to discontinue CBD-OS after the 26-week intermediate review visit but remain on study will form the SOC treatment arm. These participants will taper off CBD-OS and complete a safety follow-up.
[b]Participants who decide to discontinue CBD-OS after the 52-week final review visit will taper off CBD-OS and complete a safety follow-up. For participants who wish to remain on CBD-OS after the study, the 52-week final review visit is the last study visit. CBD, cannabidiol; CBD-OS, CBD oral solution; SOC, standard of care.

Results

Demographic and clinical characteristics

Table 2. Baseline demographic and clinical characteristics

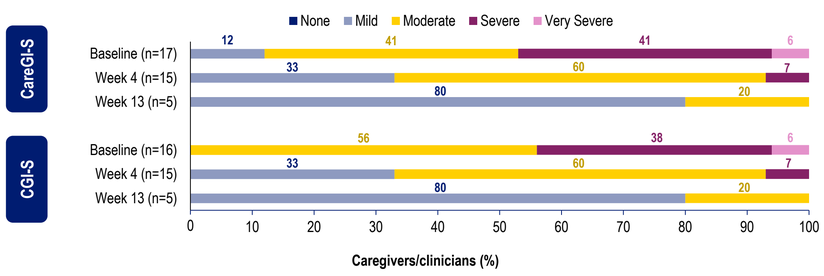
	CBD (n=17)
Age, years	
Mean (SD)	22.6 (9.94)
Median (range)	21.0 (5–42)
Sex, n (%)	
Male	8 (47.1)
Female	9 (52.9)
Number of participants with seizure at screening, n (%)[a]	8 (47.1)
Average number of total seizures per 28 days at baseline, mean (SD)[a]	4.1 (7.1)
Number of ASMs at baseline, median (range)	3 (1–5)
ASMs at baseline, n (%)	
Topiramate	6 (35.3)
Everolimus	5 (29.4)
Lamotrigine	5 (29.4)
Valproic acid	2 (11.8)
Clobazam	1 (5.9)

[a]Considers participants with a seizure type recorded at screening. The average number of total seizures per 28 days at baseline is calculated from seizure diary records. ASMs, antiseizure medications; CBD, cannabidiol; SD, standard deviation.

- At the time of this prespecified intermediate analysis, 24 participants had enrolled, 19 had started CBD, and 4 discontinued the study
- In participants with ≥1 postbaseline assessment (n=17), the median (range) age was 21 (5–42) years (**Table 2**)
- The most common concomitant antiseizure medications used were topiramate (n=6 [35%]), everolimus (n=5 [29%]), and lamotrigine (n=5 [29%])

Symptom severity outcomes

Figure 2. Caregiver- and clinician-reported global impression of severity for behavioural problems using CareGI-S and CGI-S scales, respectively, at Weeks 4 and 13



CareGI-S, Caregiver Global Impression of Severity; CGI-S, Clinician Global Impression of Severity.

- A smaller proportion of both caregivers and clinicians rated behavioural problems as severe or very severe on CareGI-S and CGI-S at Weeks 4 and 13 compared with baseline (**Figure 2**)

Behavioural outcomes

Table 3. Change from baseline in MPB on TAND-SQ and ABC subscales at Week 13

	Baseline (n=17), mean (SD)	Week 13 (n=5), mean (SD)	Change from baseline at Week 13 (n=5), mean (95% CI)[a]
MPB NRS value on TAND-SQ	8.8 (1.01)	4.4 (3.05)	−4.6 (−8.1, −1.1)
TAND-SQ clusters			
Overall impact score	4.6 (2.19)	2.3 (1.16)	−1.5 (−2.5, −0.5)
Scholastic	6.7 (3.81)	4.6 (4.78)	0.3 (−6.2, 6.7)
Neuropsychological	5.5 (3.07)	2.4 (1.96)	−1.6 (−3.2, −0.1)
Autism spectrum disorder–like	3.9 (2.74)	2.1 (1.42)	−1.5 (−3.5, 0.4)
Dysregulated behaviour	3.9 (3.15)	1.3 (1.60)	−3.5 (−6.5, −0.5)
Overactive/impulsive	3.9 (2.90)	0.6 (0.44)	−2.9 (−7.1, 1.3)
Mood/anxiety	3.5 (2.01)	2.5 (2.47)	−0.8 (−1.4, −0.2)
Eat/sleep	3.7 (2.92)	2.2 (1.89)	−1.1 (−2.7, 0.5)
ABC subscales			
Irritability	15.5 (9.06)	8.0 (4.47)	−12.2 (−22.3, −2.1)
Social withdrawal	9.9 (7.45)	2.2 (1.48)	−4.2 (−10.4, 2.0)
Stereotypic behaviour	6.3 (4.77)	1.2 (1.64)	−4.8 (−9.0, −0.6)
Hyperactive non-compliance	16.6 (10.22)	5.4 (2.51)	−11.0 (−25.1, 3.1)
Inappropriate speech	3.9 (3.45)	1.4 (1.67)	−2.2 (−4.9, 0.5)

[a]95% CI for the mean change from baseline was calculated using the normal approximation method.
ABC, Aberrant Behavior Checklist; CI, confidence interval; MPB, most problematic behavior; NRS, numerical rating scale; SD, standard deviation; TAND, tuberous sclerosis complex–associated neuropsychiatric disorder; TAND-SQ, TAND Self-Report, Quantified Checklist.

- At baseline (n=17), the mean (SD) MPB numerical rating scale (NRS) value was 8.8 (1.01), suggesting severe TAND problems; the most common manifestations were mood swings (n=4 [24%]) and aggressive outbursts (n=3 [18%]) (**Table 3**)
- At Week 13 (n=5), mean (95% CI) change from baseline in MPB NRS was −4.6 (−8.1, −1.1), suggesting an improvement in behavioural outcomes
- Of seven TAND-SQ clusters, the greatest changes were in dysregulated behaviour[a] and overactive/impulsive scores, indicating a notable improvement in behavioural outcomes over time
- The greatest changes in ABC were in irritability and hyperactive non-compliance

[a]Dysregulated behaviour, also known as emotional dysregulation, means difficulty controlling one's emotions. These may manifest as angry outbursts, anxiety, depression, substance abuse, suicidal thoughts, self-harm, and other self-damaging behaviours.

Safety outcomes

Table 4. Summary of treatment-emergent adverse events

TEAE summary	CBD (n=19)
Number of participants with at least one TEAE, n (%)	12 (63%)
Diarrhoea	8 (42%)
Vomiting	2 (11%)
Lethargy	2 (11%)
Decreased appetite	2 (11%)
Haematochezia	1 (5%)
Gastroenteritis	1 (5%)
COVID-19	1 (5%)
Gastroenteritis viral	1 (5%)
Pharyngitis streptococcal	1 (5%)
Hypersomnia	1 (5%)
Aspartate aminotransferase increased	1 (5%)
Transaminases increased	1 (5%)
Hypokalaemia	1 (5%)
Oropharyngeal pain	1 (5%)
Productive cough	1 (5%)
Urinary incontinence	1 (5%)
Skin and subcutaneous tissue disorders	1 (5%)

CBD, cannabidiol; TEAE, treatment-emergent adverse event.

- Any AEs occurred in 12/19 participants (63%) (**Table 4**)
- Four participants (21%) discontinued due to AEs (diarrhoea, hypersomnia, increased transaminase, and rash)

Conclusions

- Although the analysis is limited by small patient numbers, the prespecified 3-month intermediate analysis of the open-label EpiCom study showed improvements in TAND-SQ and ABC subscales after initiating CBD
- The safety profile was consistent with previous studies; however, full safety data will be reported at study conclusion

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References: 1. Vanclooster S, et al. *J Neurodev Disord.* 2022;14(1):13. **2.** de Vries PJ, et al. *J Neurodev Disord.* 2023;15(1):32. **3.** Electronic Medicines Compendium (eMC). Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2025. Available from: https://www.medicines.org.uk/emc/product/10781/smpc/print (Accessed 9 May 2025). **4.** European Medicines Agency. Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf (Accessed 9 May 2025). **5.** US Food and Drug Administration. Epidiolex® Prescribing information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210365s021lbl.pdf (Accessed 9 May 2025). **6.** Marshall J, et al. *J Child Neurol.* 2023;38(6-7):394–406. **7.** Van Eeghen AM, et al. Poster presented at WCN 2023.

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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: NCT05864846 (EpiCom).

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