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Background

- A plant-derived, highly purified pharmaceutical formulation of cannabidiol (CBD) is approved in the United States for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex.¹
- CBD Expanded Access Program (EAP) was initiated in 2014 to provide compassionate access to CBD for patients with diverse treatment-resistant epilepsies (TREs) at 35 US epilepsy centers.²
- The program continued until January 2019, and the 4-year results demonstrated that add-on CBD treatment was associated with a reduction in seizure frequency through 192 weeks of treatment and the safety profile was consistent with the established safety profile of CBD.³
- In the overall EAP population, the median age of patients was 13.5 years, and the majority were pediatric patients (88%).³
- In this analysis of the EAP, effectiveness and safety in adult patients were evaluated.

Objective

- To present the effectiveness and safety results of CBD treatment in adult patients (aged ≥18 years) with TREs from the CBD EAP.

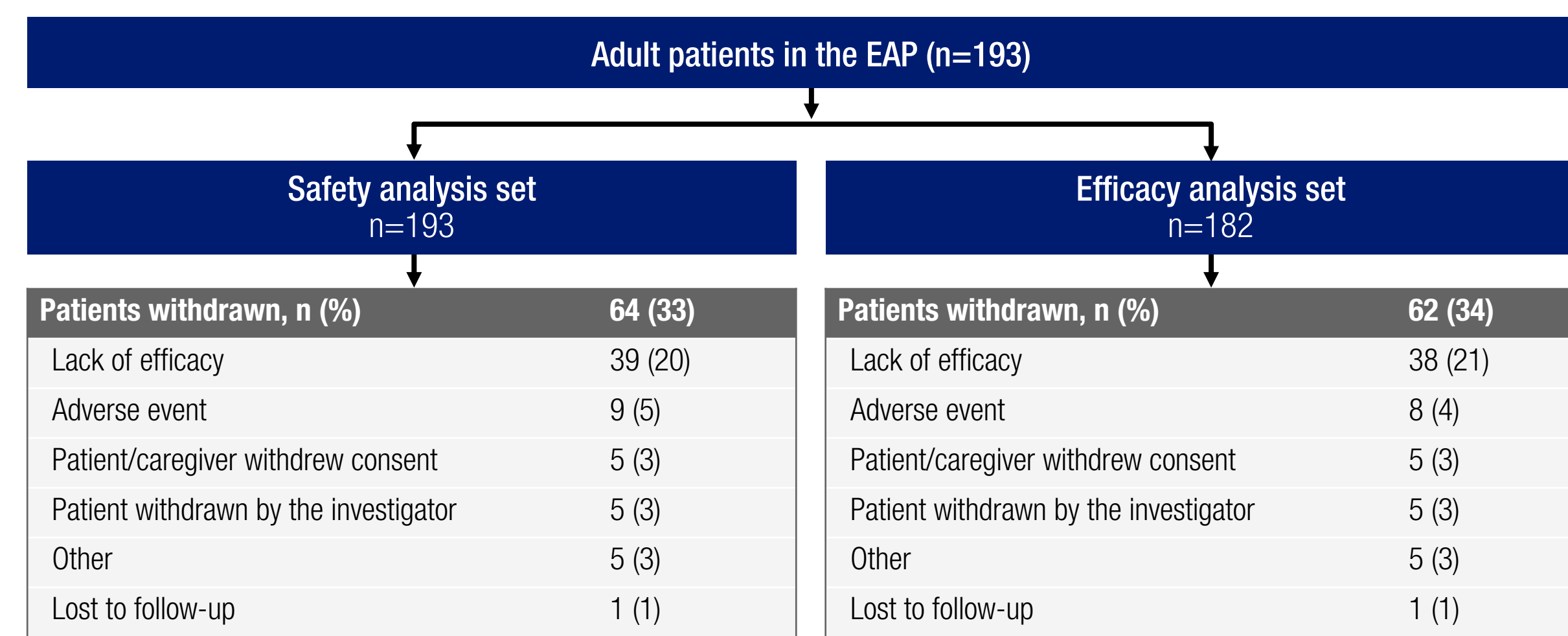
Methods

- Although some eligibility criteria varied by site, all patients in this study had TRE and were receiving stable doses of antiseizure medications for ≥4 weeks before enrollment.
- Patients received plant-derived, highly purified CBD (Epidiolex®; 100 mg/mL oral solution) starting at 2–10 mg/kg/d and titrated up to tolerance or maximum of 25–50 mg/kg/d, at the discretion of the study site.
- Each site provided seizure frequency per week, based on patient/caregiver diaries, and the effectiveness through 144 weeks of treatments with CBD was evaluated as
 - The percentage change from baseline in median monthly frequency of convulsive, focal-onset (focal seizures with or without impaired awareness and focal to bilateral tonic-clonic seizures), and total seizures across 12-week intervals.
 - The ≥50%, ≥75%, and 100% responder rates across 12-week intervals.
- Change in the overall condition of patients was assessed using the Subject/Caregiver Global Impression of Change scale and the Physician Global Impression of Change scale.
- Safety results were reported for the full follow-up, up to 252 weeks.
- The study was conducted with Epidiolex®, and the results do not apply to other CBD-containing products.

Results

Figure 1. Patient disposition

- Of 892 patients in the overall safety analysis set, 193 (22%) were adults.



EAP, Expanded Access Program.

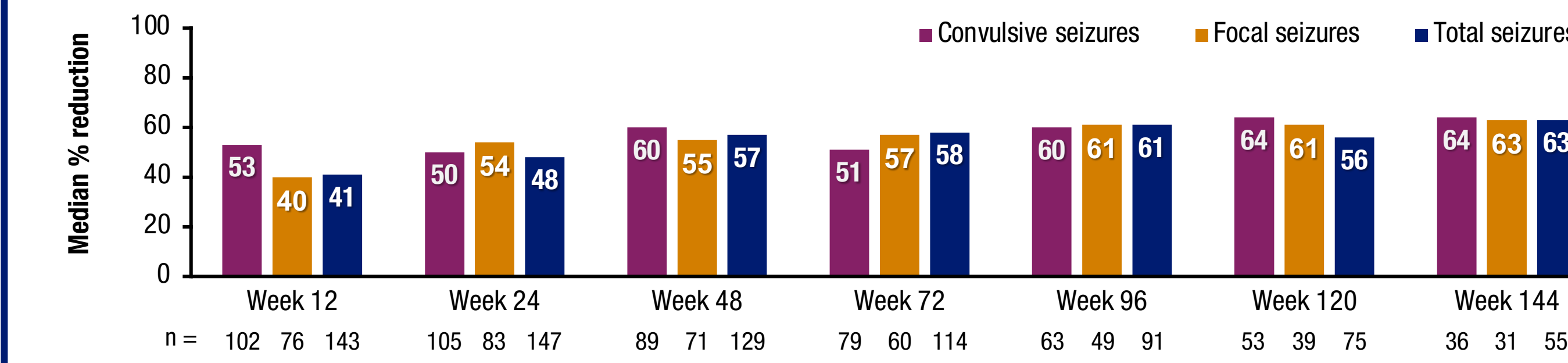
Table 1. Baseline characteristics and CBD exposure

	Safety population (n=193)	Efficacy population (n=182)
Mean age, years (min, max)	27.3 (18.0, 74.5)	27.1 (18.0, 74.5)
Sex, n (%)		
Female	99 (51)	93 (51)
No. of ASMs at baseline, median (min, max) [n]	3 (1, 7) [192]	3 (1, 7) [181]
Most common (>20%) ASMs at baseline, n (%)		
Clobazam	72 (37)	68 (37)
Levetiracetam	66 (34)	61 (34)
Lamotrigine	63 (33)	58 (32)
Lacosamide	56 (29)	53 (29)
Valproate	56 (29)	53 (29)
Diagnosis at baseline, n (%)		
LGS	27 (14)	26 (14)
DS	16 (8)	14 (8)
TSC	7 (4)	7 (4)
CDKL5, Aicardi syndrome, dup15q syndrome, or FIRES	5 (3)	5 (3)
Other	116 (60)	109 (60)
Unknown	22 (11)	21 (12)
Baseline median (Q1, Q3) monthly seizure frequency [n]		
Convulsive	—	22 (6, 60) [127]
Focal	—	23 (9, 56) [101]
Total	—	40 (15, 100) [181]
CBD exposure		
Median time on CBD, days (range)	733 (15–1742)	750 (15–1742)
Median total daily dose, mg/kg/d (Q1, Q3)	20 (15, 25)	20 (15, 25)

ASM, antiseizure medication; CBD, cannabidiol; CDKL5, cyclin-dependent kinase-like 5 deficiency disorder; DS, Dravet syndrome; dup15q syndrome, chromosome15q11.2-13.1 duplication syndrome; FIRES, febrile infection-related epilepsy syndrome; LGS, Lennox-Gastaut syndrome; Q1, first quartile; Q3, third quartile; TSC, tuberous sclerosis complex.

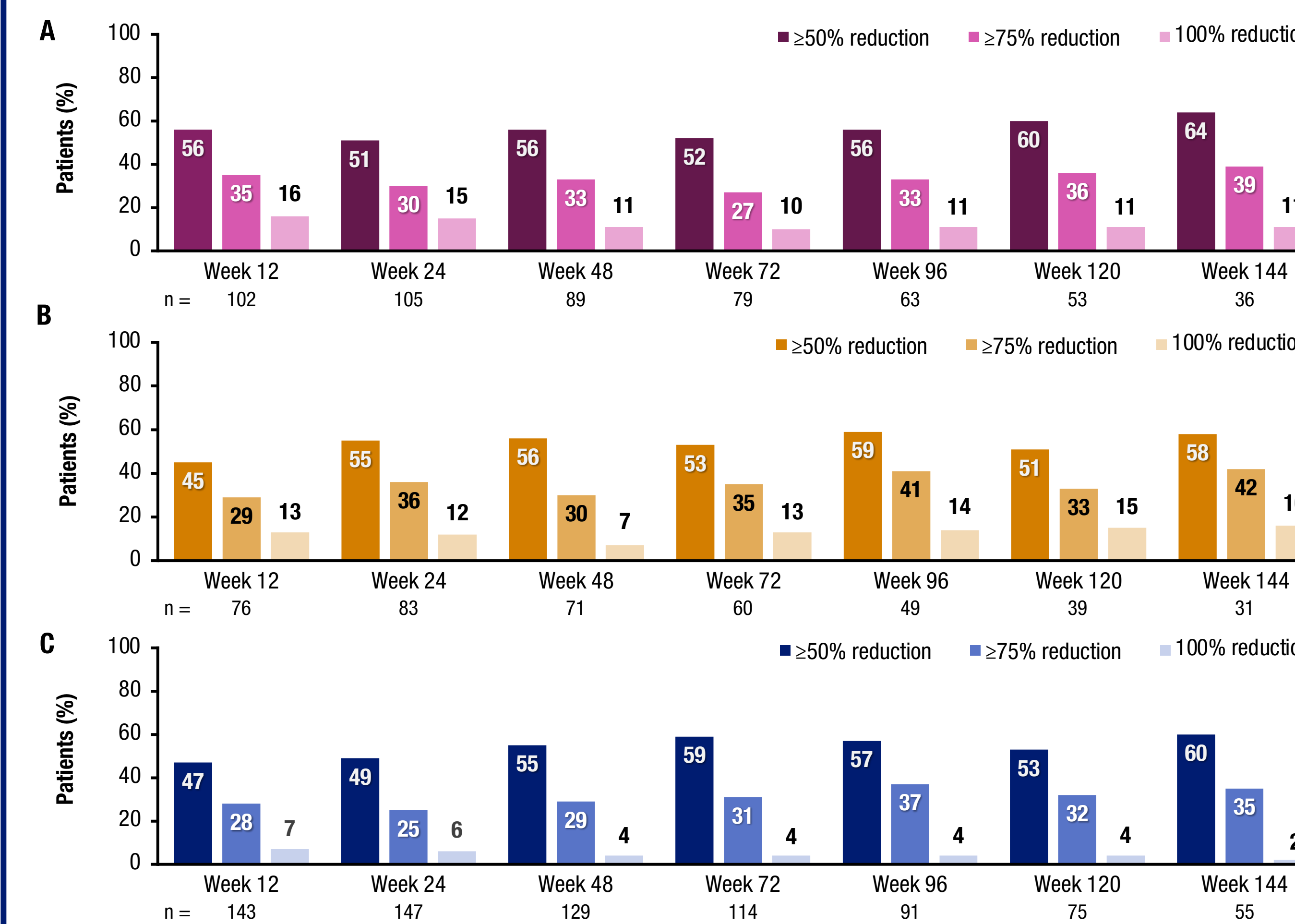
Efficacy results

Figure 2. Median percentage reduction from baseline in convulsive, focal, and total seizures



- Across 12-week visit intervals (data available via QR code), CBD treatment was associated with a median percent reduction of 45%–64% in convulsive seizures, 40%–63% in focal seizures, and 41%–63% in total seizures.
- Similar reductions were observed in the frequency of convulsive (45%–65%), focal (47%–90%), and total (52%–74%) seizures among patients taking median total daily CBD dose ≤25 mg/kg/d (the approved dose; data available via QR code).

Figure 3. Treatment responder rates for (A) convulsive, (B) focal, and (C) total seizures

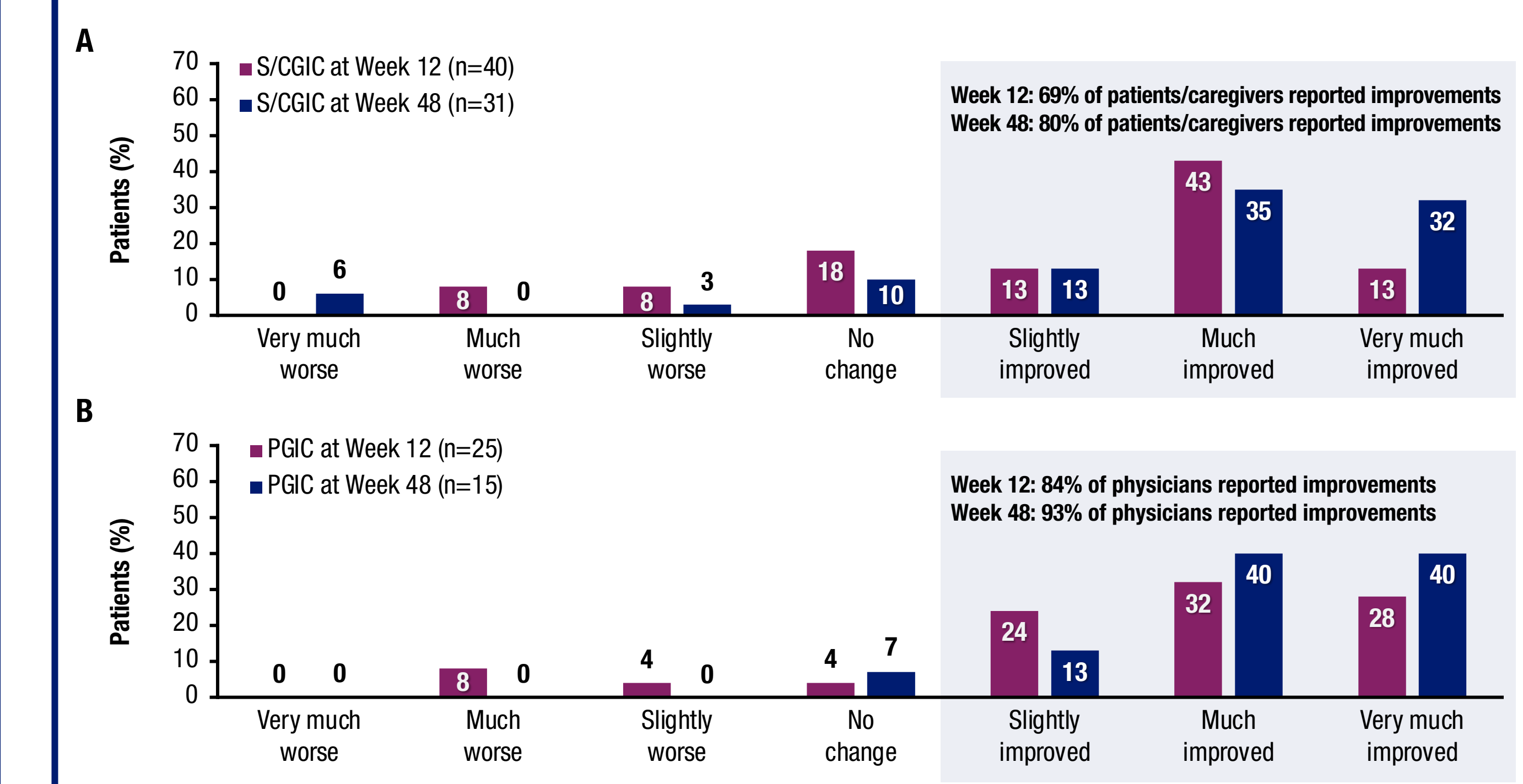


- Across 12-week visit intervals (data available via QR code), convulsive seizure responder rates (≥50%, ≥75%, and 100% reduction) ranged from 49%–64%, 27%–39%, and 7%–16% of patients, respectively.
- Responder rates for focal seizures ranged from 45%–59%, 29%–42%, and 7%–16% of patients, respectively, across the 12-week visit intervals.
- Total seizure responder rates ranged from 47%–60%, 25%–38%, and 2%–7% of patients, respectively.
- Similar rates were observed among patients taking median total daily CBD dose ≤25 mg/kg/d (data available via QR code).

Conclusions

- Among adult patients receiving CBD treatment in the EAP:
 - Add-on CBD treatment was associated with a reduction in the frequency of convulsive and total seizures that was similar to the overall population (convulsive seizures, 50%–67%; total seizures, 46%–66%)³ through 144 weeks of treatment.
 - Median percent reduction in focal seizures ranged between 40% and 63% and 45%–59% of patients had ≥50% reduction from baseline across all visit intervals.
 - At least 47% of patients had ≥50% reduction in total seizures and ≥25% of patients had profound reductions of ≥75% across all 12-week visit intervals through 144 weeks.

Figure 4. (A) Subject/Caregiver Global Impression of Change and (B) Physician Global Impression of Change



PGIC, Physician Global Impression of Change; S/CGIC, Subject/Caregiver Global Impression of Change.

Safety results

Table 2. Summary of AEs

Patients, n (%)	CBD (n=193)
TEAEs	
Any AEs	178 (92)
Any TRAEs	153 (79)
AEs leading to permanent discontinuation	16 (8)
Serious AEs	76 (39)
Treatment-related serious AEs	14 (7)
Deaths	2 (1)
TRAEs reported in ≥10% of patients by MedDRA preferred term	
Diarrhea	95 (49)
Somnolence	46 (24)
Decreased appetite	25 (13)
Fatigue	22 (11)

AE, adverse event; CBD, cannabidiol; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- Most frequently reported serious adverse events (AEs) in ≥5% of patients were convulsion (20 [10%]) and status epilepticus (11 [6%]).
- Most frequently reported AEs leading to treatment discontinuation (>1% of patients) were constipation, diarrhea, and lethargy in 3 patients (2%) each.
- Liver-related AEs in >1% of patients were increased alanine amino transferase (ALT), increased aspartate aminotransferase (AST), and abnormal liver function test (5% each).
- The 2 deaths during the study because of hyponatremia and neoplasm were deemed unrelated to treatment by the investigator.

Laboratory investigations

- Elevation in ALT/AST levels >3x the upper limit of normal (ULN) occurred in 15 patients (8%) out of 190.

- The majority of patients/caregivers and physicians reported improvements in the overall condition of patients on the S/CGIC and PGIC scales, respectively, at the 12- and 48-week visits.
- The safety profile of CBD was consistent with that reported previously in the overall EAP analysis and the randomized controlled trials.^{3–8}
- Limitations include the open-label unblinded nature of the study and intersite variability in patient eligibility criteria, data collection, and seizure type classification.
- These results show beneficial effect of CBD in adults with TRE in a real-world setting and provide insight into the safety and effectiveness of CBD when used in the adult clinical practice setting.

References: 1. Jazz Pharmaceuticals. Epidiolex® (cannabidiol) oral solution [prescribing information]. 2023. [https://www.epidiox.com/sites/default/files/pdfs/1120/EPX-03645-1120_EPIDIOLEX_\(cannabidiol\)_USPI.pdf](https://www.epidiox.com/sites/default/files/pdfs/1120/EPX-03645-1120_EPIDIOLEX_(cannabidiol)_USPI.pdf). 2. Szafarski JP et al. *Epilepsia*. 2018;59:1540-1548. 3. Szafarski JP et al. *Epilepsia*. 2023;64:619-629. 4. Devinsky O et al. *N Engl J Med*. 2018;378:1888-1897. 5. Devinsky O et al. *N Engl J Med*. 2017;376:2011-2020. 6. Thiele EA et al. *Lancet*. 2018;391:1085-1096. 7. Miller I et al. *JAMA Neurol*. 2020;77:613-621. 8. Thiele EA, et al. *JAMA Neurol*. 2021;78:285-292.

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Disclosures: Previously presented at The American Epilepsy Society Annual Meeting (AES), 2023. All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. **JPS** and **SRH** have consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc; **TBS**, **TG**, and **FS** are employees of Jazz Pharmaceuticals, Inc. 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 years of age.



Supplementary Material

Efficacy results
Figure S1. Median percentage reduction from baseline in convulsive, focal, and total seizures across 12-week intervals

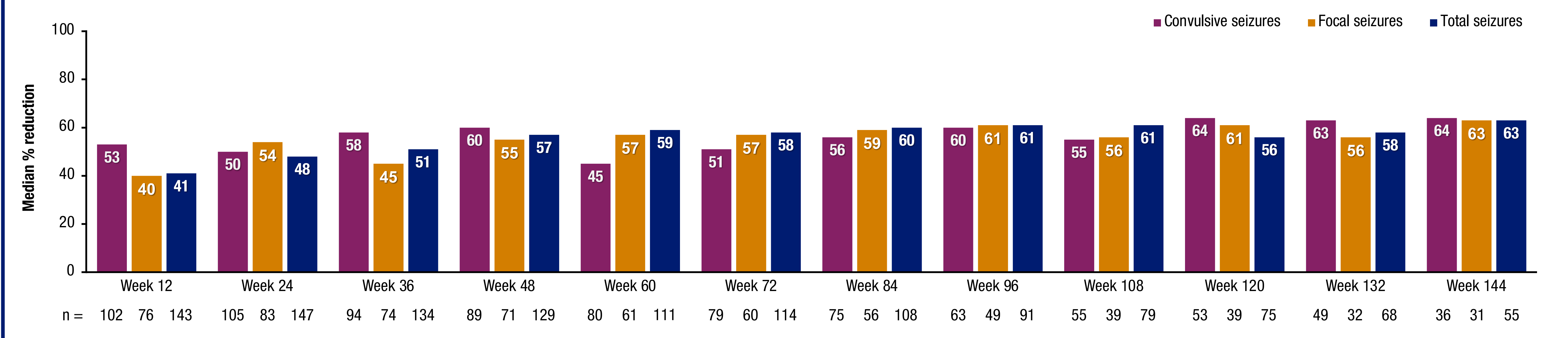


Figure S2. Treatment responder rates for (A) convulsive, (B) focal, and (C) total seizures across 12-week intervals

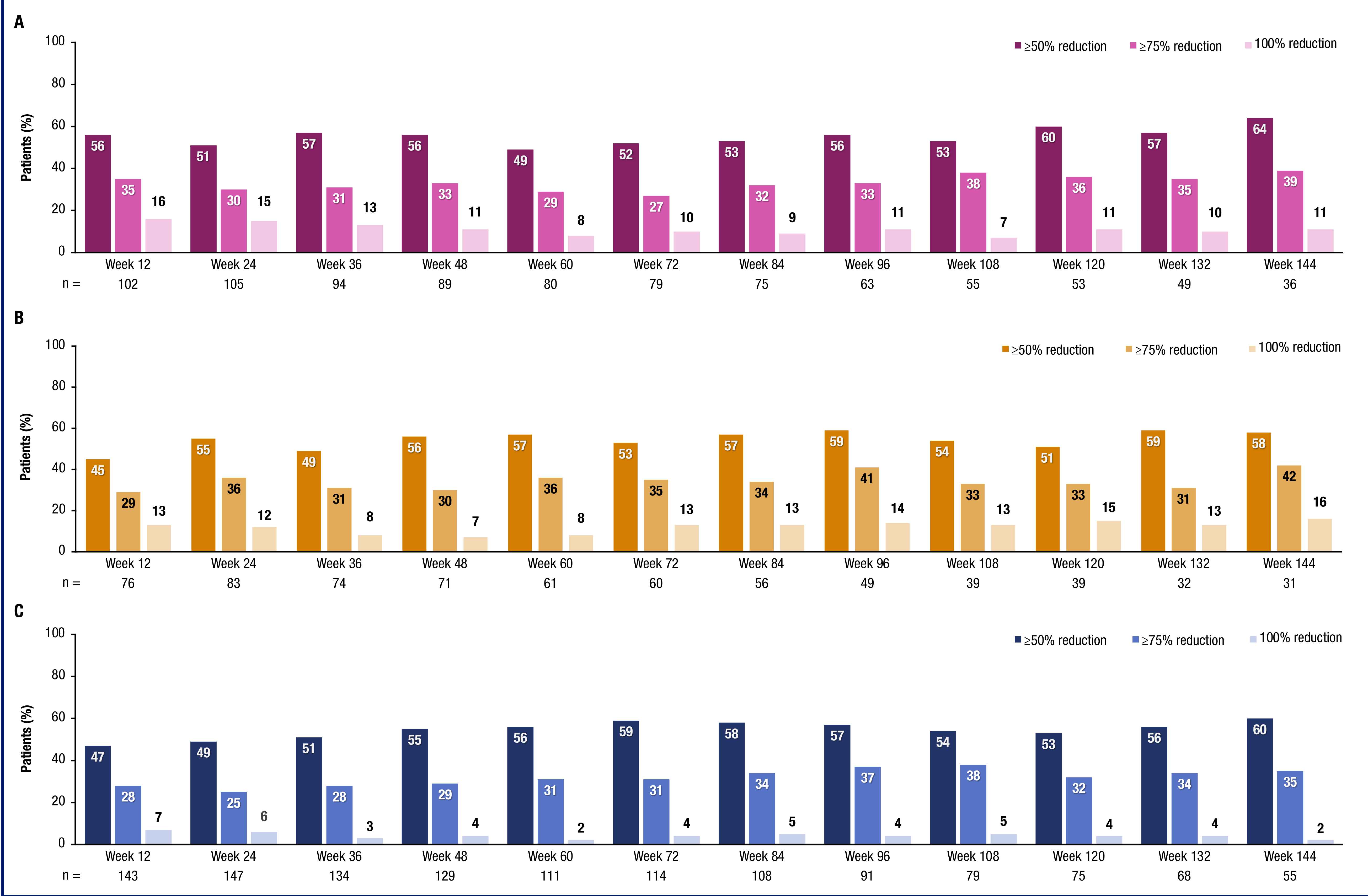


Figure S3. Median percentage reduction from baseline in convulsive, focal, and total seizures among adult patients on median total daily CBD dose of ≤25 mg/kg/d

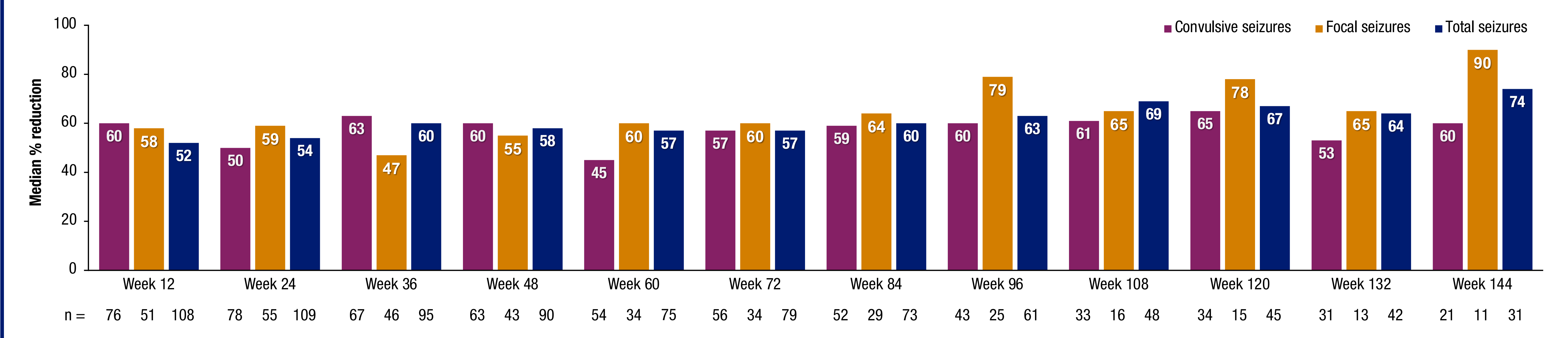


Figure S4. Treatment responder rates for (A) convulsive, (B) focal, and (C) total seizures among adult patients on median total daily CBD dose of ≤25 mg/kg/d

