Long-Term Effectiveness of Cannabidiol Against Focal-Onset Seizures in Treatment-Resistant Epilepsies

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- 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
- These results were previously presented at the American Epilepsy Society 2023 annual meeting
- This study was conducted with Epidiolex®, and results do not apply to other CBD-containing products

CBD, cannabidiol; ICMJE, International Committee of Medical Journal Editors.

Background and Objective

Background

- CBD is approved in the US for the treatment of seizures associated with LGS, DS, or TSC in patients ≥1 year of age[1]
  - In the US, the recommended maintenance dosage of CBD is 10–20 mg/kg/d for LGS and DS and 25 mg/kg/d for TSC[1]
- Patients with TRE received compassionate access to CBD through an EAP across 35 US epilepsy centers from January 2014 to January 2019
- Four-year results from the EAP demonstrated that CBD was associated with reduction in seizure frequency through 192 weeks of treatment[2]
  - Furthermore, reduction was observed in the frequency of both convulsive and nonconvulsive seizures with CBD through 144 weeks of treatment[3]
- The effect of CBD specifically in focal-onset seizure reduction in the real world is not well-defined

Objective

- We aimed to evaluate the effectiveness of CBD treatment for focal-onset seizures in patients with TRE treated in the CBD EAP

CBD, cannabidiol; DS, Dravet syndrome; EAP, Expanded Access Program; LGS, Lennox-Gastaut syndrome; TRE, treatment-resistant epilepsy; TSC, tuberous sclerosis complex; US, United States.

1. Epidiolex® (cannabidiol) oral solution prescribing information. Jazz Pharmaceuticals, Inc.; 2023. . Accessed on February 14, 2024. https://www.epidiolex.com/sites/default/files/pdfs/1120/EPX-03645-1120_EPIDIOLEX_(cannabidiol)_USPI.pdf. **2.** Szaflarski JP et al. *Epilepsia*. 2023;64(3):619-629. **3.** Flamini RJ et al. *Epilepsia*. 2023;64(8):e163.

Methods

- Eligibility criteria:
  - All patients had TRE and were receiving stable doses of antiseizure medications for ≥4 weeks before enrollment
  - Some eligibility criteria varied by site
- Patients received plant-derived, highly purified CBD (100 mg/mL oral solution) starting at 2–10 mg/kg/d and further titrated based on clinical response and tolerance to a maximum dose of 25–50 mg/kg/d (at discretion of study site)

Efficacy endpoints

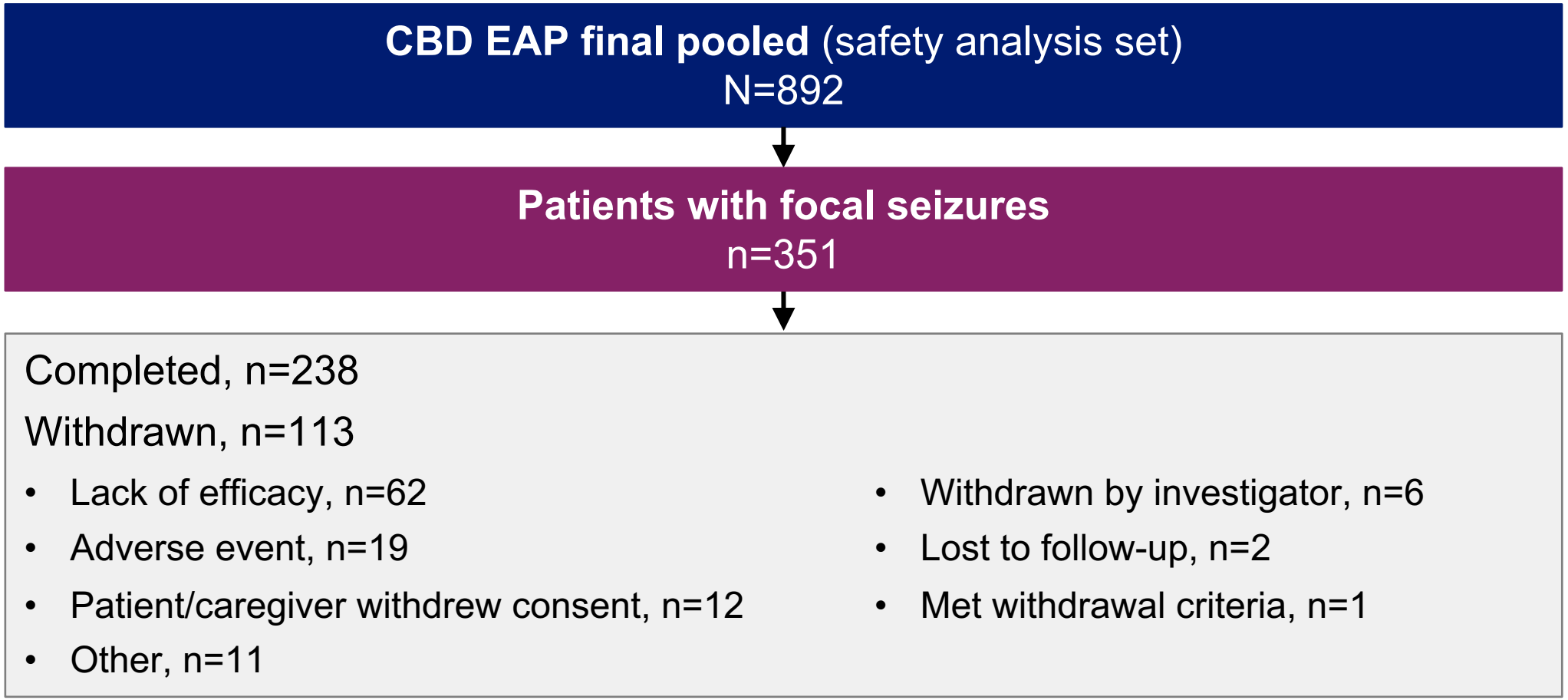
- Percentage change from baseline in median monthly frequency of focal-onset seizures
- Responder rates (≥50%, ≥75%, and 100% reduction) across 12-week intervals through 144 weeks of treatment

Safety endpoints[a]

- AEs
- Serious AEs
- AEs leading to discontinuation
- Deaths

[a]Safety results reported for full follow-up.
AE, adverse event; CBD, cannabidiol; TRE, treatment-resistant epilepsy.

Results – Patient Disposition



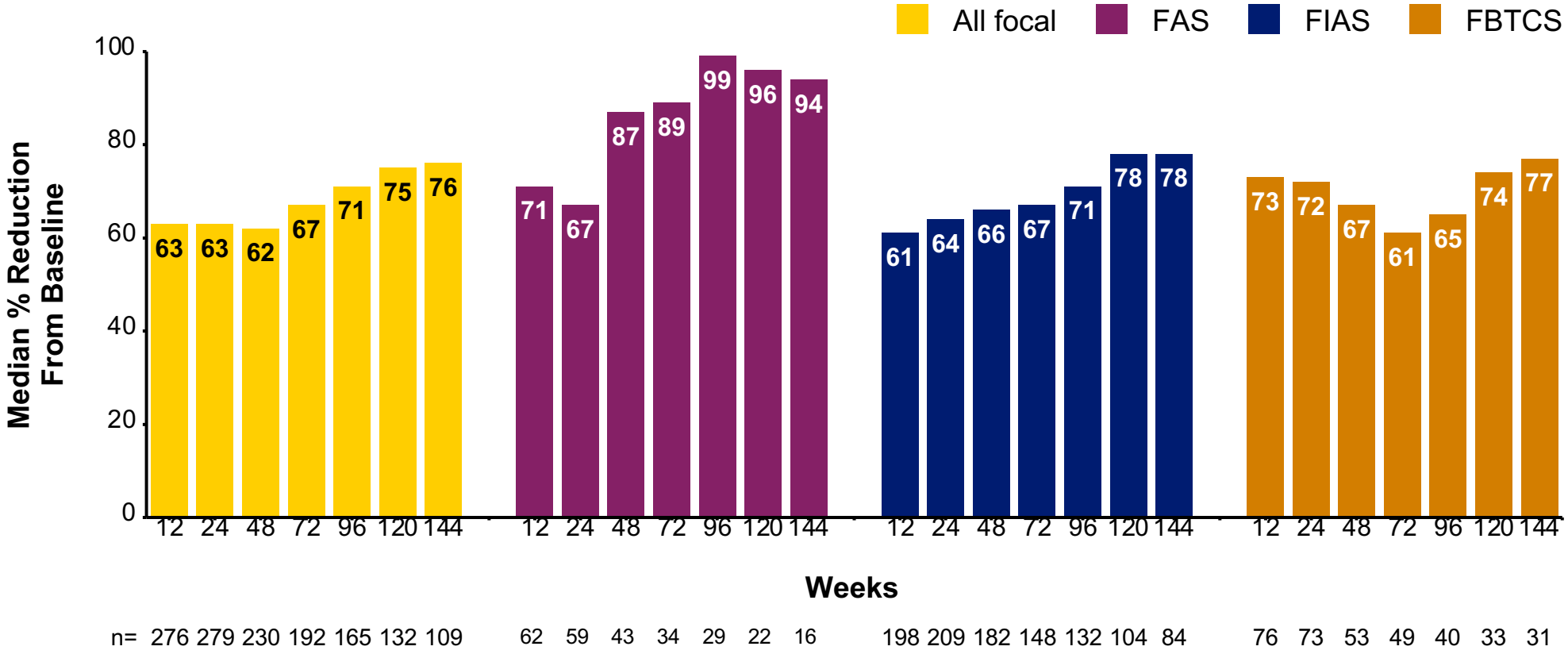
CBD, cannabidiol; EAP, Expanded Access Program.

Results – Baseline Characteristics and CBD Exposure

	Efficacy population (n=348)
Mean age, years (min, max)	15.8 (0, 73)
Male sex, n (%)	179 (51)
No. of ASMs at baseline, median (min, max) [n]	3 (0, 10) [348]
Most common (>20%) ASMs at baseline, n (%)[a]	
Clobazam	150 (43)
Levetiracetam	124 (35)
Lacosamide	96 (27)
Lamotrigine	93 (26)
Valproate	75 (21)
Diagnosis at baseline, n (%)	
TSC	28 (8)
LGS	27 (8)
DS	24 (7)
Other	192 (55)
Unknown	77 (22)
Baseline median (Q1, Q3) monthly seizure frequency [n]	
FAS	28.0 (4, 87) [77]
FIAS	22.4 (7, 76) [259]
FBTCS	12.0 (4, 41) [93]
All focal seizures	25.8 (8, 88) [345]
CBD exposure	
Median time on CBD (range), days [n][b]	700 (281–1177) [347]
Median total daily dose (IQR), mg/kg/d [n][c]	22.0 (15–25) [347]

[a]Data from safety population (n=351). [b]Median time on CBD for safety population (range), days: 684 (281–1177) [n=350]. [c]Median total daily dose for safety population (IQR), mg/kg/d: 21.6 (15–25) [n=349].
ASM, antiseizure medication; CBD, cannabidiol; DS, Dravet syndrome; FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; IQR, interquartile range; LGS, Lennox-Gastaut syndrome; Q1, first quartile; Q3, third quartile; TSC, tuberous sclerosis complex.

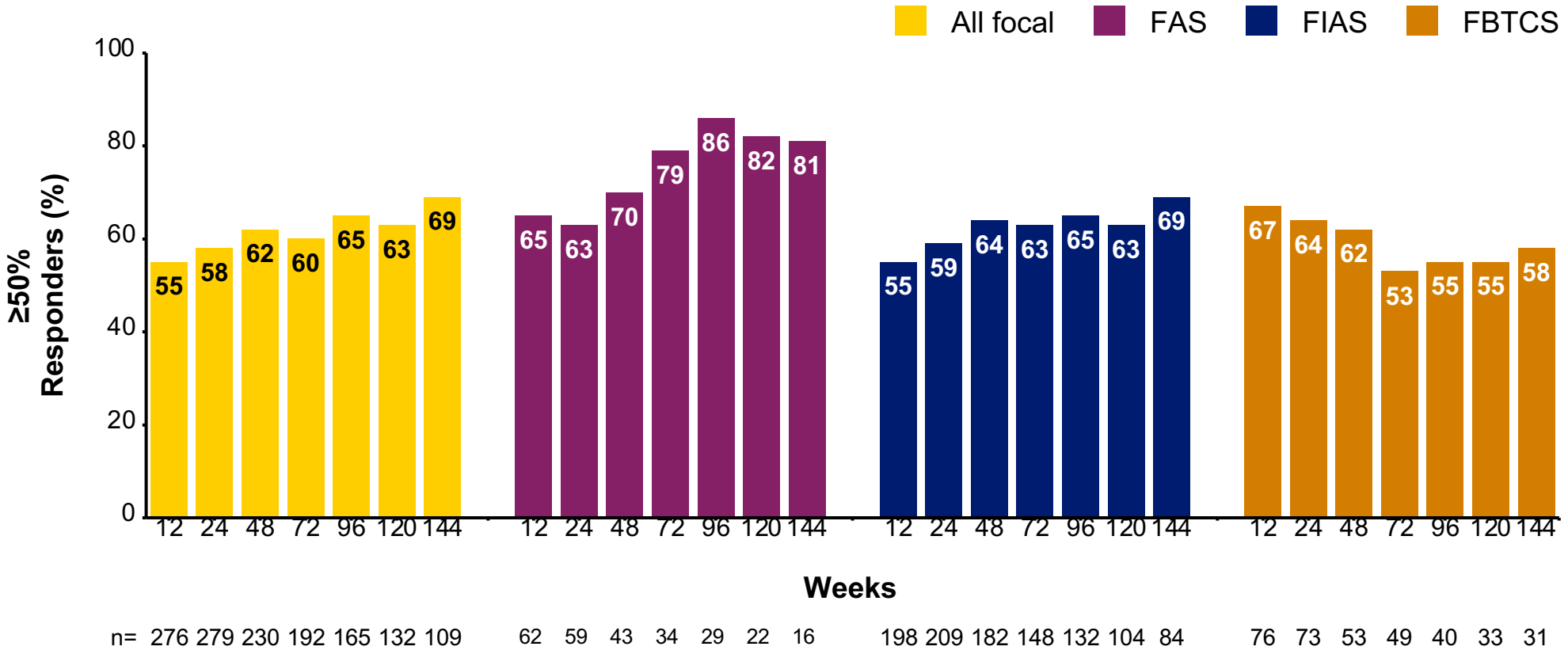
Results – Median Percentage Reduction From Baseline in Focal Seizures



- Across 12-week visit intervals (additional supplemental data available via QR code), CBD treatment was associated with a median reduction of 62%–76% in all focal seizures, 67%–99% in FAS, 61%–78% in FIAS, and 50%–81% in FBTCS

CBD, cannabidiol; FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

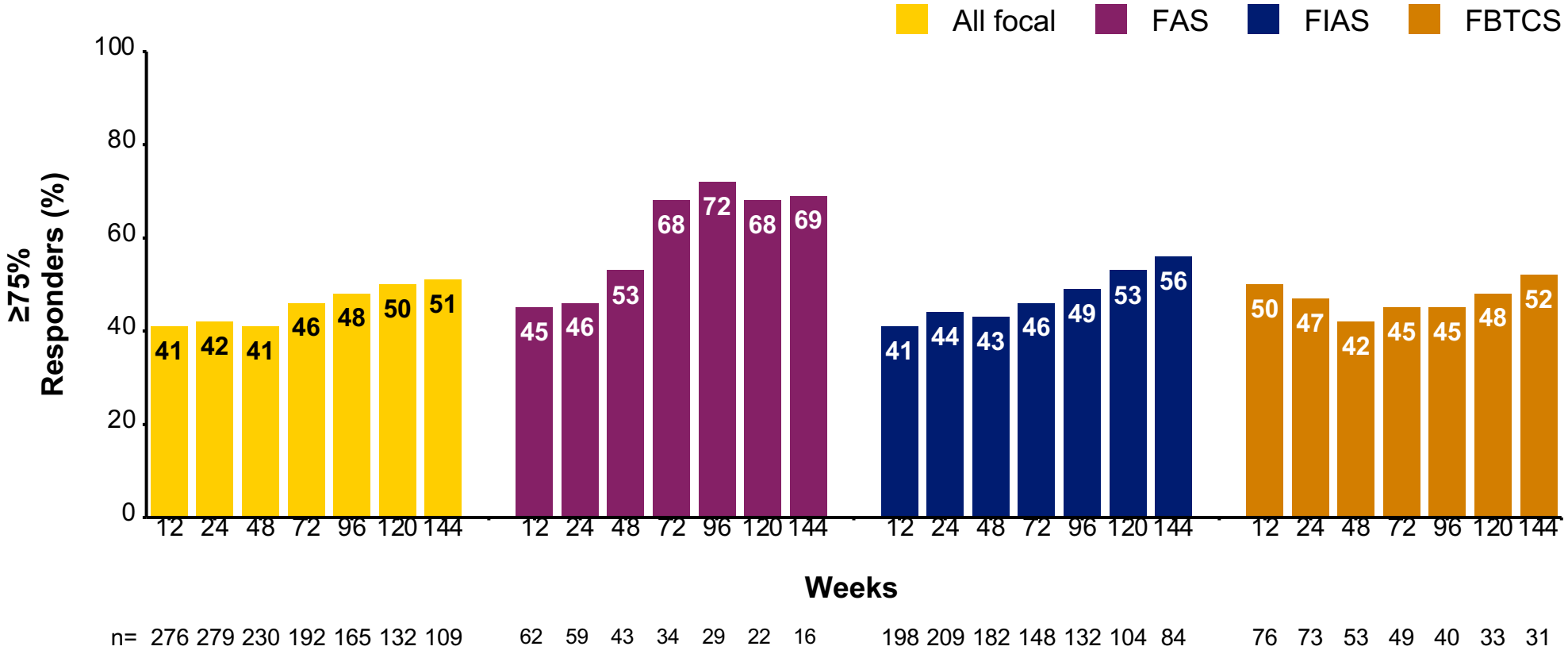
Results – Percentage of Patients With ≥50% Reduction in Focal Seizures



- Across 12-week visit intervals (additional supplemental data available via QR code), ≥50% responder rates through 144 weeks were 55%–69% for all focal seizures, 61%–88% for FAS, 55%–69% for FIAS, and 52%–69% for FBTCS

FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

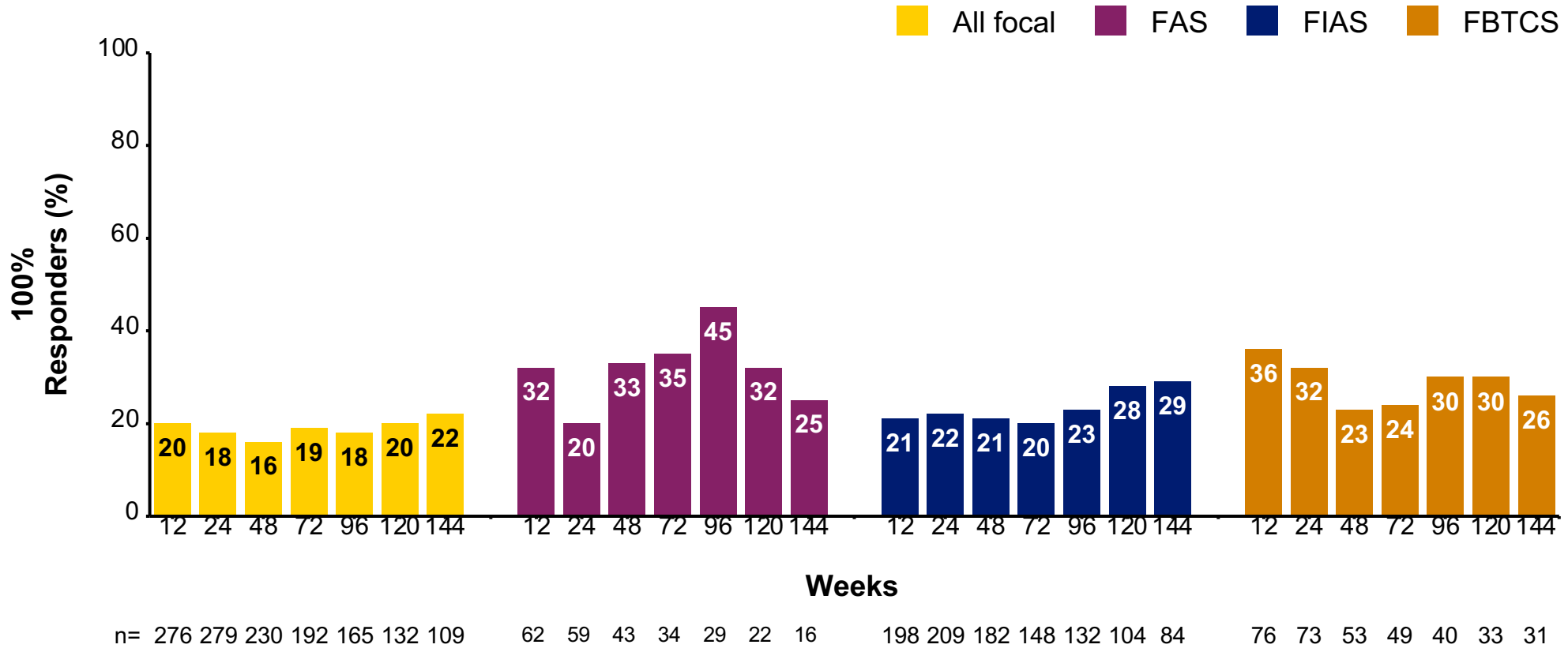
Results – Percentage of Patients With ≥75% Reduction in Focal Seizures



- Across 12-week visit intervals (additional supplemental data available via QR code), ≥75% responder rates through 144 weeks were 41%–51% for all focal seizures, 45%–72% for FAS, 41%–56% for FIAS, and 41%–54% for FBTCS

FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

Results – Percentage of Patients With 100% Reduction in Focal Seizures



- Across 12-week visit intervals (additional supplemental data available via QR code), 100% responder rates through 144 weeks were 14%–23% for all focal seizures, 20%–46% for FAS, 18%–29% for FIAS, and 23%–36% for FBTCS

FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

Results – Safety

Patients, n (%)	Safety population (n=351)
TEAEs	
Any AEs	315 (90)
Any TRAEs	241 (69)
AEs leading to permanent discontinuation	23 (7)
Serious AEs	132 (38)
Deaths	5 (1)
TRAEs in ≥5% of patients by MedDRA preferred term	
Diarrhea	105 (30)
Somnolence	62 (18)
Decreased appetite	35 (10)
Fatigue	32 (9)
Weight decreased	22 (6)
Dizziness	18 (5)
Sedation	18 (5)

AE summary

- Most frequently reported serious AEs: convulsion (11%), status epilepticus (5%), pneumonia (5%), vomiting (3%), dehydration (3%)
- Most frequently reported AEs leading to treatment discontinuation: convulsion, diarrhea, constipation, decreased weight, lethargy (all 1%)
- Deaths were considered unrelated to treatment according to the investigators

Laboratory investigations

- Liver-related AEs in >1% of patients: increased ALT (n=15 [4%]), increased AST (n=15 [4%]), abnormal liver function test (n=11 [3%])
- Rate of treatment-emergent ALT >3X ULN: 10% (n=34/347)
- Rate of treatment-emergent AST >3X ULN: 3% (n=3/101)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; ULN, upper limit of normal.

Conclusions

- In this analysis of patients with TREs in the CBD EAP, add-on CBD was associated with a reduction in focal-onset seizures through 144 weeks
- At least 50% reduction was reported by the majority of patients across focal-onset seizure types through 144 weeks with FAS showing the greatest reduction in seizures
- The CBD safety profile in this subgroup was similar to that observed in previously reported EAP analyses and clinical trials
- Because the EAP was conducted in a real-world setting, there was no control group, and patients were not blinded. Other limitations include potential intersite variability in seizure classification and the potential impact of concomitant medications
- These results suggest that CBD may be effective against focal-onset seizures regardless of epilepsy diagnosis
- These findings offer insights into the long-term effectiveness of CBD for focal-onset seizures in a real-world clinical practice setting

CBD, cannabidiol; EAP, Expanded Access Program; FAS, focal aware seizures; TRE, treatment-resistant epilepsy.

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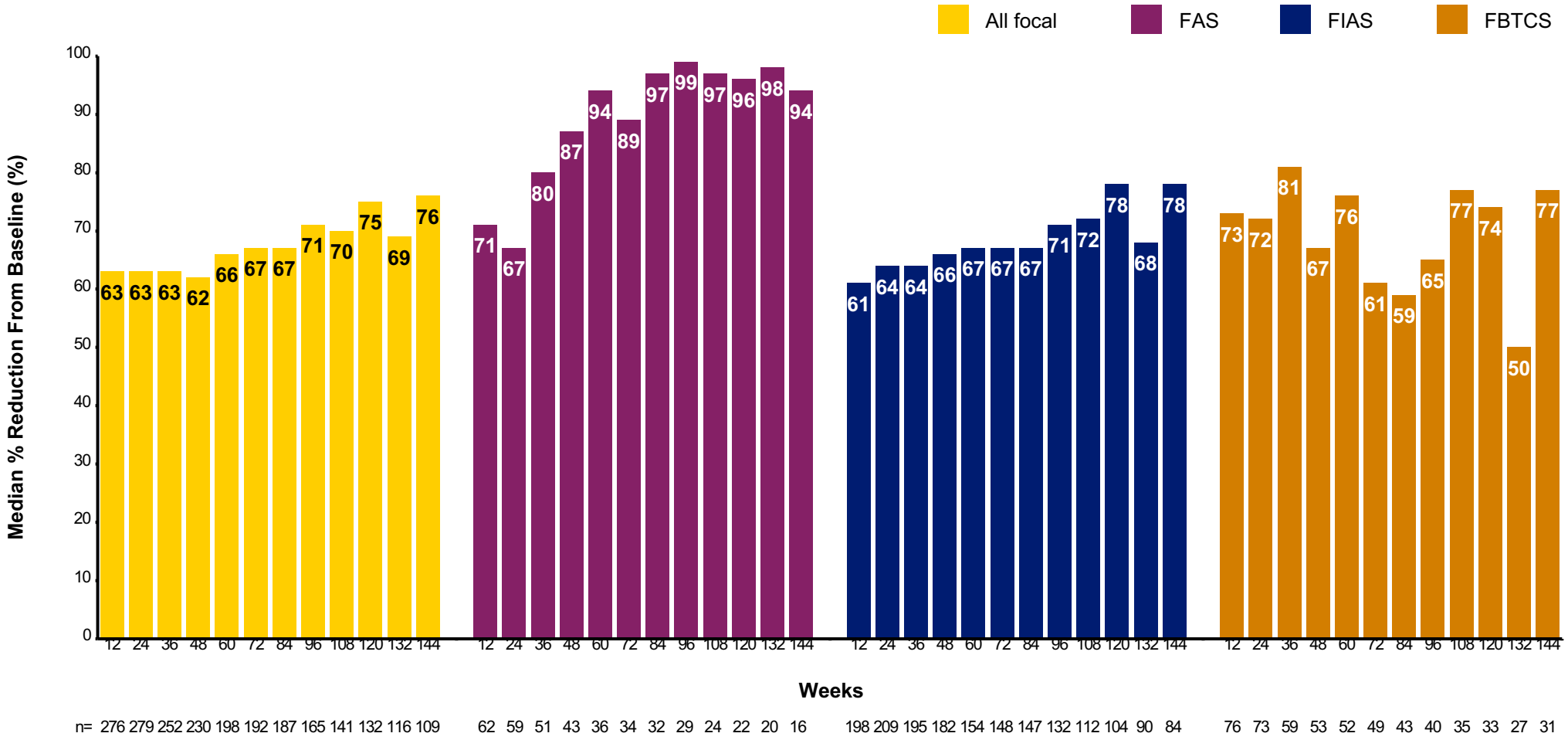
Supplementary Material

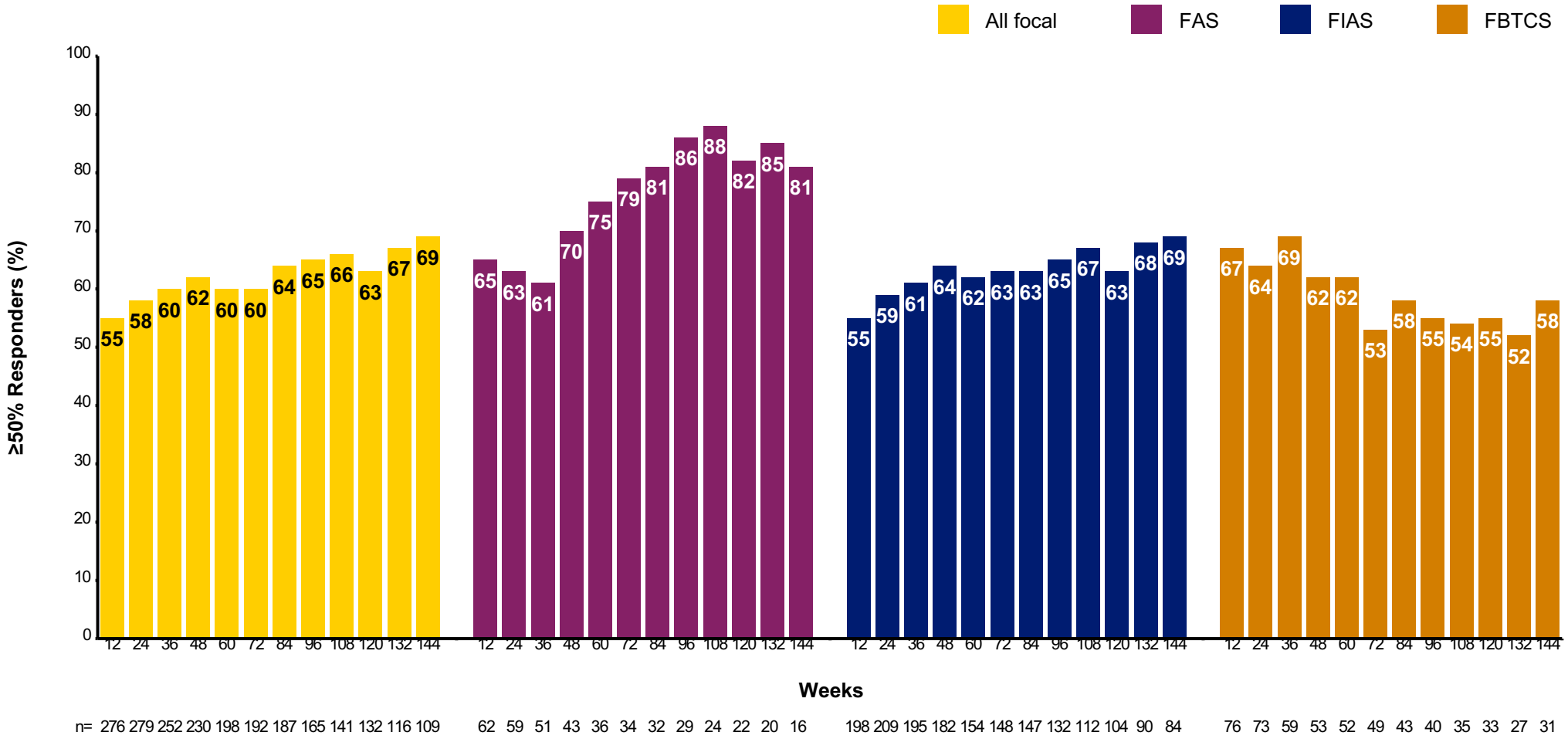
AAN 2024 Annual Meeting

Median Percentage Reduction From Baseline in Focal Seizures (12-Week Intervals)



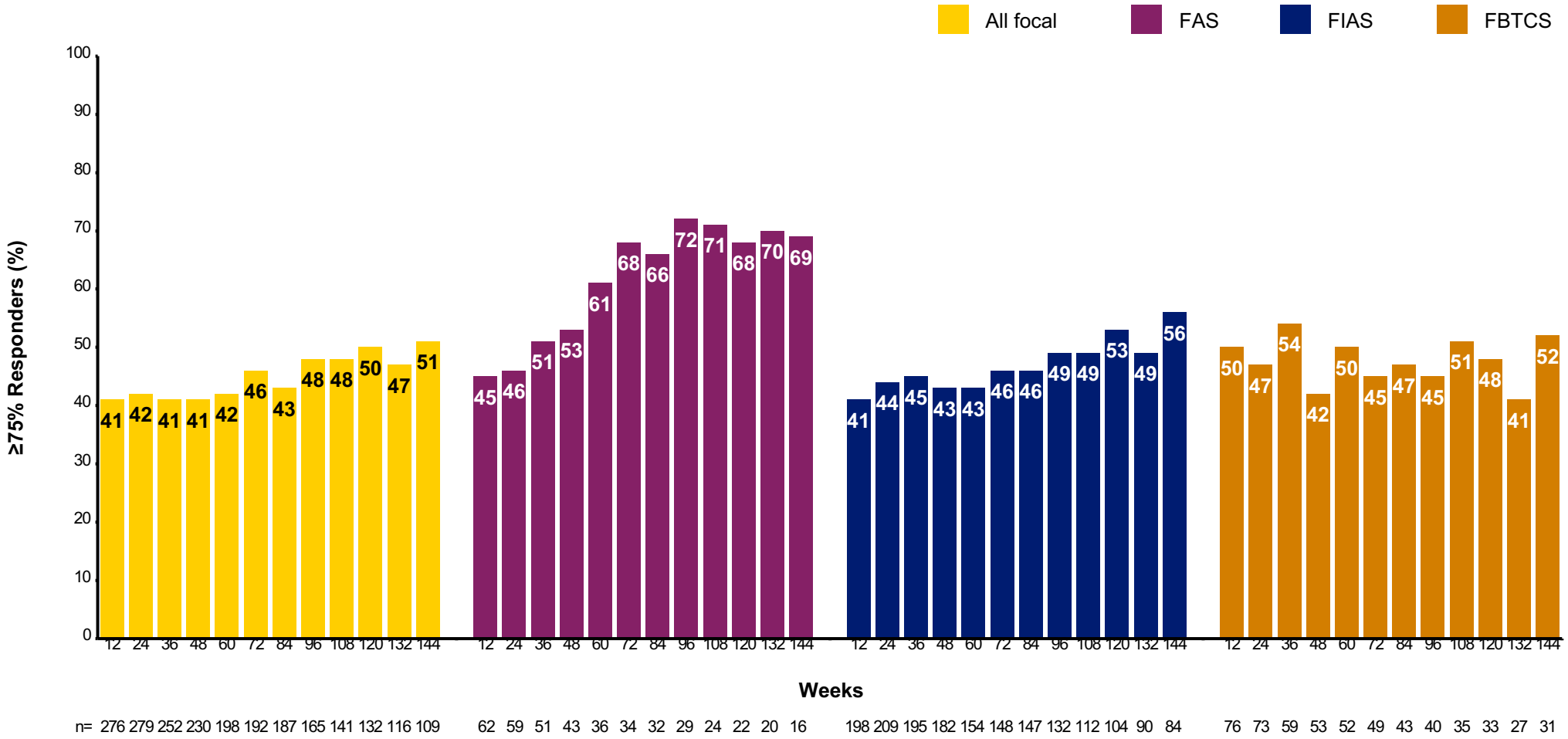
FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

Percentage of Patients With ≥50% Reduction in Focal Seizures (12-Week Intervals)



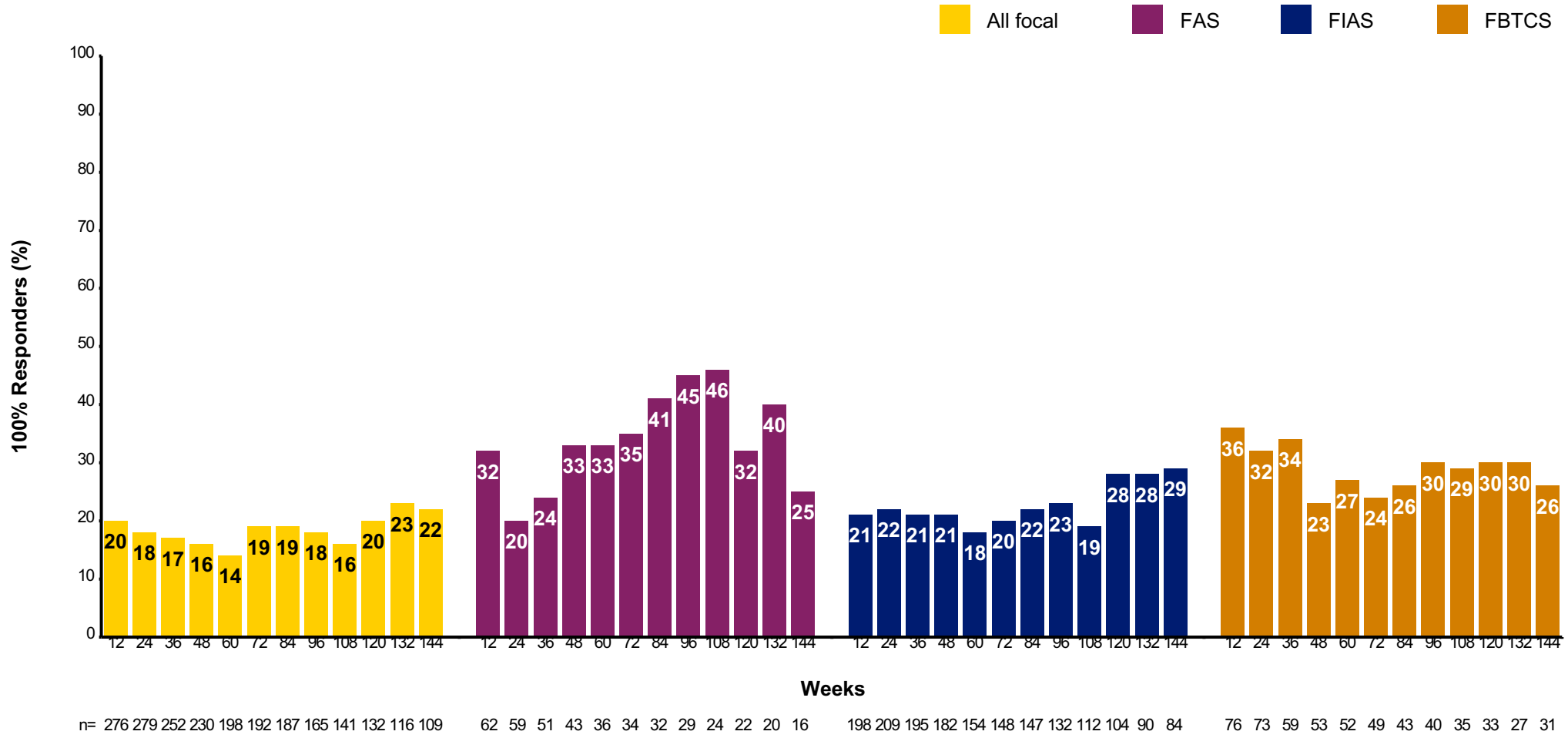
FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

Percentage of Patients With ≥75% Reduction in Focal Seizures (12-Week Intervals)



FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.

Percentage of Patients With 100% Reduction in Focal Seizures (12-Week Intervals)



FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures.