Efficacy and Tolerability of RAP-219, a Potential First-in-Class Negative Allosteric Modulator of γ8 Transmembrane AMPA Receptor Regulatory Protein (TARPγ8): Impact on RNS Long Episodes and Focal Seizures

Poster 2.498

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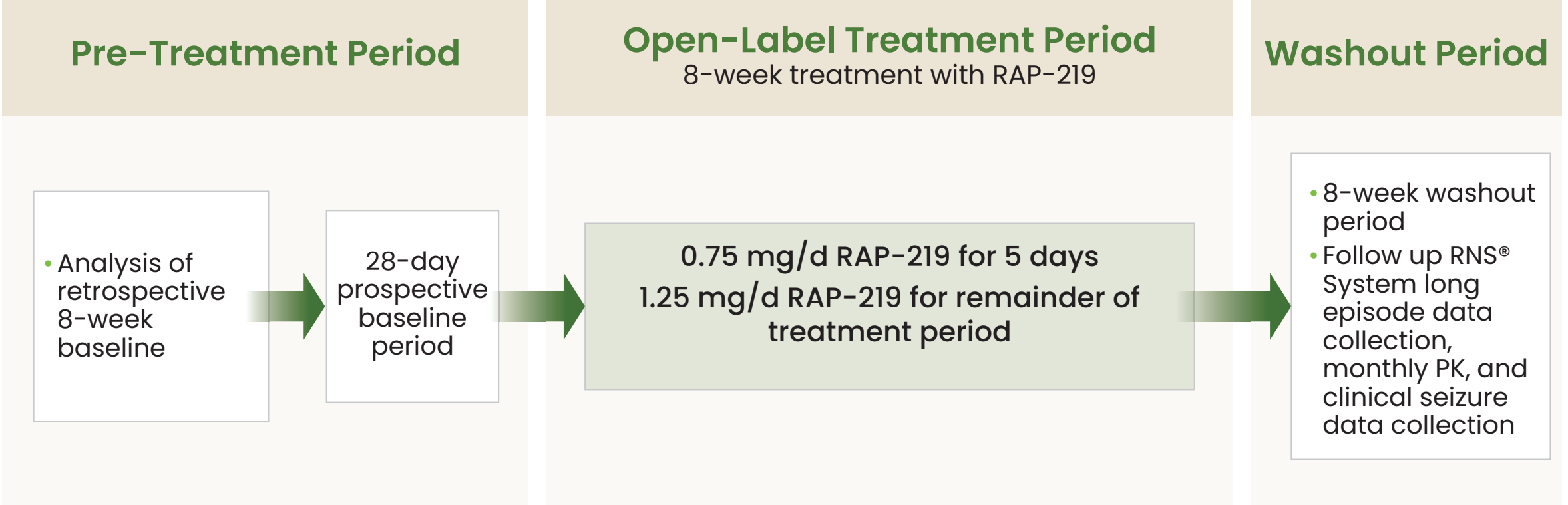
Background

- New antiseizure medications (ASMs) for drug-resistant focal epilepsy with novel mechanisms of action and improved tolerability are needed
- Transmembrane AMPA receptor regulatory protein (TARP)-γ8 is highly expressed in the neocortex and mesial temporal lobe (MTL), regions of the brain where nearly all focal onset seizures (FOS) originate[1–3]
- RAP-219 is a selective and potent negative allosteric modulator of TARPγ8 offers a precision approach for the treatment of focal epilepsy via targeted AMPA receptor inhibition
- The responsive neurostimulator (RNS® System, NeuroPace) continually monitors electrocorticographic intracranial EEG activity and responds to abnormal activity[4]
  - Long episodes (LEs), measured by the RNS System, are organized epileptiform activity exceeding a clinician-specified duration
  - LEs often represent electrographic seizures and may potentially supplement seizure diaries[5]
  - Recent analyses suggest that a ≥30% reduction in LEs is associated with a ≥50% reduction in clinical seizures (CSs)[6]
- In this novel Phase 2 proof-of-concept (POC) study, the effect of RAP-219 in patients with drug-resistant FOS and an implanted RNS System was assessed
  - Key outcomes were change in LEs and CSs

Methods

- Adults (18–65 y) with drug-resistant focal epilepsy and an implanted RNS device with ≥1 lead implanted in the MTL were enrolled in this phase 2 study
- LEs were recorded by an RNS System; CSs were recorded in seizure diaries

Figure 1. Study Design



Pre-Treatment Period

- Analysis of retrospective 8-week baseline

28-day prospective baseline period

Open-Label Treatment Period
8-week treatment with RAP-219

0.75 mg/d RAP-219 for 5 days
1.25 mg/d RAP-219 for remainder of treatment period

Washout Period

- 8-week washout period
- Follow up RNS® System long episode data collection, monthly PK, and clinical seizure data collection

RNS – responsive neurostimulator.

References

1. Maher MP, et al. *J Pharmacol Exp Ther*. 2016;357(2):394-414.
2. Coombs ID, et al. *Mol Pharmacol*. 2022;101(5):343-56.
3. Kato AS, et al. *Nat Med*. 2016;22(12):1496-501.
4. Bergey GK, et al. *Neurology*. 2015;84:768.
5. Quigg M, et al., *Epilepsy Res*. 2020; 161:106302
6. Gammaitoni AR, et al., American Epilepsy Society Annual Meeting 2024. December 6-10, 2024, Los Angeles, CA. Poster 1.494.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria[a]	Exclusion Criteria[b]
• Adults 18–65 years old with drug-resistant focal epilepsy • RNS System device requirements: – ≥1 electrode implanted within the MTL ≥15 months before screening – Stable device settings for ≥8 weeks before screening – Had ≥16 LEs and ≥1 CS during an 8-week retrospective analysis period – >50% electrographic seizure and LE concordance[c] • ≤4 concomitant ASMs with stable dose for ≥8 weeks before screening	• Epilepsy surgery ≤12 months before screening • Use of >4 concomitant ASMs • Use of perampanel ≤12 weeks before screening • Ketogenic diet with any regimen changes within 12 weeks before screening – Stable ketogenic diet allowed

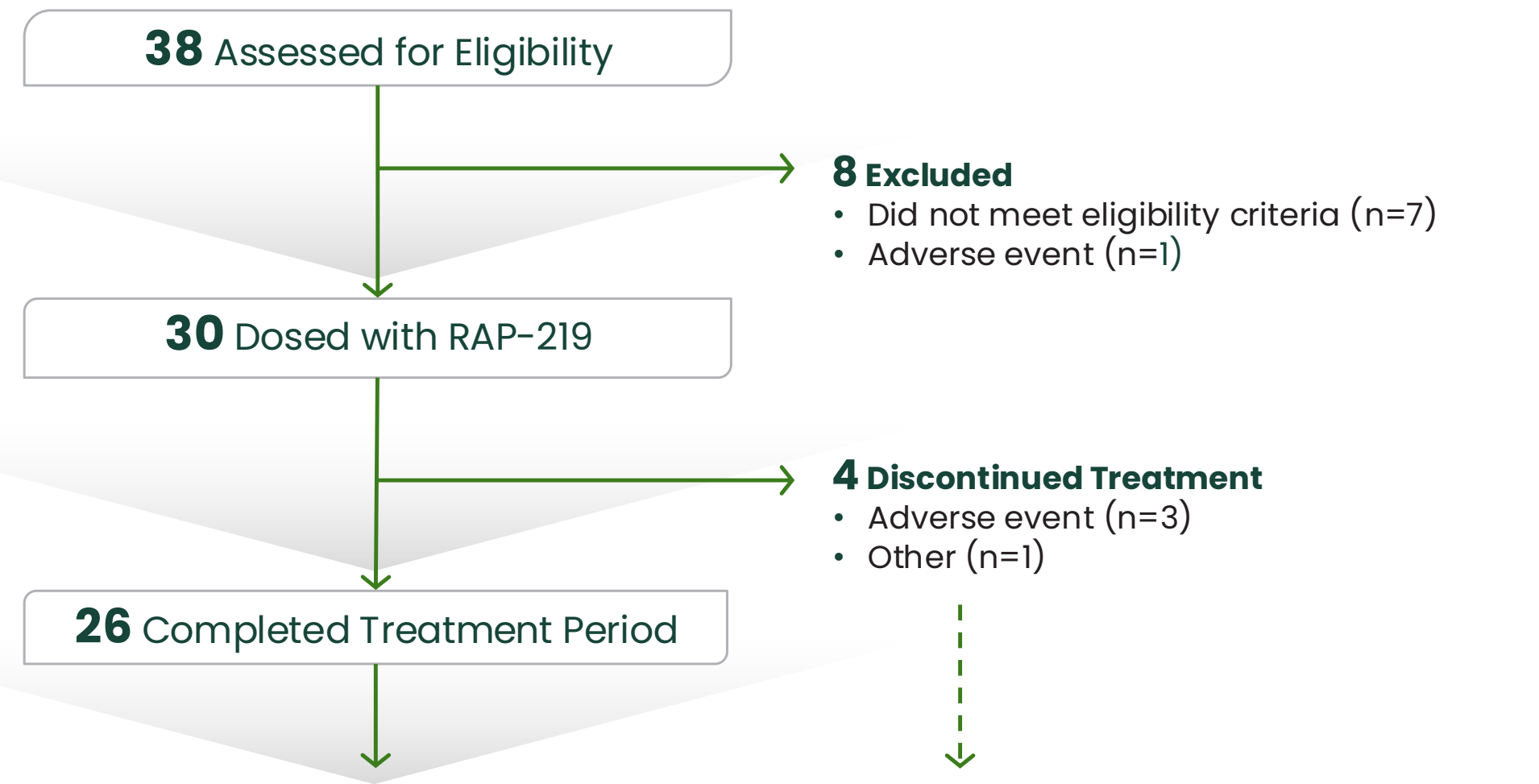
[a]Does not include all inclusion criteria. [b]Does not include all exclusion criteria. [c]Evaluated by the Central Epileptologist Review Team, consisting of a panel of epileptologists from the ESC.
ASM – antiseizure medication; **CS** – clinical seizure; **ESC** – Epilepsy Study Consortium; **LE** – long episode; **MTL** – mesial temporal lobe; **RNS** – responsive neurostimulator.

Outcomes

- Median percentage change in LE and CS frequency from baseline to Weeks 1–8
  - The combined 8-week retrospective and 4-week prospective periods served as the baseline for LEs
  - The 4-week prospective period served as the baseline for CSs
- Responder rates for LE and CS reductions, with LE thresholds of ≥30%, ≥50%, ≥75%, and 100% and CS thresholds of ≥50%, ≥75%, and 100%, were analyzed
- Incidence of AEs

Results

Figure 2. Patient Disposition



38 Assessed for Eligibility

8 Excluded
- Did not meet eligibility criteria (n=7)
- Adverse event (n=1)

30 Dosed with RAP-219

4 Discontinued Treatment
- Adverse event (n=3)
- Other (n=1)

26 Completed Treatment Period

Analysis Population

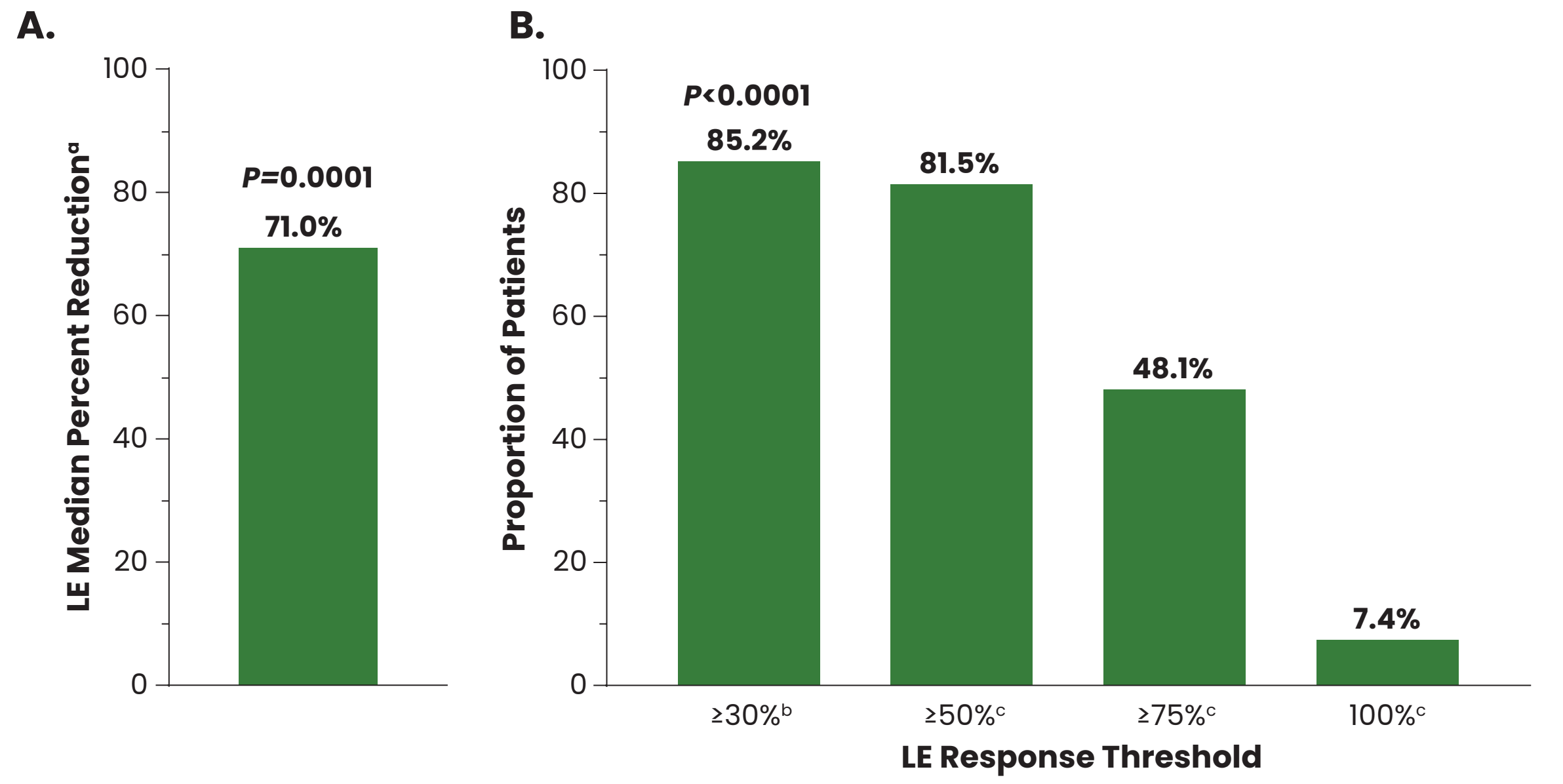
- Safety population: N=30
- Modified intent-to-treat (mITT) population (LE efficacy): N=27
  - Not included from the safety population: 2 patients with <3 weeks of treatment; 1 patient with an RNS setting change
- mITT-CS population (CS efficacy): N=25
  - Not included from the mITT population: 2 patients with no CSs during the prospective baseline

Table 2. Demographics and Baseline Characteristics

	Safety Population N=30
Male, n (%)	18 (60)
Age at study entry, y, mean ± SD	40.1 ± 10.4
Age at first seizure, y, mean ± SD	16.6 ± 9.4
LE frequency per 28 days[a], median (range)	48 (8-751.7)[a]
CS frequency per 28 days[b], median (range)	10 (0.8-13.5)[b]
Number of concomitant ASMs, median (range)	3 (1-4)
1 concomitant ASM, n (%)	2 (7)
2 concomitant ASMs, n (%)	7 (23)
3 concomitant ASMs, n (%)	14 (47)
4 concomitant ASMs, n (%)	7 (23)
Most commonly used ASMs, n (%)	
Lamotrigine	15 (50)
Levetiracetam	12 (40)
Cenobamate	11 (37)
Zonisamide	9 (30)
Clobazam	7 (23)
Lacosamide	7 (23)
Years since RNS System implantation, median (range)	4.6 (2-11)
Concordance between LEs and electrographic seizures, median (range)	92 (30-100)[a]

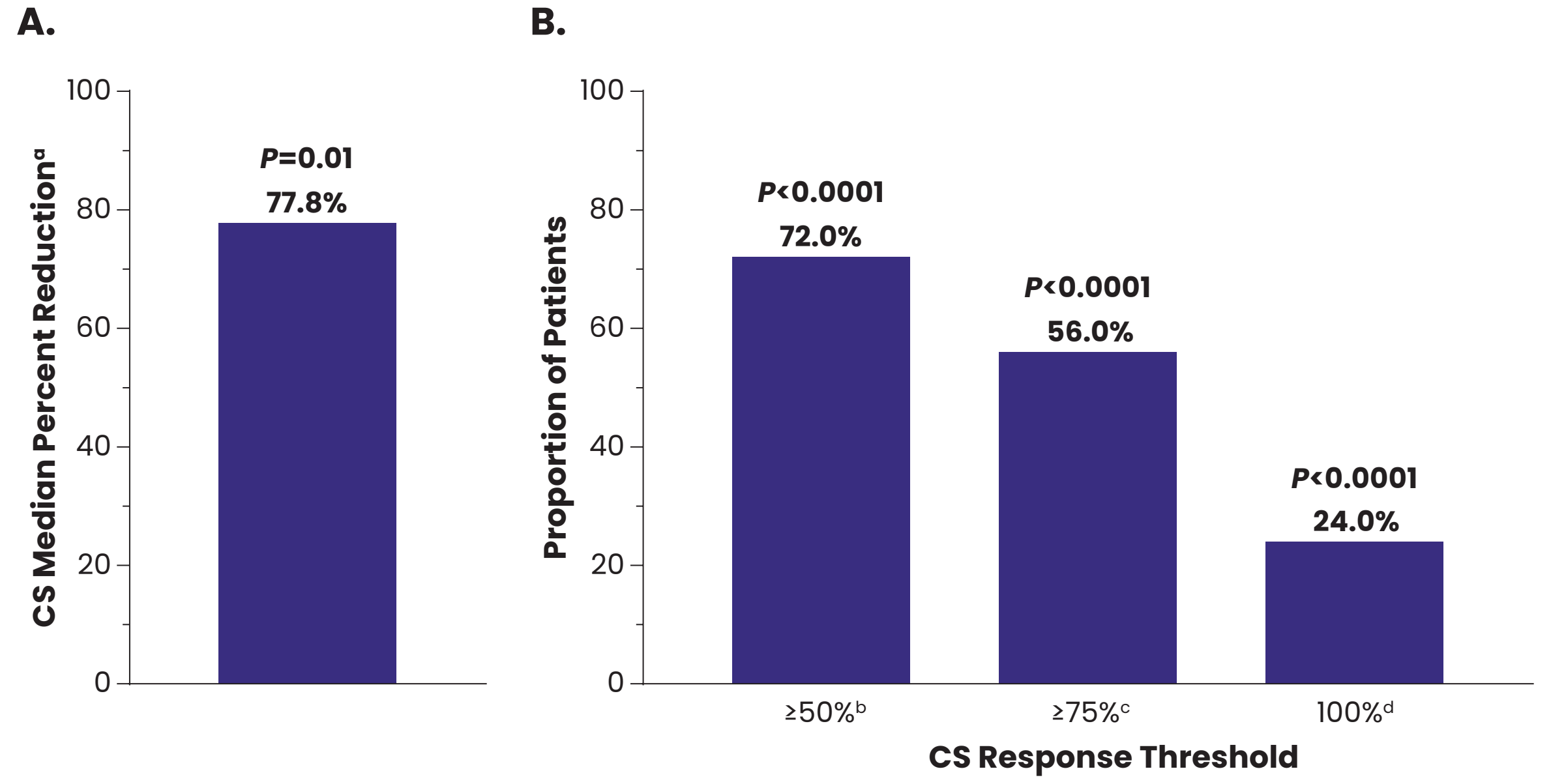
[a]mITT population (N=27). [b]mITT-CS population (N=25).
ASM – antiseizure medication; **CS** – clinical seizure; **LE** – long episode; **RNS** – responsive neurostimulator; **SD** – standard deviation.

Figure 3. Weeks 1–8 A. Median LE Percent Reduction From Baseline and B. ≥30%, ≥50%, ≥75%, and 100% Responder Rates Following Treatment With RAP-219



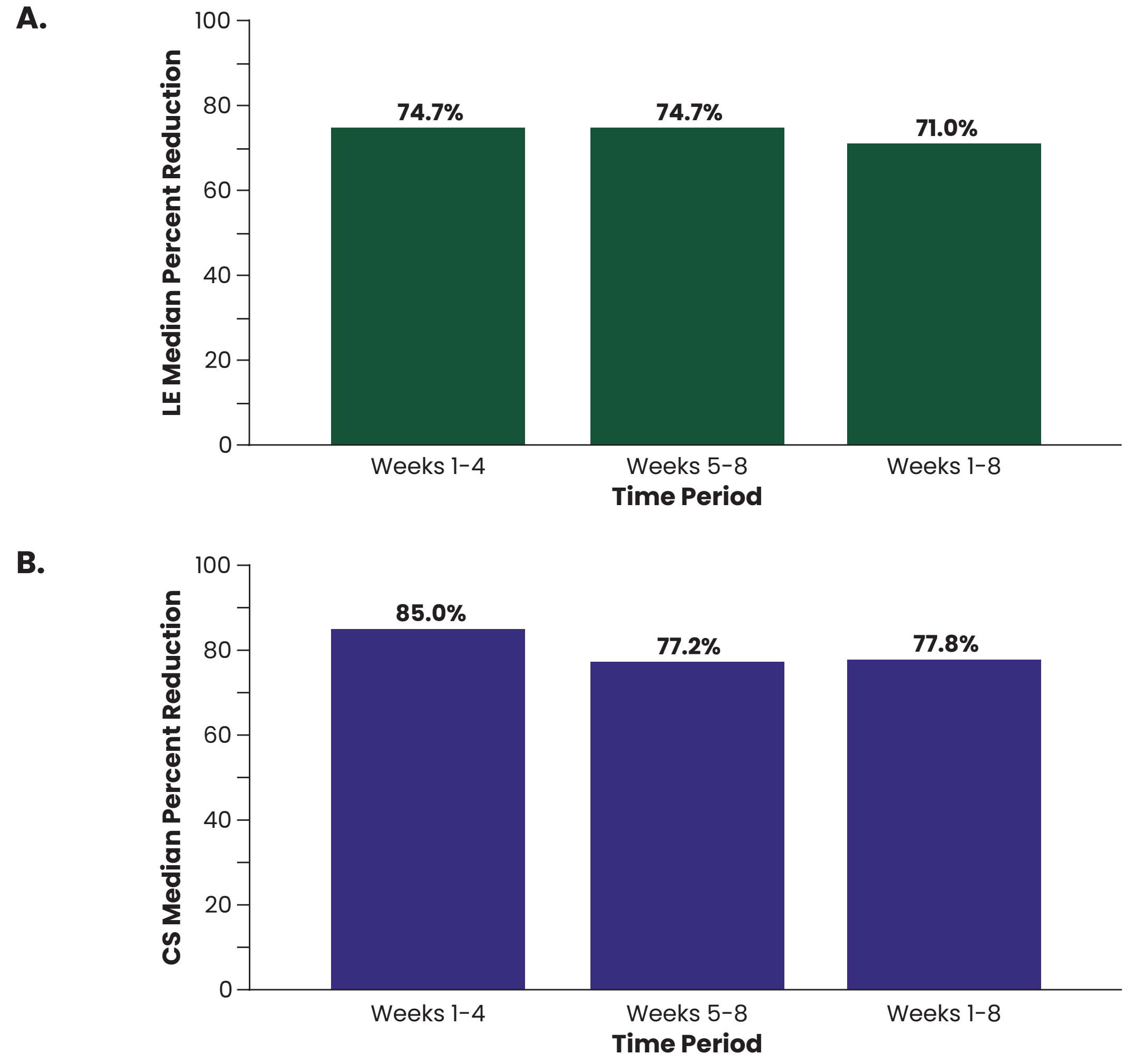
[a]Median percent change statistical comparison used the Wilcoxon signed rank test to determine if the percent change in LE was greater than 0%. [b]Responder analysis statistical comparison was based on a one-sample exact test to determine whether the proportion of responders was >10%. [c]Statistical comparisons were not made for other cut points. 95% confidence intervals for responder analysis were based on Clopper-Pearson exact binomial: ≥50%, (61.9, 93.7); ≥75%, (28.7, 68.1); 100%, (0.9, 24.3).
LE – long episode.

Figure 4. Weeks 1–8 A. Median CS Percent Reduction From Baseline and B. ≥50%, ≥75%, and 100% Responder Rates Following Treatment With RAP-219



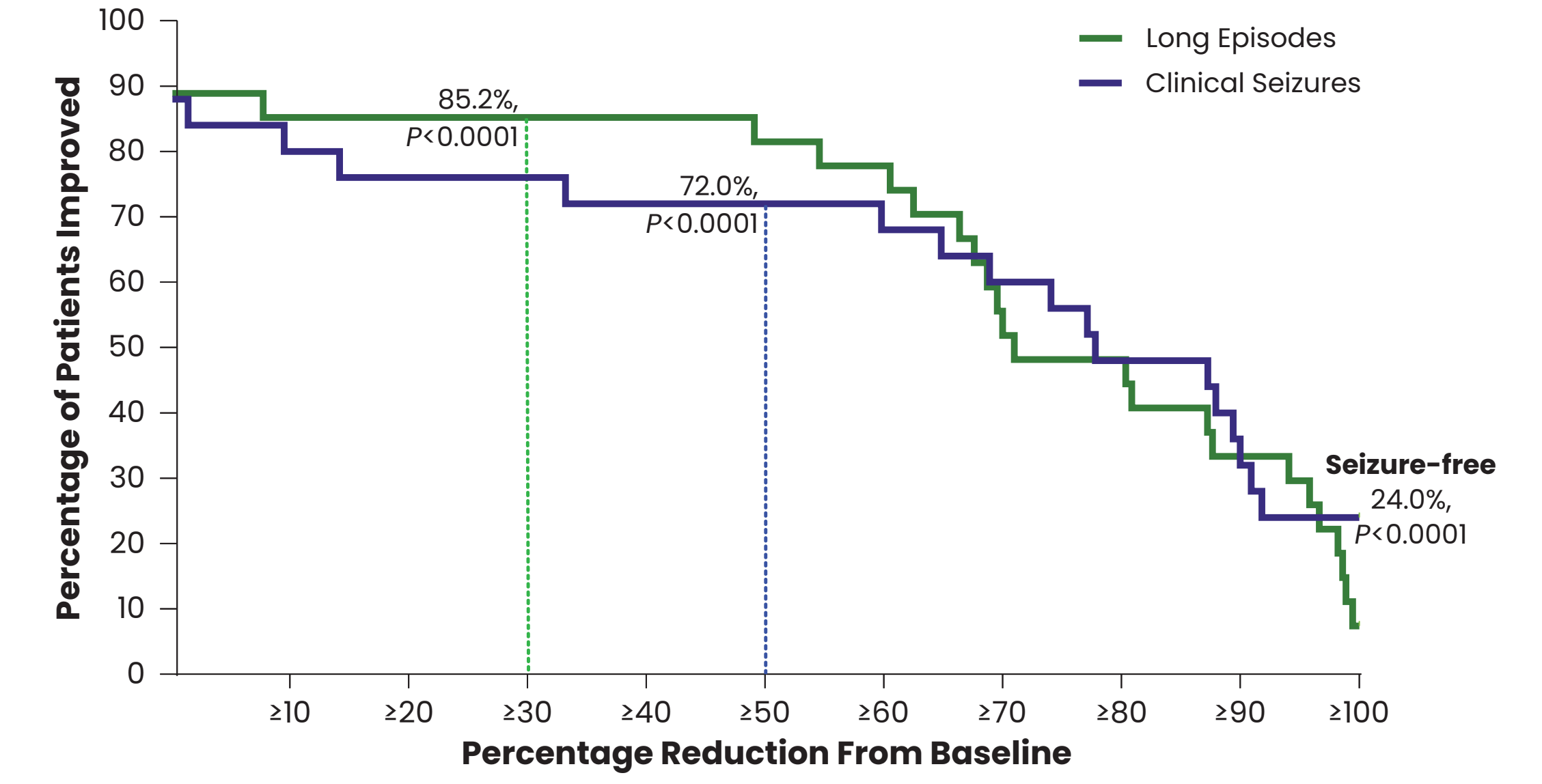
[a]Statistical comparison for median percent change used the Wilcoxon signed-rank test to determine if the median percent reduction from baseline in CS was greater than 20%. [b,c,d]Responder analysis statistical comparison was based on a one sample exact test to determine whether the proportion of responders was: (b) >20%; (c) >7%; (d) >1.5% for the ≥50% responder, ≥75% responder, and 100% (seizure freedom) groups.
CS – clinical seizure.

Figure 5. Effect of RAP-219 Observed During Weeks 1–4 and 5–8 on A. LEs and B. CSs



CS – clinical seizure; **LE** – long episode.

Figure 6. Cumulative Response for Long Episodes and Clinical Seizures



CS – clinical seizure; **LE** – long episode.

Safety

Table 4. Treatment-Emergent Adverse Events (Weeks 1–8)

	Safety Population (N=30)
Any TEAE, n (%)	25 (83.3)
TEAE leading to study drug discontinuation[a]	3 (10)
Grade 1 TEAE (mild)	15 (50)
Grade 2 TEAE (moderate)	10 (33.3)
Grade ≥3 TEAE (severe)	0
TEAEs reported in ≥10% of patients, n (%)	
Dizziness	8 (26.7)
Headache	5 (16.7)
Fatigue	4 (13.3)
Fall	3 (10)
Nausea	3 (10)
Somnolence	3 (10)

[a]TEAEs leading to study discontinuation: worsening of preexisting memory impairment (Grade 1); panic attack (Grade 1); worsening of preexisting anxiety (Grade 2).
TEAE – treatment-emergent adverse event.

Conclusions

- Treatment with RAP-219 provided statistically significant and clinically meaningful improvement in LE frequency (objective biomarker) and CS frequency
  - Improvements were consistent across the entire treatment period
- Clinically meaningful improvement in LE and CS frequencies were observed in 85% and 72% of patients, respectively (**Figure 6**)
  - Complete seizure freedom over the entire treatment period (Titration + Maintenance) was achieved by 24% of patients
- RAP-219 treatment was generally well tolerated, with a 10% discontinuation rate secondary to TEAEs and no severe or serious AEs or clinically significant laboratory, vital signs, or ECG abnormalities noted during the treatment period
- These results support advancing RAP-219 into Phase 3 studies

Acknowledgments

The authors thank Mari Willeman, PhD, and Anthony DiLauro, PhD, of the Sensified Division of Woven Health Collective, LLC, for writing and editorial assistance, which were funded by Rapport Therapeutics, Inc.

Presented at AES Annual Meeting 2025, December 5–9, 2025, Atlanta, GA.

Disclosures

WWM, NN, NW, ARG: Rapport Therapeutics, Inc: employee and stock ownership.
IHQ: NeuroPace: research funding to institution. Rapport Therapeutics: research funding to institution.
DF: Epilepsy Study Consortium: research services from Biogen, Biohaven, Cerebral Therapeutics, Cerevel, Encoded, Epalex, Équilibre, Jazz Pharmaceuticals, Jannsen, Longboard, Lundbeck, Marinus, Modulite, Neurocrine, Ono, Praxis, PureTech, Rapport Therapeutics, SK Life Science, Supernus, UCB, and Xenon. Paid consultant for Neurelis Pharmaceuticals and Meili Technologies. Travel support from the Epilepsy Foundation. Research support from NINDS, NeuroPace, Epitel, and CDC unrelated to this work. Equity interests in Neuroview Technology.
PL: Nothing to disclose.
VRR: NeuroPace, Inc: consulting/advisory and grant funding; Medtronic, Inc: funding grants.
KAD: Rapport Therapeutics: consulting fees, travel/meeting support, advisory board participation. Epilepsy Foundation: travel support. NeuroPace: advisory board participation, travel/meeting support. NINDS: research support unrelated to this work.
BSG: Rapport Therapeutics: employee during the time of the submitted work, including travel/meeting support and all IP during employment; stock ownership; separation agreement.
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JAF: Epilepsy Foundation, Epilepsy Study Consortium: Salary support for consulting work and/or attending Scientific Advisory Boards for Acadia, Acuta Capital Partners, AgriThera, Alterity, Angelini, Autifony, Axonis, Baergic, Beacon Biosignals, Biogen, Biohaven, Bloom, Bright Minds, Camp4, Cerebral Therapeutics, Cerecin, Cerevel, Cognizance Biomarkers, Cowen and Company, Crossject, Eisai, Encoded, Engrail, Epalex, Epitel, Équilibre, Genentech, Grin Therapeutics, IQVIA RDS, iQure, Janssen, Jazz Pharmaceuticals, Korro, Leal, Lipocine, LivaNova, Longboard, Marinus, Modulight.bio, Neumirna, Neurocrine, Neuronetics., NeuroPace, NeuroPro, Neuroventis, Ono Pharmaceutical, Otsuka, Ovid, Paladin Labs, Praxis, PureTech, Rapport Therapeutics, Receptor Holdings, Sage, SK Life Science, Stoke, Supernus, Takeda, Third Rock Ventures, UCB, Ventus, Vida Ventures Management, and Xenon. Epilepsy Study Consortium: Research support funded by Eisai and UCB. President, Board of Directors. Epilepsy Foundation: Chief Medical/Innovation Officer. Epilepsy Study Consortium, the Epilepsy Foundation, Angelini, Biohaven, Cerebral Therapeutics, Cowen and Company, Longboard, Neurelis, Neurocrine, NeuroPace, Praxis, Rapport, SK Life Science, Stoke, Takeda, and Xenon: Travel/meal reimbursement related to research, advisory meetings, or presentation of results at scientific meetings. GW/FACES/OneBFoundation, NINDS, and UCB: Research support. Lancet Neurology, Neurology Today: Editorial board.

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