Efficacy and Tolerability of RAP-219, a Potential First-in-Class Negative Allosteric Modulator of γ8 TARP: Impact on RNS Long Episodes and Clinical Seizures

William W. Motley, MD, DPhil; *Imran H. Quraishi, MD, PhD; Neal M. Nolan, MD; Daniel Friedman, MD; Patrick Landazuri, MD; Vikram R. Rao, MD; Kathryn A. Davis, MD; Bradley S. Galer, MD; Nancy Wyant, BA; Martha J. Morrell, MD; Arnold R. Gammaitoni, PharmD; Jacqueline A. French, MD*

American Academy of Neurology Annual Meeting
April 21, 2026

rapport™ therapeutics

Disclaimer

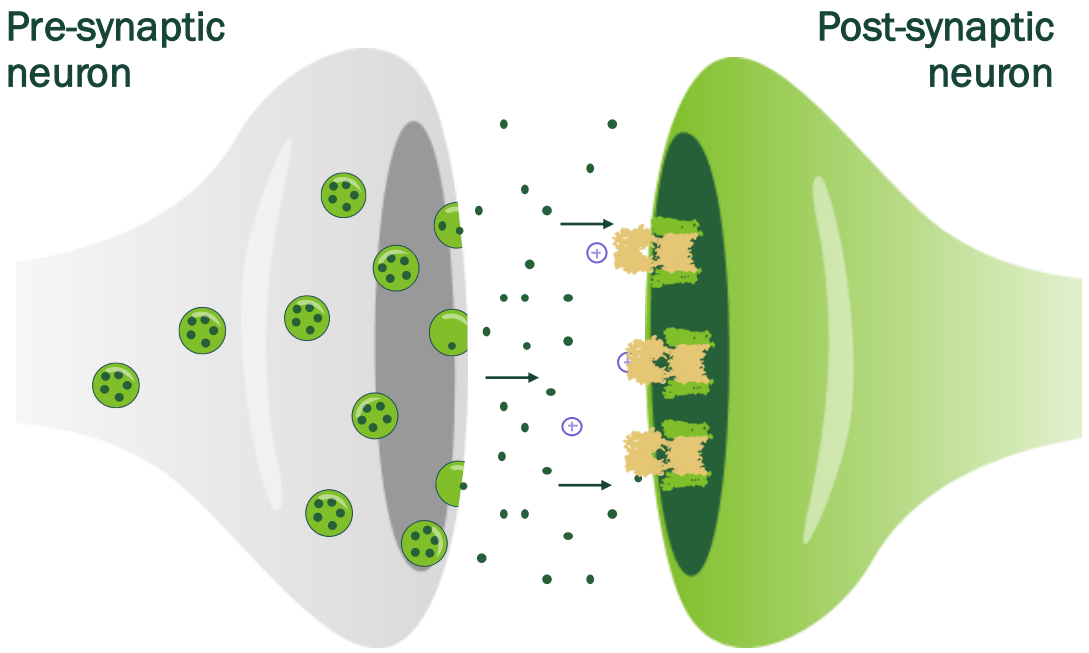
This presentation contains “forward-looking statements” within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, each as amended. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, but are not limited to, express or implied statements regarding: the clinical development of RAP-219 for the treatment of focal onset seizures, primary generalized tonic-clonic seizures, and bipolar mania, including the initiation, timing, progress and results of the ongoing and planned clinical trials; expectations for the efficacy, tolerability, and commercial potential of RAP-219; the potential multi-billion dollar market opportunity for RAP-219 in focal onset seizures, if approved; expectations for the development of a long-acting injectable formulation of RAP-219; the prioritization of the Company’s α6β4 program, including the development candidate’s potential in chronic pain and migraine and the Company’s IND-enabling activities; the deferral of further investment in the RAP-219 diabetic peripheral neuropathic pain program; the potential of Rapport’s RAP technology platform; and expectations for Rapport’s uses of capital, including its cash runway into the second half of 2029. Forward looking statements are based on management’s current expectations and are subject to risks and uncertainties that could negatively affect Rapport’s business, operating results, financial condition and stock value. Factors that could cause actual results to differ materially from those currently anticipated include: risks relating to the Company’s research and development activities; Rapport’s ability to execute on its strategy including obtaining the requisite regulatory approvals on the expected timeline, if at all; uncertainties relating to preclinical and clinical development activities; the Company’s dependence on third parties to conduct clinical trials, manufacture its product candidates and develop and commercialize its product candidates, if approved; Rapport’s ability to attract, integrate and retain key personnel; risks related to the Company’s financial condition and need for substantial additional funds in order to complete development activities and commercialize a product candidate, if approved; risks related to regulatory developments and approval processes of the U.S. Food and Drug Administration and comparable foreign regulatory authorities; risks related to establishing and maintaining Rapport’s intellectual property protections; and risks related to the competitive landscape for Rapport’s product candidates; as well as other risks described in “Risk Factors,” in the Company’s Annual Report on Form 10-K and most recent Quarterly Report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in Rapport’s subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent Rapport’s views only as of today and should not be relied upon as representing its views as of any subsequent date. Rapport expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in its expectations or any changes in events, conditions or circumstances on which any such statement is based, except as required by law, and claims the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

rapport™ therapeutics

William Motley is an employee of, and has stock ownership, in Rapport Therapeutics, Inc.

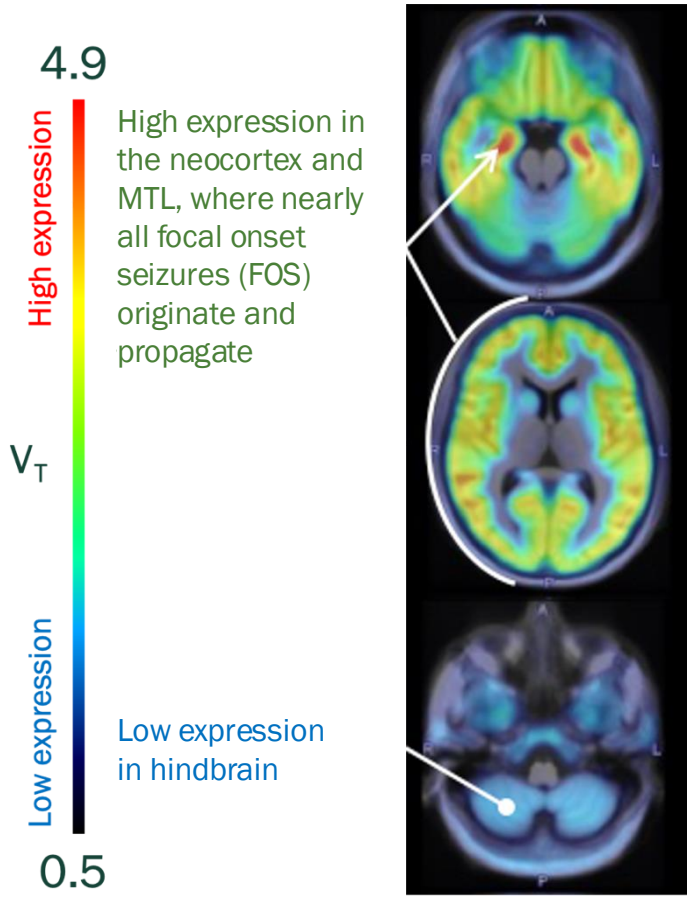
RAP-219 Target, TARPγ8, is Selectively Expressed in Brain Regions Where Focal Onset Seizures Originate

RAP-219 is a NAM of AMPA Receptors (AMPARs) Bound by TARPγ8



AMPA-type glutamate receptors are the primary mediators of excitatory synaptic transmission in the central nervous system

TARPγ8 Clinical PET[a]



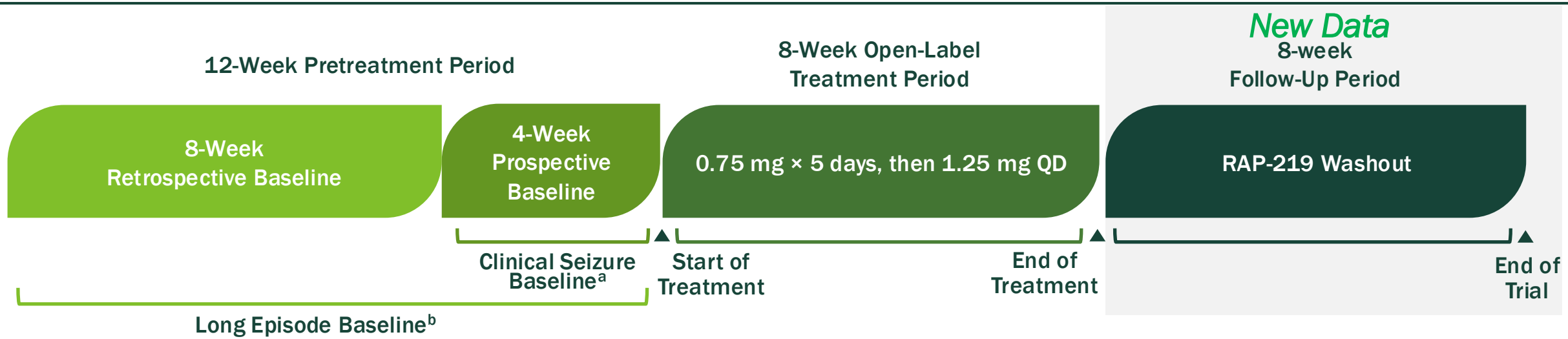
rapport™ therapeutics

LEGEND: AMPA receptor/TARPγ8 Glutamate Na+

[a]Greene et al, American Epilepsy Society (AES) 2025 Annual Meeting, Poster #3.355.

FOS – focal onset seizures; MTL – mesial temporal lobe; NAM – negative allosteric modulator; PET – positron emission tomography; TARPγ8 -- γ8 transmembrane AMPAR regulatory protein; V_T – total volume of distribution.

Phase 2a Trial in Patients With Drug-Resistant Focal Onset Seizures



Key Entry Criteria

1. Drug-resistant FOS
2. RNS® probe implanted in seizure onset zone within mesial temporal lobe (MTL) ≥15 months before screening
3. Stable RNS System settings and other therapies
4. ≥16 long episodes (LEs) during 8-week retrospective review period
5. ≥1 clinical seizure (CS) reported during 8-week retrospective review period
6. >50% concordance between LEs and electrographic seizures

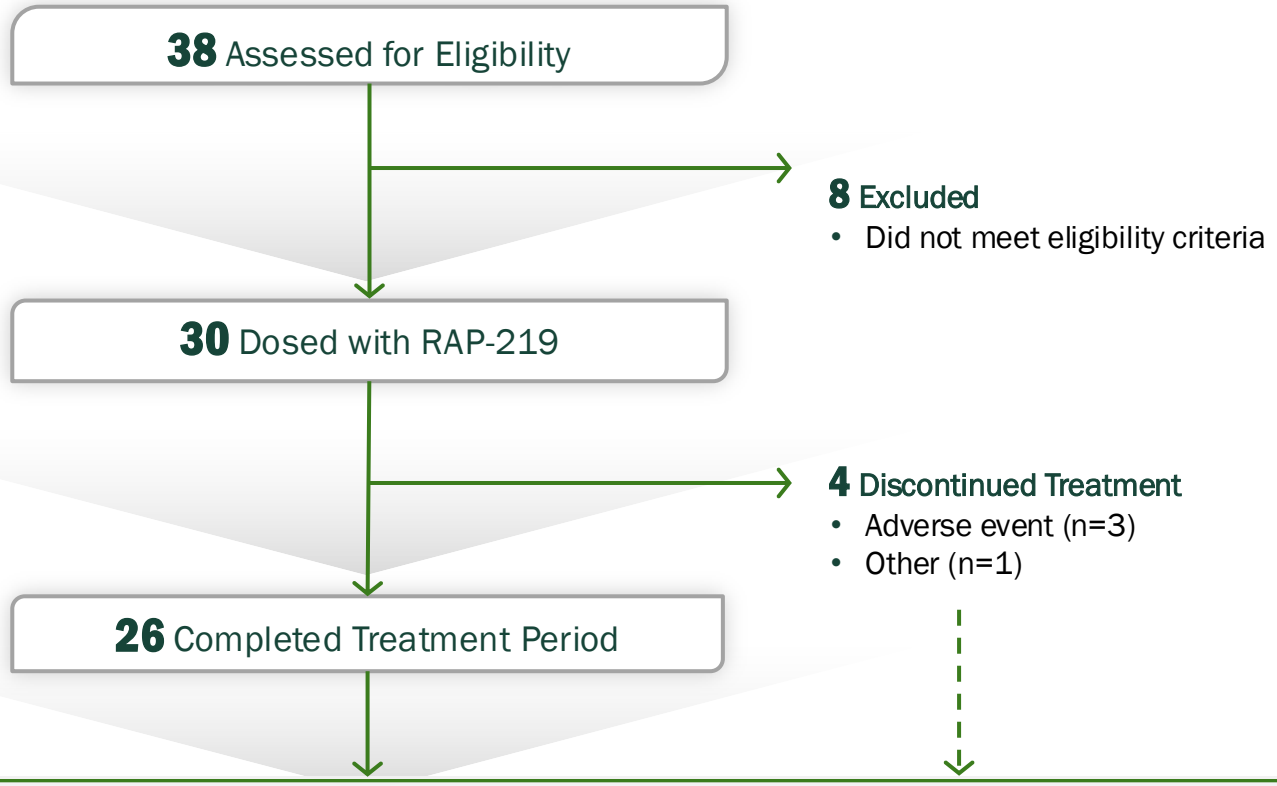
Key Endpoints

- **LE reduction** (power determinations based on this outcome measure)
  - Proportion of patients with ≥30% reduction compared with LE baseline
  - Median percent change from LE baseline
- **CS reduction**
  - Proportion of patients with ≥50% reduction compared with pretreatment baseline
  - Proportion of patients who achieved seizure freedom
  - Median percentage change from baseline

rapport™ therapeutics

[a]Patients with no clinical seizures during the prospective baseline period were allowed to enter the treatment period.
[b]LE baseline was defined as the 12 weeks preceding the initiation of treatment (the combination of the 8-week retrospective and 4-week prospective baseline periods).
CS – clinical seizure; FOS – focal onset seizures; LE – long episode; MTL – mesial temporal lobe; RNS – responsive neurostimulator; QD – once daily.

Patient Disposition and Analysis Populations



Analysis Populations

- → Safety population (N=30)
- → mITT population for LE efficacy (N=27)
  - Safety population minus 2 patients with <3 weeks of treatment and 1 patient with RNS setting change
- → mITT-CS population for clinical seizure efficacy (N=25)
  - mITT population minus 2 patients who did not have clinical seizures during prospective baseline
- → Completed follow-up (N=29)

mITT: patients with ≥3 weeks or treatment, ≥70% adherence, and no RNS system detection or stimulation setting changes. mITT-CS: patients in the mITT with ≥1 CS during the prospective baseline.
CS – clinical seizure; LE – long episode; mITT – modified intent-to-treat; RNS – responsive neurostimulator.

Patient Demographic and Baseline Characteristics

Highly Drug-Resistant FOS Patients are Representative of Those in Registrational Trials

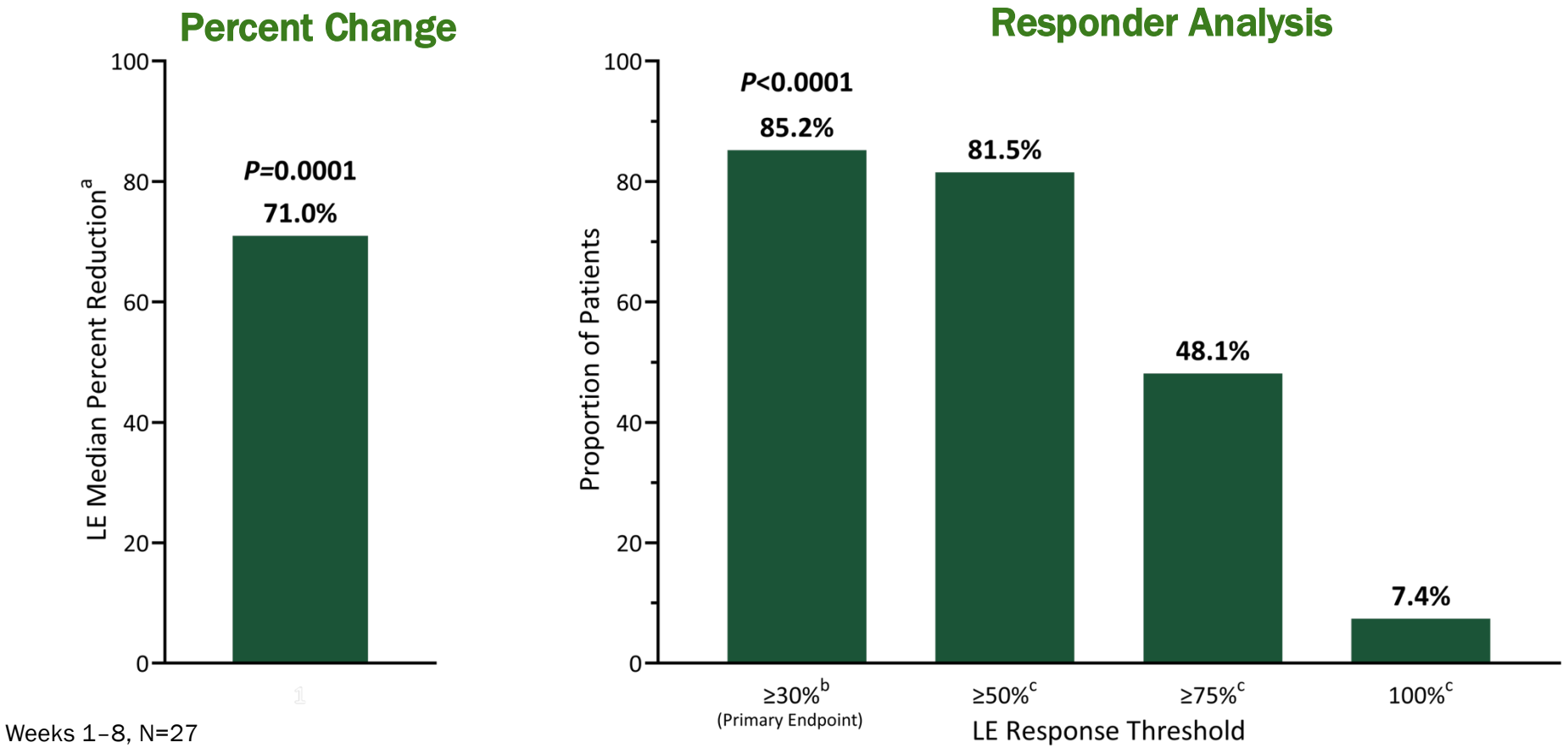
Safety Population	N=30
Age, years, mean (SD)	40.1 (10.4)
Age at first seizure, years, mean (SD)	15.8 (9.3)
Sex, male, n (%)	18 (60)
Years since RNS implantation, median (range)	4.6 (2–11)
No. of concomitant ASMs	
Median (range)	3 (1–4)
1, n (%) | 2, n (%) | 3, n (%) | 4, n (%)	2 (7) | 7 (23) | 18 (60) | 3 (10)
Most frequent concomitant ASMs[a], n (%)	
Lamotrigine	15 (50)
Levetiracetam	12 (40)
Cenobamate	11 (37)
Zonisamide	9 (30)
Clobazam	7 (23)
Lacosamide	7 (23)

rapport™ therapeutics

[a]Maintenance ASMs in ≥20% of patients at baseline.
ASM – antiseizure medication; FOS – focal onset seizures; MTL – mesial temporal lobe; RNS – responsive neurostimulator; SD – standard deviation.

Primary Endpoints Achieved With High Statistical Significance

71% Reduction in LEs; 85.2% Responder Rate (≥30% LE Reduction)

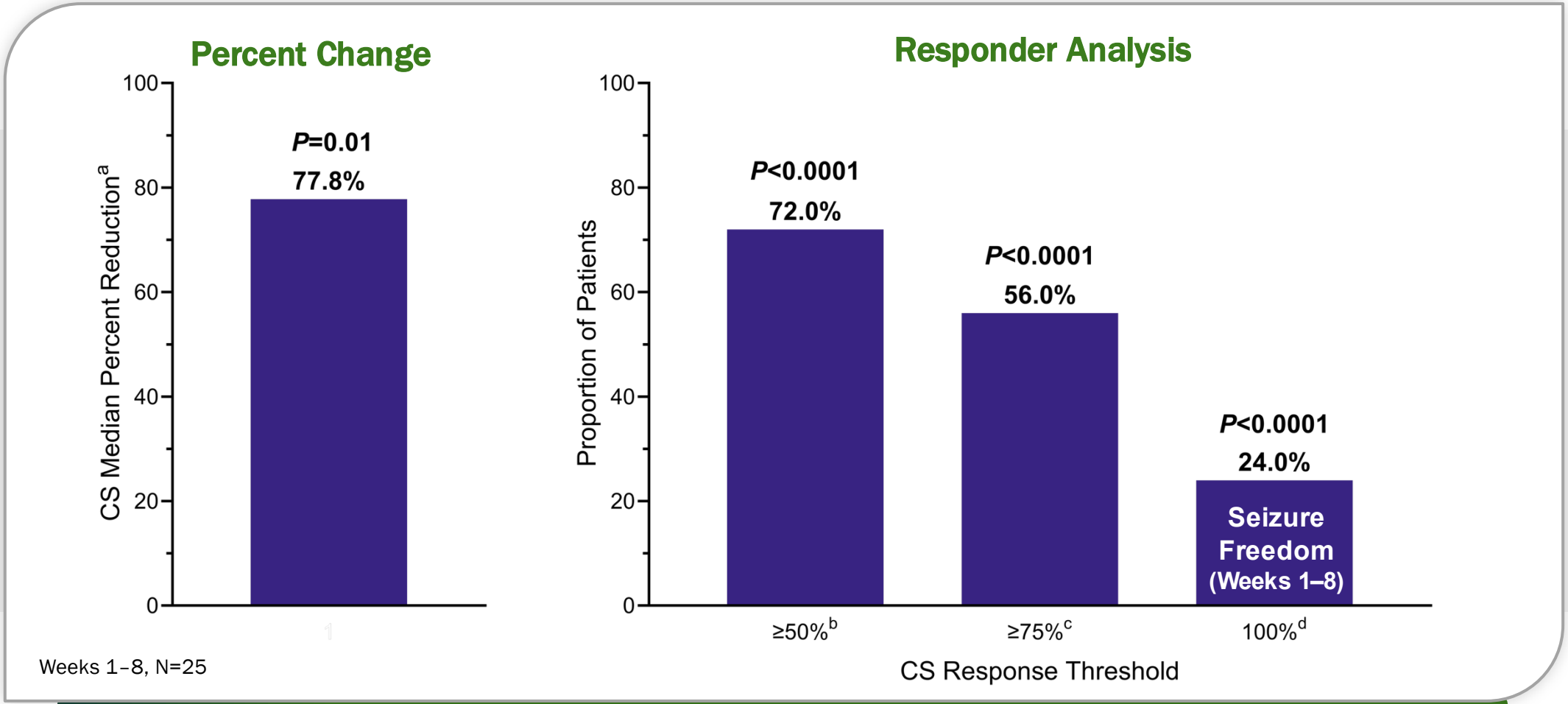


48 LEs at baseline (median, per 28 days); 92% electrographic seizure / LE concordance[d]

[a]Median percent change statistical comparison used the Wilcoxon signed rank test to determine if the % 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 is >10%. [c]Statistical comparisons were not made for other cut points. 95% confidence intervals for responder analysis – Clopper-Pearson exact binomial: ≥50%, (61.9, 93.7); ≥75%, (28.7, 68.1); 100%, (0.9, 24.3). [d]Concordance at baseline was determined by an independent epileptologist reviewer.
LE – long episode.

Clinical Seizure Secondary Endpoints Achieved with Statistical Significance

77.8% Reduction in CSs; 72% Responder Rate (≥50% CS Reduction)

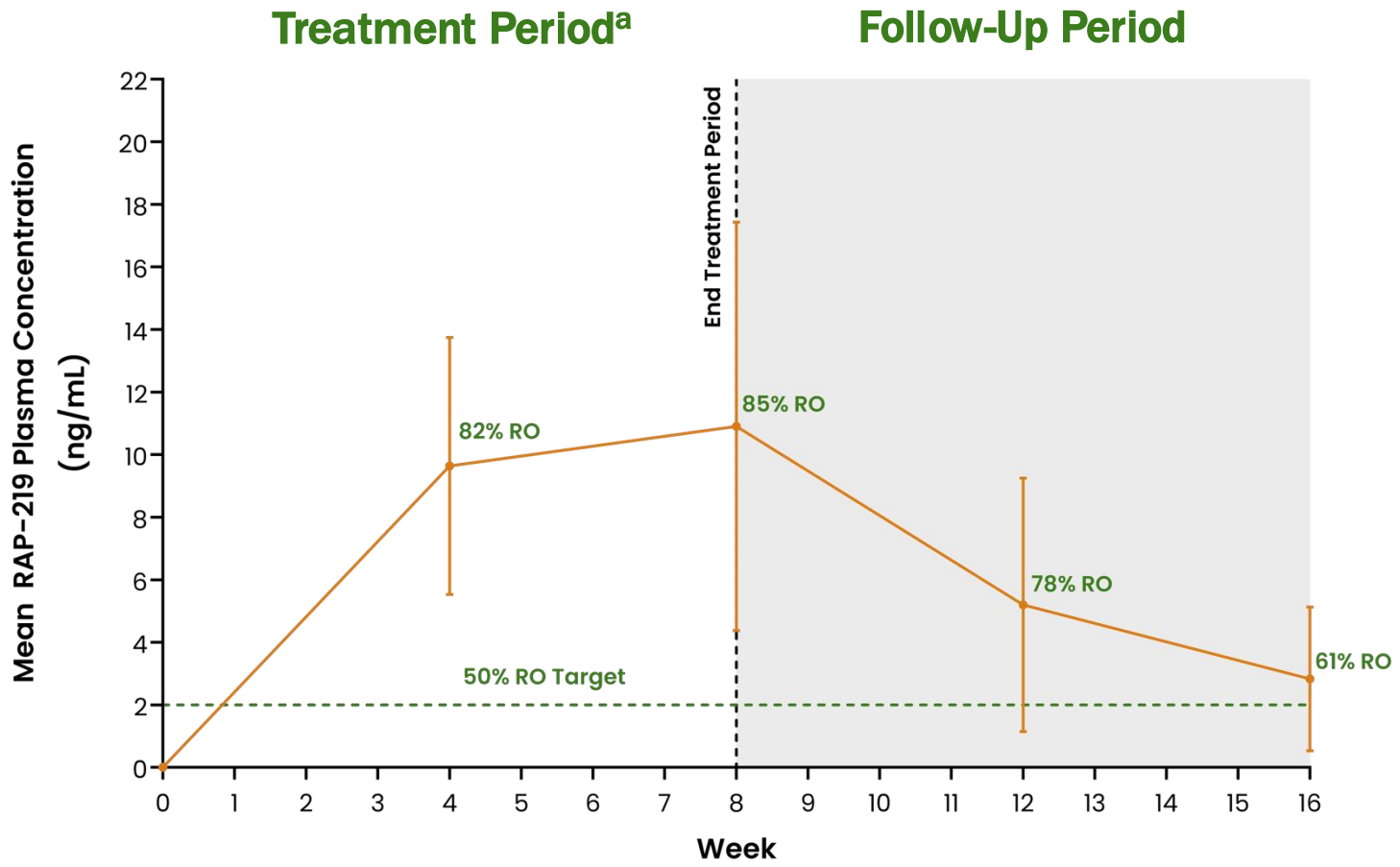


10 clinical seizures at baseline (median, per 28 days)

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

Observed RAP-219 Mean Plasma Concentrations

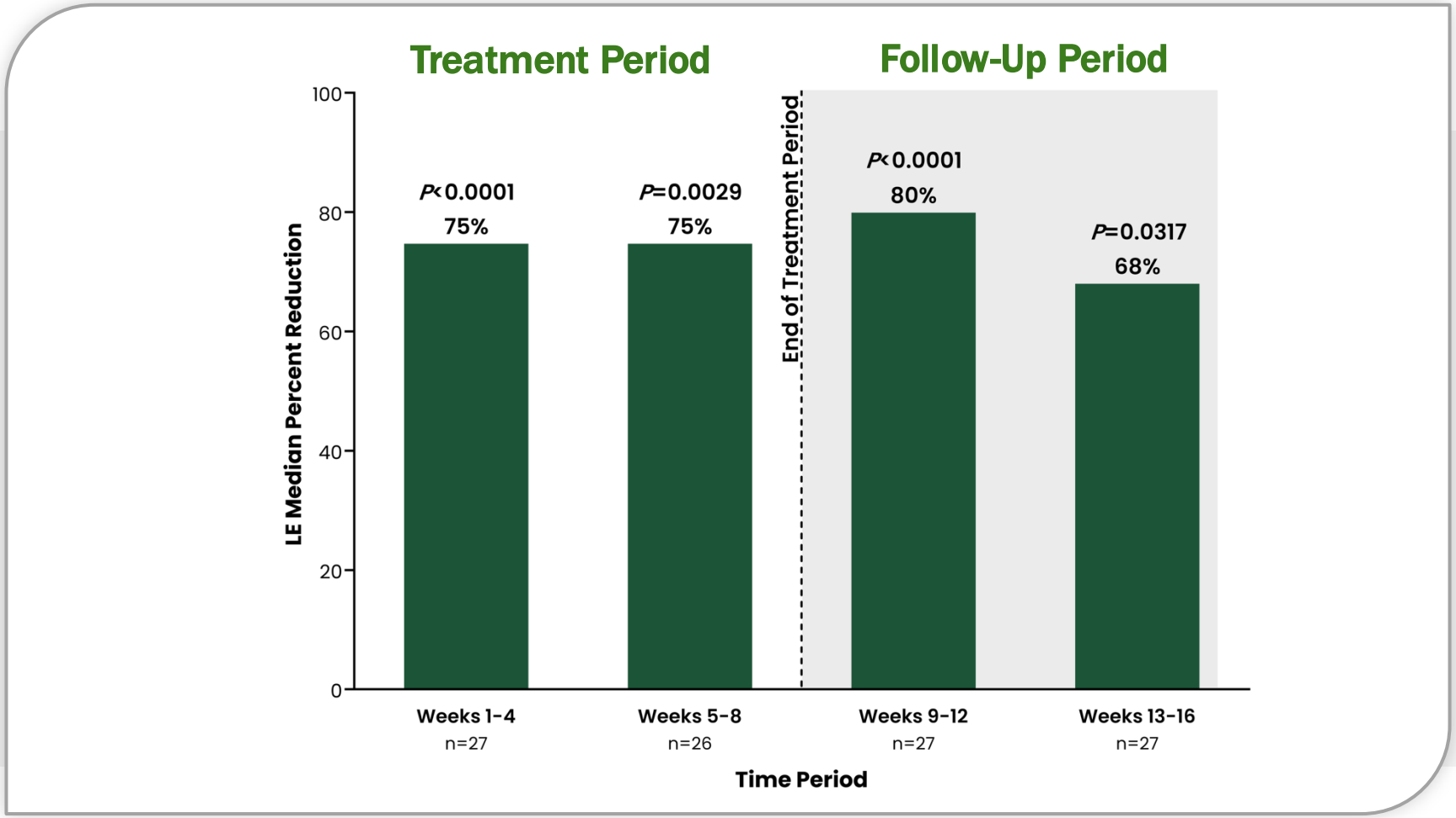
22-Day Half-Life Results in Concentrations Above Target 50% RO Throughout Follow-Up



[a]RAP-219 0.75 mg/day for 5 days, followed by RAP-219 1.25 mg/day for the remainder of the 8-week treatment period.

Effect of RAP-219 on Long Episodes in Follow-Up Period

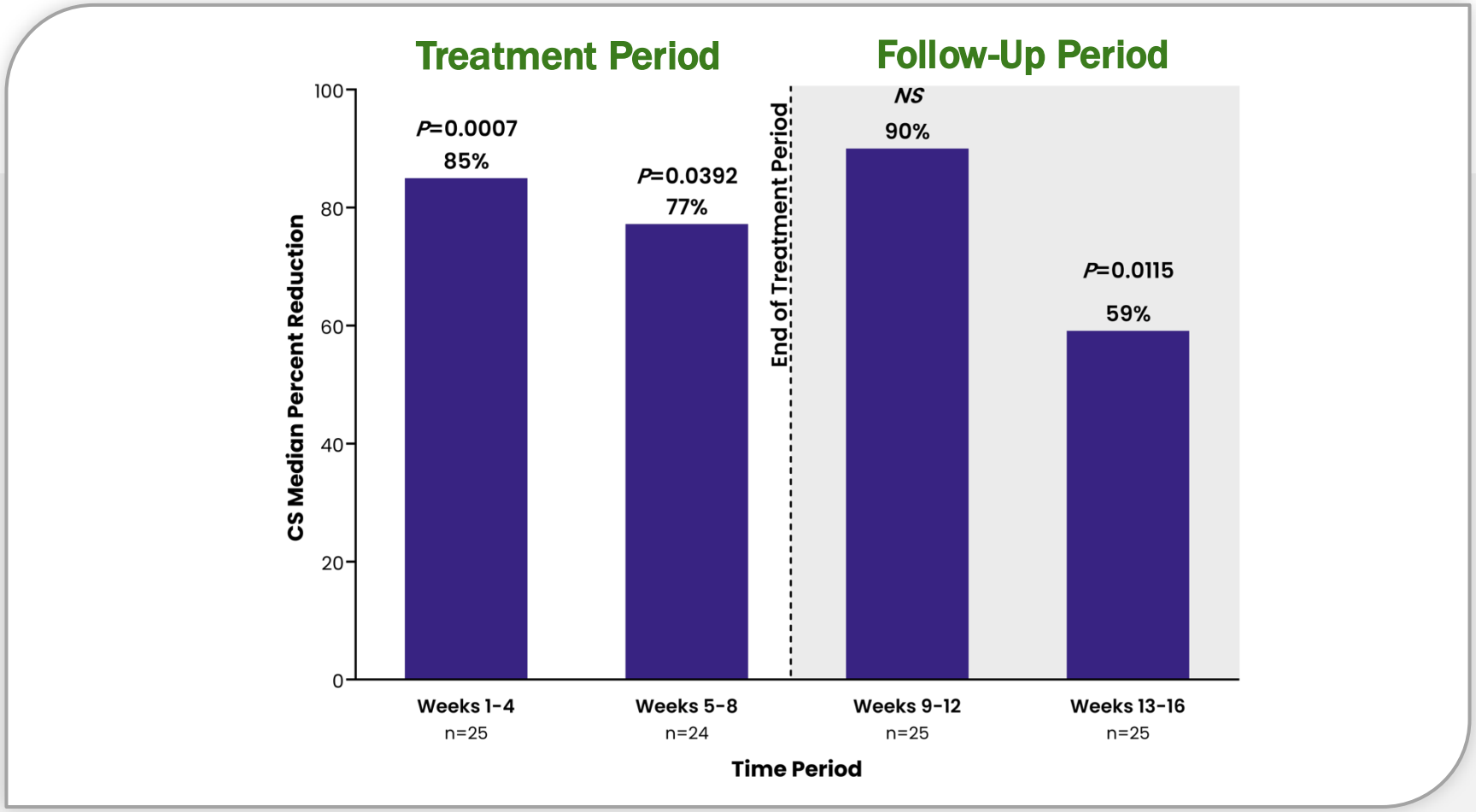
Significant and Durable LE Reduction Throughout Follow-Up, Consistent With Sustained RAP-219 Exposures



Median percent change statistical comparisons used the Wilcoxon signed-rank test to determine if the median percentage change in LE from baseline was greater than 0%.
LE – long episode; RO – receptor occupancy.

Effect of RAP-219 on Clinical Seizures in Follow-Up Period

Clinically Meaningful Reduction in CSs Throughout Treatment and Follow-Up



Median percent change statistical comparisons used the Wilcoxon signed-rank test to determine if the median percentage change in CS from baseline was greater than 20%.
CS – clinical seizure; NS, not significant (*P*>0.05); RO – receptor occupancy.

RAP-219 was Generally Well Tolerated

10% Discontinuation Rate Due to TEAEs

Safety Population	Treatment Period Weeks 1–8 (N=30)	Follow-Up Period Weeks 9–16 (N=30)
Any TEAE, n (%)	25 (83.3)	10 (33.3)
TEAE related to study drug	23 (76.7)	2 (6.7)
TEAEs by grade		
Grade 1 TEAE (mild)	15 (50.0)	7 (23.3)
Grade 2 TEAE (moderate)	10 (33.3)	0
Grade 3 TEAE (severe)	0	3 (10.0)*
TEAEs reported overall, in ≥10% of patients, n (%)		
Dizziness	8 (26.7)	0
Headache	6 (20.0)	0
Fatigue	4 (13.3)	0
Fall	3 (10.0)	1 (3.3)
Nausea	3 (10.0)	0
Somnolence	3 (10.0)	0
Memory impairment	2 (6.7)	1 (3.3)

rapport™ therapeutics

***All three grade 3 events met SAE criteria due to hospitalization and were assessed by the investigator as unrelated to study drug.**

TEAEs were reported during the Study Period (Treatment Period [Weeks 1–8] and Follow-Up Period [Weeks 9–16]).

TEAE – treatment-emergent adverse event.

RAP-219 Progressing into Phase 3 FOS Registrational Trials

Emerging Best-in-Class Profile, if Approved

Potential for Best-in-Class Efficacy

Phase 2a results demonstrated statistically significant reductions in LEs and CSs

Generally Well Tolerated

All TEAEs were mild or moderate

10% discontinuation rate

Ease of Use

Once-daily dosing, rational polypharmacy potential, low risk of drug-drug interactions, and long half-life

Long-Acting Injectable

Developing first ever LAI for epilepsy patients, providing IP extension leading to potential commercial upside

Advancing RAP-219 Development on Strong Phase 2 Data:

- Initiating two global, multi-center, placebo-controlled **Phase 3 clinical trials** in FOS in Q2
- Progressing **NDA-enabling activities**
- Expanding into Phase 3 program in **primary generalized tonic-clonic seizures**
- Continuing Phase 2 trial in bipolar mania
- For more information, email RAP-219-FOS@rapportrx.com

rapport™ therapeutics

CSs – clinical seizures; FOS – focal onset seizure; IP – intellectual property; LAI – long-acting injectable; LEs – long episodes; TEAE – treatment-emergent adverse event..