Effect of RAP-219 on Seizure Severity in Adults With Drug-Resistant Focal Onset Seizures and an Implanted Responsive Neurostimulator (RNS) System: Analysis of a Phase 2a Proof-of-Concept Study

Arnold R. Gammaitoni, PharmD[1]; Jacqueline A. French, MD[2]; Neal M. Nolan, MD[1]; Allison Little, PharmD[1]; Taneeta M. Ganguly, MD[3]; Shiling Ruan, PhD[1]; Dileep Nair, MD[4]; Nancy Wyant, BA[1]; Kathryn A. Davis, MD[3]; William W. Motley, MD[1]

[1]Rapport Therapeutics, Inc., Boston, MA, USA; [2]NYU Comprehensive Epilepsy Center, New York, NY, USA; [3]University of Pennsylvania, Philadelphia, PA, USA; [4]Cleveland Clinic, Cleveland, OH, USA

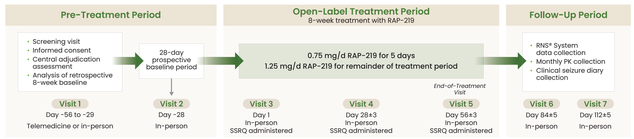
Background

- The main goal of treatment with an antiseizure medication (ASM) is to eliminate or greatly reduce the frequency of seizures
  - However, another important aspect of treatment response is the impact of the ASM on seizures that remain
- The ability of an ASM to reduce the impact of seizures on daily activity or seizure severity is of clinical importance to both patients and clinicians[1,2]
  - Seizure severity is associated with quality of life (QoL) and may be affected independently of improvement in seizure frequency[3]
  - Multiple patient-reported outcome measures of seizure severity are available; however, burdensome requirements, number of questions, and time required to complete the questionnaire may affect practical clinical practice and research use[4,5]
  - The Seizure Severity Response Questionnaire (SSRQ) used in this study includes 4 questions (domains) on a 10-point Likert scale
  - The SSRQ was developed by Rapport in collaboration with an experienced epilepsy investigator to assess seizure severity; validation is ongoing
- Transmembrane AMPA receptor regulatory protein (TARP)–γ8 is highly expressed in the neocortex and mesial temporal lobe (MTL), the brain regions where seizures originate and propagate[6-8]
- RAP-219 is a selective and potent negative allosteric modulator of TARPγ8, an AMPA receptor associated accessory protein that controls receptor gating and function
- Following treatment with RAP-219 in an 8-week phase 2a open-label study in adults (18–65 y) with drug-resistant FOS and an implanted responsive neurostimulator (RNS® System, NeuroPace);[9]
  - Clinically significant (≥50%) reduction in seizure frequency was observed in 72% of patients
  - Seizure freedom was achieved by 24% of patients
- In this post-hoc analysis, change in seizure severity in patients with drug-resistant FOS following treatment with RAP-219 was assessed in patients reporting moderate or greater (defined as ≥4 out of 10) impairment at baseline

Methods

- During the 8-week phase 2a study, patients received RAP-219 0.75 mg/d (5 d) followed by RAP-219 1.25 mg/d thereafter (**Figure 1**)
- Seizure severity was assessed using patient responses to the SSRQ
  - The SSRQ was administered at each study visit (Day 1 [baseline], Day 28, and Day 56 [end of treatment])

Figure 1. Study Design



PK – pharmacokinetic; **RNS** – responsive neurostimulator; **SSRQ** – Seizure Severity Response Questionnaire.

  - The SSRQ consists of four questions using a Likert scale (0–10, from least to most severe; **Figure 2**)

Figure 2. Seizure Severity Reporting Questionnaire

Seizure severity will be assessed by asking participants to respond to the following 4 questions using a 0–10 numerical rating scale and circling the number that best describes how their seizures have impacted them since their last study visit. The questions will be administered at each study visit starting with Visit 3:

1. How long it has taken to recover after you've had a seizure(s).
   0 1 2 3 4 5 6 7 8 9 10
   Less than an hour — Most of the day
2. How has your ability to think or concentrate been affected after you've had a seizure(s).
   0 1 2 3 4 5 6 7 8 9 10
   No problem thinking/concentrating — Unable to concentrate/think
3. How much have your seizure(s) interfered with your daily activities.
   0 1 2 3 4 5 6 7 8 9 10
   No interference — Greatly interfered
4. How would you rate the overall intensity of your seizure(s).
   0 1 2 3 4 5 6 7 8 9 10
   Minimal — Most intense I've ever experienced

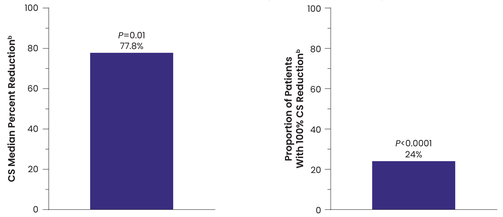
SSRQ – Seizure Severity Reporting Questionnaire.

- To assess the impact of RAP-219 in the subgroup of patients with moderate or greater impairment (score ≥4 for each individual question) at baseline, a predefined analysis in the SAP was to test whether the median percent change from baseline was greater than 0 using a Wilcoxon signed-rank test

Results

Impact on Seizure Frequency

Figure 3. Median Percent Change in CS Frequency and Proportion of Patients Achieving Seizure Freedom With Treatment With RAP-219 (Weeks 1–8, n=25[a])



[a]mITT-CS population: Not included from the Safety population–2 patients with <3 weeks of treatment, 1 patient with RNS setting change, and 2 patients with no CSs during the prospective baseline. [b]Median percent change statistical comparison used the Wilcoxon signed-rank test to determine if the percent change in CS was greater than 20%. [c]Responder analysis statistical comparison was based on a one sample exact test to determine whether the proportion of the responders was >1.5%.
CS – clinical seizure.

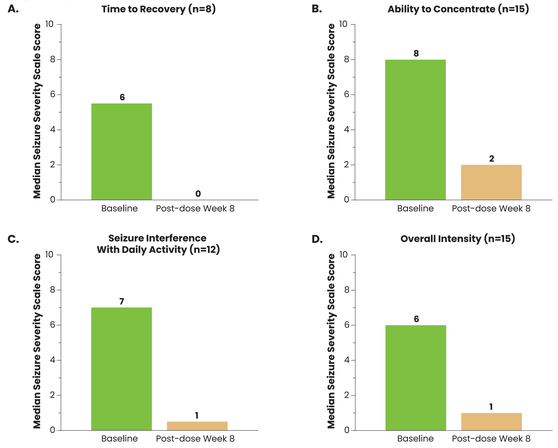
Table 1. Demographics and Baseline Characteristics

	Safety Population[a] N=30
Age at study entry, y, mean ± SD	40.1 ± 10.4
Age at first seizure, y, mean ± SD	16.6 ± 9.4
Male, n (%)	18 (60)
Clinical seizure frequency per 28 days, median (range)	10 (0.8–314.6)
Number of concomitant ASMs, median (range)	3 (1–4)
Most commonly used ASMs, n (%)	
Lamotrigine	15 (50)
Levetiracetam	15 (50)
Cenobamate	11 (37)
Zonisamide	9 (30)
Clobazam	7 (23)
Lacosamide	7 (23)

[a]The safety population consists of patients who were dosed with RAP-219.
ASM – antiseizure medication; **mITT** – modified intent-to-treat; **SD** – standard deviation.

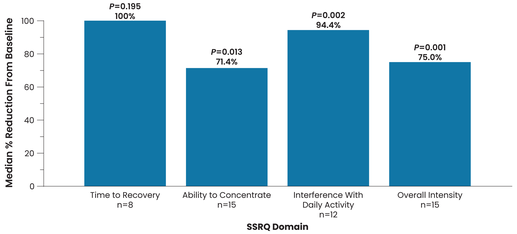
Impact on Seizure Severity

Figure 4. Reduction from Baseline to Week 8 of Treatment With RAP-219 in All SSRQ Domains



SSRQ – Seizure Severity Reporting Questionnaire.

Figure 5. Percentage Reduction From Baseline to Week 8 Following Treatment With RAP-219 in SSRQ Domains



Wilcoxon signed-rank test (null hypothesis: median % change from baseline = 0%)
SSRQ – Seizure Severity Response Questionnaire.

Table 2. Treatment-Emergent Adverse Events (Weeks 1–8)

	Safety Population N=30[a]
Any TEAE, n (%)	25 (83.3)
TEAE leading to study drug discontinuation[b]	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]The safety population consists of patients who were dosed with RAP-219. [b]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

- In patients with drug-resistant FOS, treatment with RAP-219 resulted in significant and clinically meaningful reductions in clinical seizure frequency
  - The SSRQ utilized in this phase 2 study offered an efficient method for assessing seizure severity and supports its use in future studies and the value of its validation
- Responses to the SSRQ suggest that treatment with RAP-219 may improve QoL in people with epilepsy by reducing time to recovery, seizure interference with daily activities, and overall seizure intensity and by improving the ability to concentrate
- 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

References

1. Tedrus GMAS, et al. *Revue Neurologique*. 2022;178(6):603–8.
2. Scott-Lennox J, et al. *Epilepsy Res*. 2001;44(1):45–63.
3. Bautista RED, et al. *Epilepsy Behav*. 2009;16(2):325–9.
4. Sancho J, et al. *Epilepsy Behav*. 2010;19:409–13.
5. Rusli RA, et al. *Epilepsy Behav*. 2023;142:109145.
6. Coombs ID, et al. *Mol Pharmacol*. 2022;101(5):343–56.
7. Maher MP, et al. *J Pharmacol Exp Ther*. 2016;357(2):394–414.
8. Greene S, et al. American Epilepsy Society (AES) Annual Meeting, Dec 5–9, 2025, Atlanta, GA, Poster 3.355.
9. Motley W, et al. American Epilepsy Society (AES) Annual Meeting, Dec 5–9, 2025, Atlanta, GA, Poster 2.498.

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.

Disclosures

ARG, NMN, AL, SR, NW, WWM: Rapport Therapeutics, Inc.: employee; stock ownership.
JAF: Salary support from the Epilepsy Foundation and from Epilepsy Study Consortium for consulting work and/or attending Scientific Advisory Boards for Acadia, Acuta Capital Partners, Agrithera, Alterity, Angelini, Autifony, Axonis, Baergic Bio, Beacon Biosignals, Biogen, Biohaven, Bloom Science, Bright Minds Biosciences, Camp4, Cerebral, Cerecin, Cerevel, Cognizance Biomarkers, Cowen and Company, Crossject, Eisai, Encoded, Engrail, Epalex, Epitel, Equilibre BioPharmaceuticals, Genentech, Grin Therapeutics, IQVIA RDS, iQure, Janssen, Jazz, Korro Bio, Leal Therapeutics, Lipocine, LivaNova, Longboard, Marinus, Modulight. bio, Neumirna, Neurocrine, Neuronetics, NeuroPace, NeuroPro, Neuroventis, Ono Pharmaceutical, Otsuka Pharmaceutical Development, Ovid, Paladin Labs, Praxis, PureTech, Rapport Therapeutics, Inc., Receptor Holdings, Saga, SK Life Science, Stoke, Supernus, Takeda, Third Rock Ventures, UCB, Ventus Therapeutics, Vida Ventures Management, and Xenon. Research support from the Epilepsy Study Consortium (funded by Eisai and UCB) Epilepsy Study Consortium/Epilepsy Foundation (funded by UCB), GW/FACES/OneBFoundation, and NINDS. Editorial board of Lancet Neurology and Neurology Today. Chief Medical/Innovation Officer for the Epilepsy Foundation. President and on the Board of Directors for the Epilepsy Study Consortium. Received travel/meal reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Angelini, Biohaven, Cerebral, Cowen and Company, Longboard, Neurelis, Neurocrine, NeuroPace, Praxis, Rapport, SK Life Science, Stoke, Takeda, and Xenon.
TMG: Epiminder, employee.
KAD: Rapport Therapeutics, Inc.: consulting fees, travel/meeting support, advisory board participation. Epilepsy Foundation: travel support. NeuroPace, Inc.: advisory board participation, travel/meeting support. NINDS: research support unrelated to this work.

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