Effect of RAP-219 on Long Episodes and Clinical Seizures in Adults With Drug-Resistant Focal Seizures and an Implanted Responsive Neurostimulator (RNS) System by Baseline Disease Severity: A Post Hoc Analysis of a Phase 2a Proof-of-Concept Study

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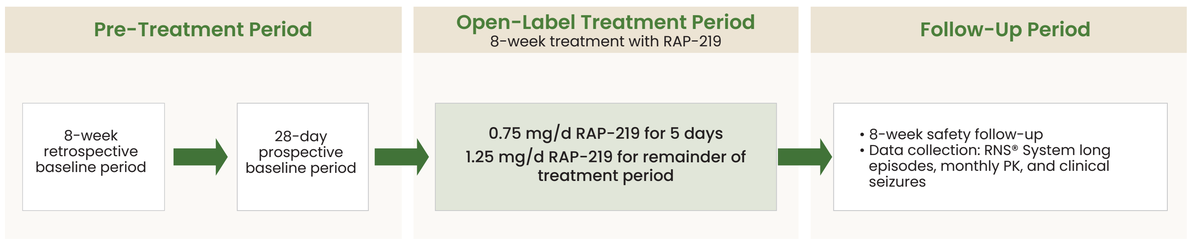
Background

- Baseline seizure frequency in patients with epilepsy may affect the observed efficacy of treatment[1]
  - Ideally, an antiseizure medication (ASM) would work equally well in patients regardless of the baseline seizure burden
- γ8 transmembrane AMPA receptor regulatory protein (TARPγ8) is highly expressed in the neocortex and mesial temporal lobe (MTL), regions of the brain associated with the initiation and propagation of focal onset seizures (FOS)[2-4]
  - AMPA receptors have been clinically validated as a therapeutic target for epilepsy[5]
  - TARPγ8 is an AMPA receptor associated accessory protein that controls receptor function and gating properties
- The efficacy of RAP-219, a potent and selective TARPγ8 negative allosteric modulator, was evaluated in adults with drug-resistant FOS and an implanted responsive neurostimulator (RNS® System, NeuroPace) in a Phase 2a proof-of-concept clinical trial[6]
  - The RNS System continuously monitors electrocorticographic intracranial EEG activity and responds to abnormal activity, including long episodes (LEs; organized epileptiform activity exceeding a clinician-specified duration)[7]
  - LEs often represent electrographic seizures
  - Following treatment with RAP-219, median frequency of LEs and clinical seizures (CSs) decreased by 71% and 77.8%, respectively
- In this post hoc analysis, we evaluated the efficacy of RAP-219 stratified by median baseline LE and CS frequencies

Methods

- The Phase 2a study included adults (18-65 y) with drug-resistant FOS and an implanted RNS System with ≥1 lead in the MTL
  - Patients were required to have ≥16 LEs and ≥1 CS during the retrospective baseline period
- LEs were recorded by the RNS System; CSs were recorded in seizure diaries

Figure 1. Study Design



PK – pharmacokinetics; **RNS** – responsive neurostimulator.

- The combined 8-week retrospective period and 4-week prospective period served as the baseline for LEs
- The 4-week prospective period served as the baseline for CSs

Outcomes

- The proportions of responders for LE and CS frequency reductions from baseline to Weeks 1-8 were evaluated
  - Thresholds for LE responders were ≥30%, ≥50%, ≥75%, and 100%
  - Thresholds for CS responders were ≥50%, ≥75%, and 100%

Subgroup analyses

- For this analysis, patients were stratified based on median baseline LE and CS frequency with:
  - Median ≤48 or >48 LEs at baseline
  - Median ≤10 or >10 CSs at baseline

Results

Figure 2. Patient Disposition

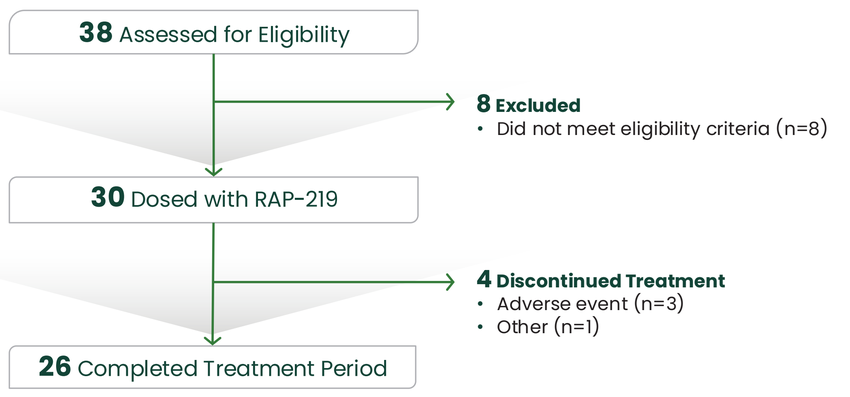


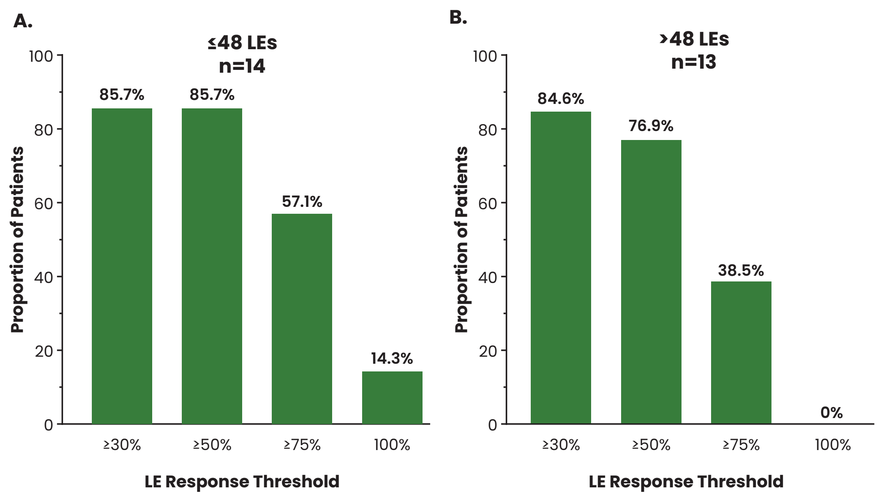
Table 1. Demographics and Baseline Characteristics

	Safety Population N=30
Male, n (%)	18 (60)
Age at study entry, y, mean ± SD	40.1 ± 10.4
LE frequency per 28 days, median (range)	48 (8.0-751.7)[a]
LE frequency ≤48, n (%)	14 (52)[a]
LE frequency >48, n (%)	13 (48)[a]
CS frequency per 28 days, median (range)	10 (0.8-314.6)[b]
CS frequency ≤10, n (%)	13 (52)[b]
CS frequency >10, n (%)	12 (48)[b]
Number of concomitant ASMs, median (range)	3 (1-4)
Years since RNS System implantation, median (range)	4.6 (2-11)
Concordance between LEs and electrographic seizures, median (range)	90 (30-100)

[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.

- Approximately 85% of patients experienced a clinically meaningful (≥30%) reduction in LE frequency in both groups (**Figure 3**)

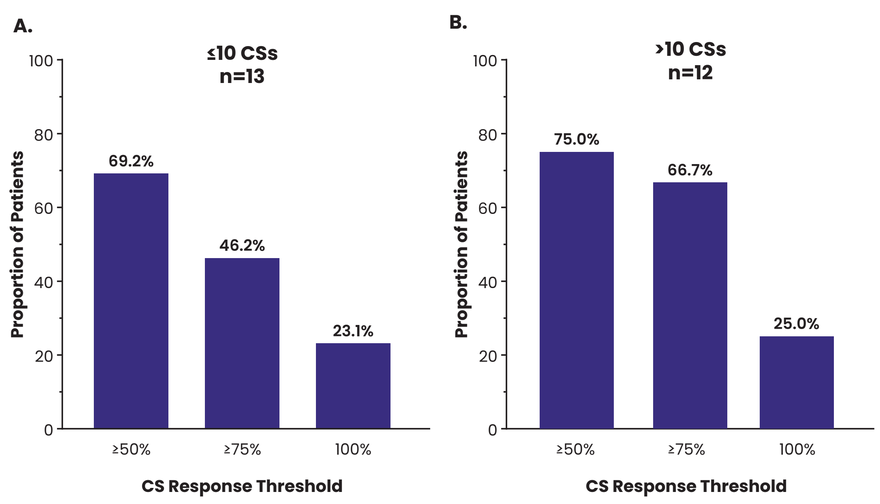
Figure 3. Proportion of LE Responders Stratified by Baseline LE Frequency A. ≤48 LEs and B. >48 LEs



LE – long episode.

- Patients with ≤10 and >10 CSs at baseline experienced clinically meaningful (≥50%) reduction in CS frequency at similar rates (**Figure 4**)

Figure 4. Proportion of CS Responders Stratified by Baseline CS Frequency A. ≤10 CSs and B. >10 CSs



CS – clinical seizure.

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

	Safety Population N=30
Any TEAE, n (%)	25 (83)
Grade 1 (mild)	15 (50)
Grade 2 (moderate)	10 (33)
Grade ≥3 (severe)	0
TEAE leading to study drug discontinuation[a], n (%)	3 (10)
TEAEs reported in ≥10% of patients, n (%)	
Dizziness	8 (27)
Headache	6 (20)
Fatigue	4 (13)
Fall	3 (10)
Nausea	3 (10)
Somnolence	3 (10)

[a]TEAEs leading to study drug discontinuation included worsening of preexisting memory impairment (Grade 1), panic attack (Grade 1), and worsening of preexisting anxiety (Grade 2).

Adverse events are coded using Medical Dictionary for Regulatory Activities version 27.0.

TEAE – treatment emergent adverse event.

Conclusions

- Treatment with RAP-219 provided clinically meaningful improvement in both LE and CS frequency, regardless of baseline disease severity
  - In patients with a median baseline LE frequency of ≤48 and >48, 85.7% and 84.6% achieved ≥30% reduction in LE frequency, respectively
  - In patients with a median baseline CS frequency of ≤10 and >10, 69.2% and 75% achieved ≥50% reduction in CS frequency, respectively
- Seizure freedom was achieved over the entire 8-week treatment period at a similar rate regardless of baseline CS frequency
  - In patients with ≤10 baseline CSs: 23.1%
  - In patients with >10 baseline CSs: 25%
- 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

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Disclosures

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ARG: 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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