Effect of RAP-219 on Long Episodes and Clinical Seizures in Adults With Focal Seizures and System Treated With Concomitant Cenobamate: A Phase 2a Post Hoc Analysis

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Background

- Cenobamate is widely viewed as one of the most effective antiseizure medication (ASM) for focal onset seizures (FOS)[1-3]
- RAP-219 is a selective and potent negative allosteric modulator of γ8 transmembrane AMPA receptor regulatory protein (TARPγ8)[4]
- An 8-week Phase 2a open-label study of RAP-219 (NCT06377930) in adults (18–65 years old) with drug-resistant FOS and an implanted responsive neurostimulator (RNS® System, NeuroPace) demonstrated that treatment with RAP-219 resulted in 71.0% and 77.8% reductions in long episode (LE) and clinical seizure (CS) frequencies, respectively[5]
- In this post hoc analysis, the efficacy and tolerability of RAP-219 in adults with drug-resistant FOS and a cenobamate-inclusive treatment regimen were investigated

Methods

- In this Phase 2a study, patients received RAP-219 0.75 mg/d (5 days), followed by RAP-219 1.25 mg/d (**Figure 1**)

Figure 1. RAP-219 Phase 2a Study Design

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

- Efficacy and safety were evaluated in a subset of patients in the modified intent-to-treat (mITT) population who had ≥1 CS during the prospective baseline period (mITT-CS) and who were treated with concomitant cenobamate during the study
- Percent changes in weekly RNS LE frequency and weekly CS frequency were calculated using their respective baseline periods:
  - For LEs, the 8-week retrospective and 4-week prospective baseline periods
  - For CSs, the 4-week prospective baseline period
- The proportion of patients who achieved a ≥30% reduction in LEs and proportion of patients who achieved a ≥50% reduction in CSs during the 8-week treatment period in comparison to their respective baseline periods were analyzed
- The incidence of treatment-emergent adverse events (TEAEs) was tabulated

Results

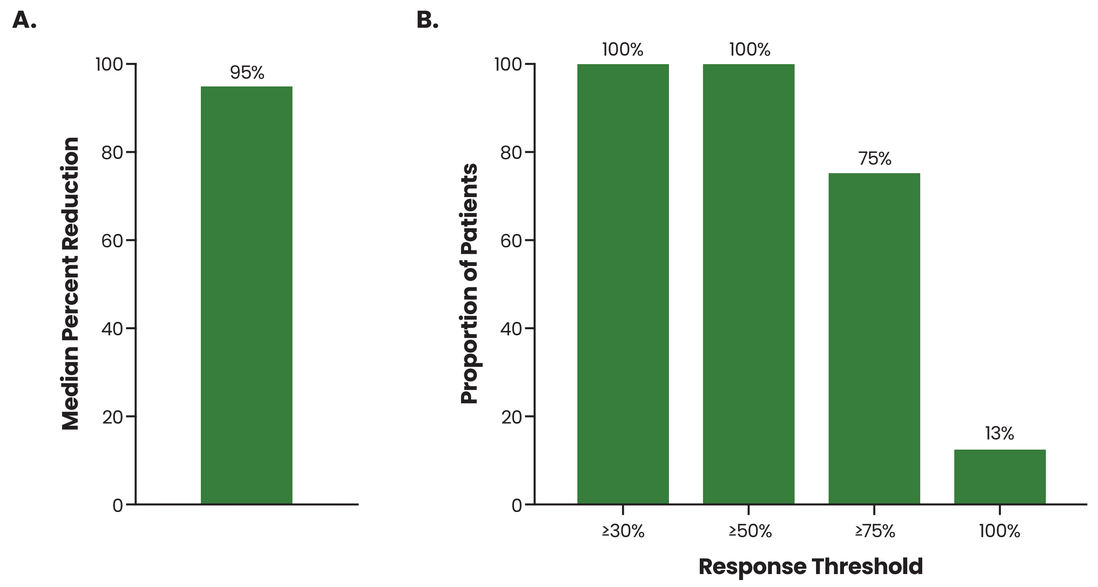
- Eight of the 30 patients in the Safety population were treated with concomitant cenobamate (150–400 mg/d; **Table 1**)
- All patients in the mITT-CS population treated with concomitant cenobamate completed the 8-week treatment with RAP-219 and completed the study
- Most demographic and baseline characteristics reported for patients treated with RAP-219 and concomitant cenobamate were comparable to the overall Safety population (**Table 1**)

Table 1. Demographics and Baseline Characteristics

	Patients Treated With Concomitant Cenobamate[a] n=8	Safety Population N=30
Age at study entry, years, mean ± SD	35.6 ± 8.8	40.1 ± 10.4
Age at first seizure, years, mean ± SD	16.4 ± 7.8	15.8 ± 9.3
Male, n (%)	1 (13)	18 (60)
Years since RNS® System implantation, median (range)	3.8 (2–7)	4.6 (2–11)
LE frequency per 28 days, median (range)	46.3 (14.7–751.7)	48.0 (8.0–751.7)[b]
CS frequency per 28 days, median (range)	13.3 (0.8–33.7)	10 (0.8–314.6)[c]
Concordance between LEs and electrographic seizures, median (range)	91 (39-100)	90 (30-100)
Number of concomitant ASMs, median (range)	3 (2–4)[d]	3 (1–4)
Most commonly used ASMs,[e] n (%)		
Lamotrigine	4 (50)	15 (50)
Levetiracetam	2 (25)	12 (40)
Cenobamate	8 (100)	11 (37)
Zonisamide	1 (13)	9 (30)
Clobazam	3 (38)	7 (23)
Lacosamide	1 (13)	7 (23)

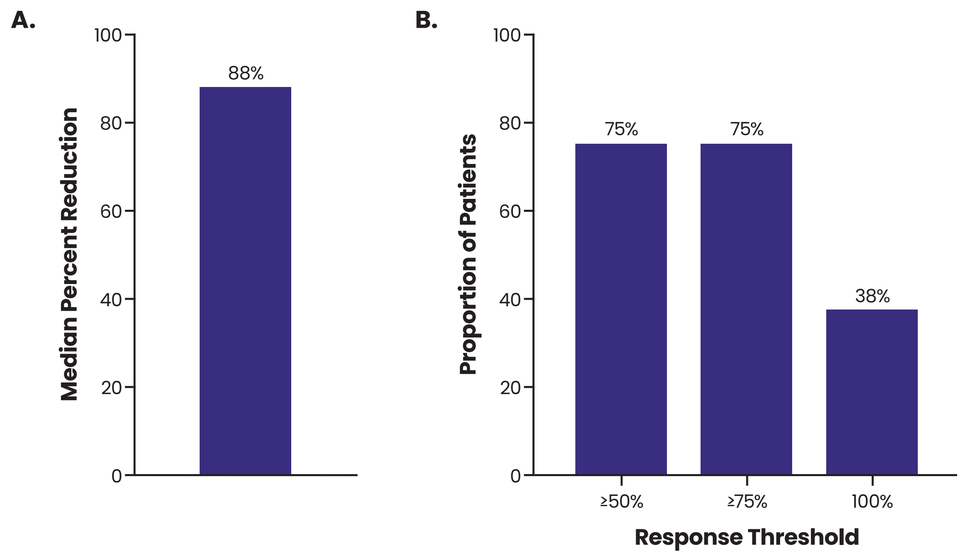
[a]Patients from the mITT-CS population who were treated with concomitant cenobamate during the study. [b]mITT population (N=27). [c]mITT-CS population (N=25). [d]Including cenobamate. [e]Most commonly used in the overall Safety population.
ASM – antiseizure medication; **CS** – clinical seizure; **LE** – long episode; **mITT** – modified intent-to-treat; **mITT-CS** – clinical seizure modified intent-to-treat; **RNS** – responsive neurostimulator; **SD** – standard deviation.

Figure 2. Weeks 1–8 A. Median LE Percent Reduction From Baseline and B. ≥30%, ≥50%, ≥75%, and 100% Responder Rates Following Treatment With RAP-219 in Patients Treated With Concomitant Cenobamate (n=8)



LE – long episode.

Figure 3. Weeks 1–8 A. Median CS Percent Reduction From Baseline and B. ≥50%, ≥75%, and 100% Responder Rates Following Treatment With RAP-219 in Patients Treated With Concomitant Cenobamate (n=8)



CS – clinical seizure.

- Of the 8 patients treated with RAP-219 and concomitant cenobamate, 5 (63%) reported ≥1 TEAE; no severe or serious TEAEs were reported during the treatment period (**Table 2**)

Table 2. Safety and Tolerability

	Patients Treated With Concomitant Cenobamate[a] n=8	Safety Population N=30
Any TEAE, n (%)	5 (63)	25 (83)
Treatment-related TEAEs	4 (50)	23 (77)
Grade 1 TEAE (mild)	1 (13)	15 (50)
Grade 2 TEAE (moderate)	4 (50)	10 (33)
Grade 3 TEAE (severe)	0	0
TEAE leading to study drug discontinuation, n (%)	0	3 (10)
TEAE leading to study drug dose reduction, n (%)	2 (25)	4 (13)

[a]Patients from the mITT-CS population who were treated with concomitant cenobamate during the study.
TEAE – treatment-emergent adverse event.

- The only TEAE that occurred in >1 patient treated with RAP-219 and concomitant cenobamate was dizziness (n=2)

Conclusions

- Patients with drug-resistant FOS and a suboptimal response (based on meeting study eligibility criteria) to a cenobamate-inclusive treatment regimen prior to RAP-219 treatment experienced significant and clinically meaningful reductions in both LEs and CSs during the RAP-219 Phase 2a study
  - Approximately 40% of patients became seizure free following the addition of RAP-219
  - Building on cenobamate's well-established efficacy, RAP-219 may provide additional seizure reduction in patients who continue to experience seizures despite cenobamate treatment
- RAP-219 was generally well tolerated
- The efficacy and safety of RAP-219 in patients who continue to experience FOS despite treatment with 1–3 concomitant ASMs will further be established in two multinational, Phase 3 randomized controlled trials

References

1. Chung SS, et al. *Neurology.* 2020;94(22):e2311-e22.
2. Krauss GL, et al. *Lancet Neurol.* 2020;19(1):38-48.
3. Klein P, et al. *Neurology.* 2022;99(10):e989-e98.
4. Bialer M, et al. *Epilepsia.* 2024;65(10):2831-57.
5. Motley WM, et al. Presented at American Epilepsy Society Annual Meeting, December 5-9, 2025, Atlanta, GA, Poster 2.948.

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