

# Safety, Tolerability, and Pharmacokinetics of RAP-219 in Healthy Volunteers

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# Background

- AMPA receptors (AMPARs), found broadly throughout the central nervous system (CNS), are a clinically validated target for epilepsy<sup>1</sup>
- Nonspecific AMPAR inhibition is associated with undesirable adverse events (AEs, ie, dizziness, abnormal gait), most often due to AMPAR expression in the hindbrain<sup>2</sup>
- Transmembrane AMPAR regulatory proteins (TARPs) are anatomically restricted accessory proteins
- TARPγ8 is enriched in the hippocampus, cortex, and amygdala and minimally expressed from the hindbrain and brainstem<sup>3,4</sup>
- RAP-219, a TARPγ8 negative allosteric modulator, has shown efficacy in preclinical seizure models without impairment on rotarod, demonstrating a broad therapeutic window (see Poster 1.390)
- The projected plasma concentration of RAP-219 to achieve the receptor occupancy (RO) associated with preclinical seizure efficacy is 7.0 ng/mL
- Here, we evaluate the pharmacokinetics (PK) and tolerability of RAP-219 and identify dosing regimens that can achieve the target RO

# Methods

- Healthy subjects (18-55 years old) were recruited to single ascending dose (SAD) and multiple ascending dose (MAD) trials
- Trials were randomized, double-blinded, and placebo-controlled
- Subjects were randomized at a 3:1 ratio (RAP-219 : placebo)
- In the SAD trial, subjects were randomized to a single oral dose of RAP-219 (0.25, 0.5, 1, 2, or 3 mg) or placebo
- In the MAD trial, subjects were randomized to a 14–28-day regimen of a once-daily oral dose of RAP-219 (target doses: 0.25, 0.5, 0.75, or 1.25 mg/d) or placebo (**Figure 1**)

### Figure 1. MAD Study RAP-219 Dose Cohorts



## included in the analysis

- NPS simulations were conducted to predict plasma concentrations following varying dosing regimens
- Safety was evaluated using the NCI-CTCAE v5.0
- Grades 1 to 5, correlating with mild AEs to AE-related death, respectively

# Results

• RAP-219 dosing cohorts: SAD and MAD, n=6 per cohort (N=30 each); Placebo: SAD, N=11; MAD, n=10

### **Table 1.** Subject Demographics for SAD and MAD Studies

	SAD N=41	MAD N=40		
Male, n (%)	37 (90.2)	31 (77.5)		
Age, years, mean±SD	39.8±10.1	40.5±8.5		
Race, n (%)				
White	22 (53.7)	19 (47.5)		
Black/African American	17 (41.5)	17 (42.5)		
Asian	1 (2.4)	1 (2.5)		
Multiple	1 (2.4)	3 (7.5)		

MAD – multiple ascending dose; SAD – single ascending dose.

### Pharmacokinetics

### SAD (Figures 2 and 3)

RAP-219 exhibited biphasic elimination, with a mean t<sub>1/2</sub> of 278±200h (~8-14 d)

### Figure 2.

Single-Dose Mean Concentration vs **Time Profiles for** RAP-219 During the First 12 Hours

Cohorts were run consecutively MAD – multiple ascending dose.

- PK and dose-limiting toxicities were evaluated
- Non-parametic superposition (NPS) simulations were conducted in Phoenix WinNonlin (v8.4) to simulate steady-state (SS) concentrations following multiple dosing regimens

### References

- 1. Potschka H, Trinka E. *Epilepsia*. 2019;60(suppl 1):22-36.
- 2. Willems LM, et al. CNS Drugs. 2023;37(6):531-44.
- 3. Maher MP, et al. J Pharmacol Exp Ther. 2016;357(2):394-414.
- 4. Coombs ID, et al. *Mol Pharmacol*. 2022;101(5):343-56.

- RAP-219 concentrations collected from SAD and MAD (Day 1) trials were



**Figure 3.** RAP-219 Exhibits Slightly Less Than Dose-Proportional Increases in C<sub>max</sub> and AUC<sub>0-144</sub> Following Single RAP-219 Dose

AUC<sub>0-144</sub> – area under the curve,

first 144 h; **C<sub>max</sub> –** maximum

concentration

![](_page_0_Figure_44.jpeg)

### MAD (Figures 4 and 5)

• RAP-219 exhibited an approximately dose-proportional increase in C<sub>max</sub> and  $AUC_{tout}$ , with a median  $t_{max}$  of ~4 h on Days 1, 14, and 28 across all cohorts

Figure 4. Mean RAP-219 Plasma Concentration for MAD Cohorts 1-5<sup>a</sup> on Day 14

MAD – multiple ascending dose ; RO – receptor occupancy.

°See Figure 1.

![](_page_0_Figure_48.jpeg)

Figure 5. Highest Tested Doses in MAD Trials Exceeded Target

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![](_page_0_Figure_51.jpeg)

### Acknowledgments

The authors thank Mari Willeman, PhD, and Anthony DiLauro, PhD, of PharmaWrite, LLC, for writing and editorial assistance, which were funded by Rapport Therapeutics, Inc.

### **NPS Simulations**

- NPS simulations and the mean calculated AUC<sub>tou</sub> accumulation ratio (8.5) from the RAP-219-102 study suggest that RAP-219 achieves SS after approximately 60 days of dosing (**Figure 6**)
- Approximately 80% of SS is achieved after 28 days of dosing
- MAD Cohort 5 NPS simulations were predictive of observed concentrations

### Figure 6. Simulated and Observed Concentration vs Time Profile for MAD Cohort 5

![](_page_0_Figure_64.jpeg)

ated, 8 weeks; Observed, 4 weeks; MAD Cohort 5: 0.75 mg/d for the first 5 d, followed by 1.25 mg/d for 23 d. MAD – multiple ascending dose; RO – receptor occupancy.

### Safety

### SAD

- In total, 51 TEAEs were reported, experienced by 19 (46%) subjects
- Most (82.4%) TEAEs were Grade 1 (mild); 9 events (17.6%) in 3 subjects were Grade 2 (moderate)
- No Grade 3 or worse TEAEs, SAEs, or dose-limiting toxicity events were observed
- Most common TEAEs at any dose: sinus tachycardia (n=5, 16.7%), anxiety (n=4, 13.3%), dizziness, paresthesia, and palpitations (n=3 each, 10%) TEAEs were dose related
- All AEs resolved during the study, with no clinically significant changes in laboratory parameters, vital signs, or ECGs following RAP-219 treatment

Disclosures

SY, BSG, WWM, SG: Rapport Therapeutics, Inc.: employee and stock ownership. Presented at AES 2024 Scientific Exhibit, December 6-10, 2024, Los Angeles, CA, USA

### MAD

- In total, 56 TEAEs were reported by 25 (62.5%) subjects (**Table 2**)
- 13 TEAEs (all Grade 1; 10 subjects) were considered related to study treatment
- No treatment-related AEs were reported in Cohorts 4 or 5, the highest dosed cohorts

### **Table 2.** Safety and Disposition Following Multiple Dosing of RAP-219 in Healthy Subjects

		14 Days of Treatment		28 Days of Treatment		
	Pooled placebo n=10	0.25 mg/d RAP-219 n=6	0.25 mg/d → 0.5 mg/d RAP-219 n=6	0.5 mg/d RAP-219 n=6	0.75 mg/d RAP-219 n=6	0.75 mg/d →1.25 mg/d RAP-219 n=6
Subjects with ≥1 TEAE, n (%)	4 (40.0)	5 (83.3)	6 (100.0)	3 (50.0)	5 (83.3)	2 (33.3)
Sinus tachycardia	0	1 (16.7)	3 (50.0)	0	0	0
Medical device site reaction	1 (10.0)	2 (33.3)	1 (16.7)	0	0	0
Headache	0	1 (16.7)	0	0	2 (33.3)	0
Insomnia	0	0	2 (33.3)	0	1 (16.7)	0
Subjects with ≥1 Grade 2 TEAE, n (%)	0	3 (50.0)	3 (50.0)	0	2 (33.3)	0
Subjects with ≥1 Grade 3 or above TEAE, n (%)	0	0	0	0	0	0

TEAEs listed include those with ≥10% incidence in all subjects who received RAP-219 treatment (n=30); Toxicity grades of TEAEs: Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=potentially life threatening, Grade 5=death related to AE. **TEAE** – treatment-emergent adverse event.

# Conclusions

- The PK from both the SAD and MAD studies were approximately doseproportional with low intra-subject variability that slightly increased with increasing doses
- Projected target RO (70%) was achieved following multiple dosing of RAP-219
- SS concentrations are expected to be achieved by approximately 60 days of dosing, with approximately 80% SS achieved by Day 28
- In Cohort 5 (highest dose), after 28 days dosing, no TEAEs greater than Grade 1 and no treatment-related TEAEs were observed
- The highest RAP-219 dose cohort (0.75 mg/d for 5 days followed by 1.25 mtg/d for 23 days) exceeded the target RO (70%) and achieved a 3-fold higher exposure compared to a single 2 or 3 mg RAP-219
- A slow titration over several days of dosing RAP-219 achieves the target therapeutic RO while attenuating the severity and frequency of TEAEs observed

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