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

Swamy Yeleswaram, PhD[1]; Bradley S. Galer, MD[1,*]; William W. Motley, MD[1]; Stephen Greene, PharmD[1]

[1]Rapport Therapeutics, Inc., Boston, MA, USA

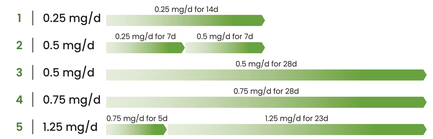
Background

- AMPA receptors (AMPARs), found broadly throughout the central nervous system (CNS), are a clinically validated target for epilepsy[1]
  - Nonspecific AMPAR inhibition is associated with undesirable adverse events (AEs, ie, dizziness, abnormal gait), most often due to AMPAR expression in the hindbrain[2]
- Transmembrane AMPAR regulatory proteins (TARPs) are anatomically restricted accessory proteins
  - TARPγ8 is enriched in the neocortex and mesial temporal lobe and minimally expressed from the hindbrain and brainstem[3,4]
- RAP–219, a TARPγ8 negative allosteric modulator, has shown efficacy in preclinical seizure models without impairment on rotarod, demonstrating a broad therapeutic window
  - 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



Cohorts were run consecutively.
MAD – multiple ascending dose.

- PK and dose-limiting toxicities were evaluated
- Non-parametric superposition (NPS) simulations were conducted in Phoenix WinNonlin (v8.4) to simulate steady-state (SS) concentrations following multiple dosing regimens
  - RAP–219 concentrations collected from SAD and MAD (Day 1) trials were included in the analysis
  - NPS simulations were conducted to predict plasma concentrations following varying dosing regimen
- 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 $t_{1/2}$ of 278±200h (~8–14 d)

Figure 2. Single-Dose Mean Concentration vs Time Profiles for RAP-219 During the First 12 Hours

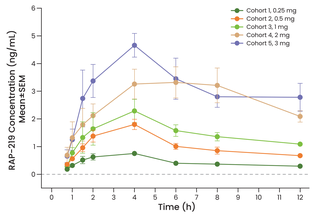
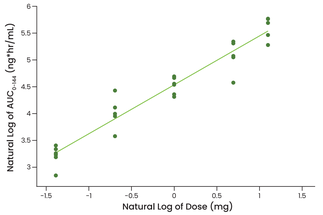


Figure 3. RAP-219 Exhibits Slightly Less Than Dose-Proportional Increases in C_{max} and AUC_{0-144} Following Single RAP-219 Dose

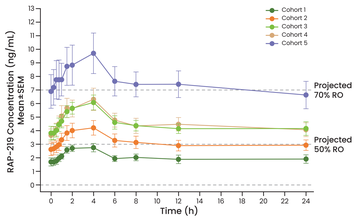


AUC_{0-144} – area under the curve, first 144 h; **C_{max}** – maximum concentration.

MAD (**Figures 4** and **5**)

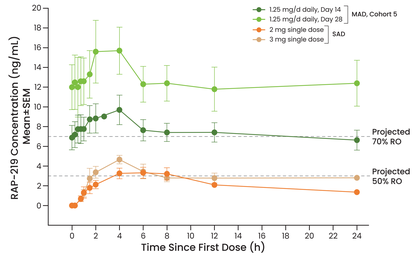
- RAP–219 exhibited an approximately dose-proportional increase in C_{max} and AUC_{tau}, with a median t_{max} of ~4 h on Days 1, 14, and 28 across all cohorts

Figure 4. Mean RAP-219 Plasma Concentration for MAD Cohorts 1–5[a] on Day 14



[a]See **Figure 1**.
MAD – multiple ascending dose ; **RO** – receptor occupancy.

Figure 5. Highest Tested Doses in MAD Trials Exceeded Target Projected 50%-70% RO Through Dosing Interval on Day 28

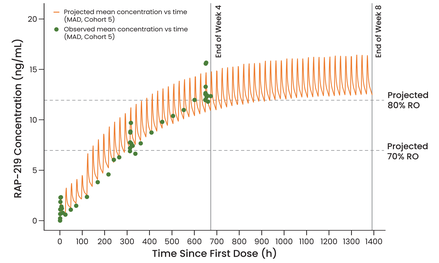


MAD Cohort 5: 0.75 mg/d for the first 5 d, followed by 1.25 mg/d for 23 d.
MAD – multiple ascending dose; **RO** – receptor occupancy; **SAD** – single ascending dose.

NPS Simulations

- NPS simulations and the mean calculated AUC_{tau} 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



Simulated, 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
  - 1 subject discontinued due to AEs of anxiety and agitation in the 2 mg group
  - All AEs resolved during the study, with no clinically significant changes in laboratory parameters, vital signs, or ECGs following RAP–219 treatment

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 dose-proportional with low intra-subject variability that slightly increased with increasing doses
- Projected target RO (50%–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
- After 28 days, QD, of RAP–219, 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 mg/d for 23 days) exceeded the target RO (50%–70%) and achieved a 3-fold higher exposure compared to a single 2 or 3 mg RAP–219 dose
  - The reduction in severity of TEAEs observed with multi-day dosing of RAP–219 suggests that a slow titration over several days to maintenance dose may attenuate TEAEs while achieving the desired RO in an acceptable time frame for clinical use

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.

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.

*At the time of the study

Disclosures

SY, BSG, WWM, SG: Rapport Therapeutics, Inc.: employee and stock ownership.

Presented at AES 2025 Scientific Exhibit, December 5–9, Atlanta, GA, USA
Originally presented at AES 2024 Scientific Exhibit, December 6–10, 2024, Los Angeles, CA, USA

Please follow the QR code for a copy of the poster.