Poster #1.390

Antiseizure Effects with Selective TARPγ8 Negative Allosteric Modulators in Preclinical Seizure Models

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Background

- AMPA receptors (AMPARs) are a clinically validated therapeutic target for epilepsy[1]
  - Broad AMPAR inhibition is associated with undesirable hindbrain-related adverse events (AEs) such as somnolence and gait disturbance[2]
- Transmembrane AMPAR regulatory proteins (TARPs) are anatomically specific mediators of AMPAR trafficking, subcellular localization, and gating; TARPγ8 is enriched in regions associated with seizures with little to no expression in the hindbrain[3,4]
- RAP-219 is a potent, selective AMPAR/TARPγ8 negative allosteric modulator (NAM) offering neuroanatomically specific AMPAR modulation for the treatment of seizures

Objectives

- To examine the efficacy and tolerability of RAP-219 in established preclinical seizure models
- To examine toleration of seizure protection after chronic dosing of a RAP-219 analog, RTX-1738

Methods

Table 1. Seizure Threshold and Protection Tested in Adult Male CF-1[a] Mice

Model	Treatment Groups	Test	Outcome	Endpoint
PTZ	• RAP-219: single dose, *p.o.* • Vehicle: single dose	PTZ infusion	Seizure threshold	• Time to first twitch and to onset of sustained clonus[b]
CK	• RAP-219: single dose, *p.o.* • RTX-1738: single dose and 7 d QD[c], *p.o.* • Vehicle: single dose and 7 d QD[c]	Corneal stimulation challenge	Seizure protection	• Racine scale score[5]
		Rotarod test	Motoric impairment	• Number of falls during 1-min period
		Open-field test	Locomotor activity	• Total distance traveled • Horizontal/vertical activity count

[a]Charles River, Portage, MI; [b]ED_{50} values: group means for twitch and clonus compared using ANOVA, followed by Dunnett's post-hoc analysis; [c]Following a 2-week washout period.

PTZ RAP-219 doses: 0.01, 0.1, and 1 mg/kg; CK RAP-219 doses: 0.01, 0.02, 0.03, 1, and 3mg/kg; RTX-1738 doses: 0.003, 0.01, 0.03, 0.1, and 0.3 mg/kg; Phenotypic secondarily generalized seizures at Racine scale score of 5.

CK – corneal kindling; **PTZ** – pentylenetetrazol; **QD** – once daily.

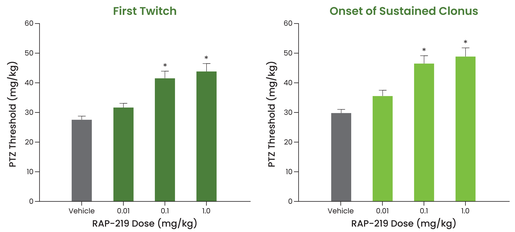
- Efficacy was plotted as a function of the mean plasma concentration (Cp) determined by pharmacokinetic (PK) analysis in naïve mice
  - Data were fitted to Hill functions to estimate ED_{50} and plasma EC_{50}
  - Receptor occupancy (RO) as a function of Cp in rat (*ex vivo* autoradiography) was analyzed to demonstrate the correspondence of the CK efficacy and RO as a function of Cp

Results

RAP-219 treatment raised the seizure threshold and provided seizure protection

- Compared to vehicle, RAP-219 at 0.1 and 1 mg/kg was associated with a significantly higher threshold to both first twitch and onset of sustained clonus in the pentylenetetrazol (PTZ) model ($P<0.01$)

Figure 1. Significant, Dose-Dependent Increase in Seizure Threshold to First Twitch and Onset of Sustained Clonus



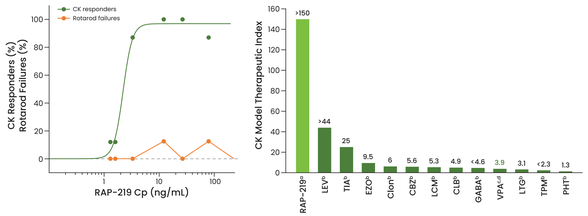
*$P<0.01$.

Time from start of PTZ infusion to first twitch and onset of sustained clonus were used to determine the PTZ threshold dose for each outcome; First twitch: ED_{50}=0.02 mg/kg; EC_{50}=2.9 ng/mL; Onset of sustained clonus: ED_{50}=0.02 mg/kg; EC_{50}=2.4 ng/mL; RAP-219 ED_{50} was 0.025 mg/kg, with a corresponding plasma EC_{50} of 2.3 ng/mL.

PTZ – pentylenetetrazol.

- Percentage of responders in the CK model increased with RAP-219 dose

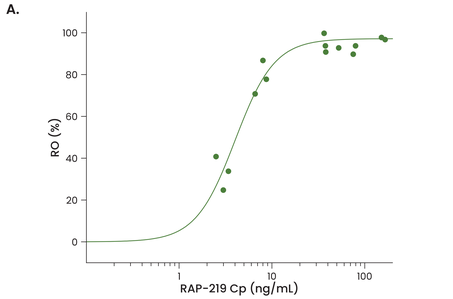
Figure 2. High Therapeutic Index as Assessed by Dose-Dependent Seizure Protection Without Motoric Impairment in the CK Model



[a]Data on file, Rapport Therapeutics, Inc.; [b]https://panache.ninds.nih.gov; [c]Metcalf CS et al. *Epilepsia* 2017;58(6):1073–84; [d]Rowley NM et al. *Epilepsy Res.* 2010;92(2–3):163–9.

CBZ – carbamazepine; **CLB** – clobazam; **CK** – corneal kindling; **Clon** – clonazepam; **EZO** – ezogabine; **GABA** – gabapentin; **LCM** – lacosamide; **LTG** – lamotrigine; **LEV** – levetiracetam; **PHT** – phenytoin; **TIA** – tiagabine; **TPM** – topiramate; **VPA** – valproate.

Figure 3. A. RAP-219 RO EC_{50} of 3.3 ng/mL Cp in Rat (4 h) and **B.** Maximal Protection With RAP-219 at Predicted Human RO (~70% RO and Corresponding Cp ~7 ng/mL)

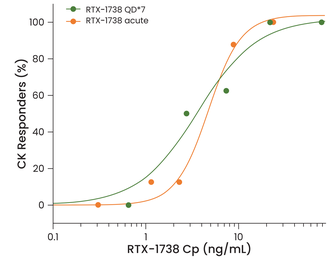


CK – corneal kindling; **Cp** – plasma concentration; **QD** – once daily; **RO** – receptor occupancy.

RTX-1738 RO EC_{50} value of 3.2 ng/mL

- No differences in locomotor activity were observed between vehicle and any RTX-1738 dose

Figure 4. Efficacy of RAP-219 Analog, RTX-1738, Remains Similar in CK Model Over 7 Days



Maximal protection was observed for RTX-1738 with RO ~90%, and Cp ~10 ng/mL; Acute: ED_{50} of 0.05 mg/kg with a corresponding plasma EC_{50} of 4.7 ng/mL; Chronic: ED_{50} of 0.01 mg/kg and a corresponding plasma EC_{50} of 3.6 ng/mL.

CK – corneal kindling; **Cp** – plasma concentration; **QD** – once daily; **RO** – receptor occupancy.

Conclusions

- RAP-219, a novel and selective AMPAR/TARPγ8 NAM currently in Phase 2 development for the treatment of focal and generalized seizures, provided potent, dose-dependent antiseizure effects in both the PTZ and CK preclinical seizure models
  - Maximal protection was observed with 70% RO and RAP-219 Cp of 7 ng/mL
  - Antiseizure effects were maintained over 7-day QD oral dosing with a RAP-219 analog
- Exposures that produced antiseizure effects did not impair motor function, yielding a high therapeutic index
- These results are consistent with targeted inhibition of AMPARs based on the neurospecificity of TARPγ8 expression (hippocampus, cortex, amygdala) while avoiding AEs associated with hindbrain AMPAR inhibition such as somnolence, motoric impairment, and falls

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Disclosures

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