RAP-219 a Novel, Potent, and Selective Negative Modulator of AMPAR/TARPγ8

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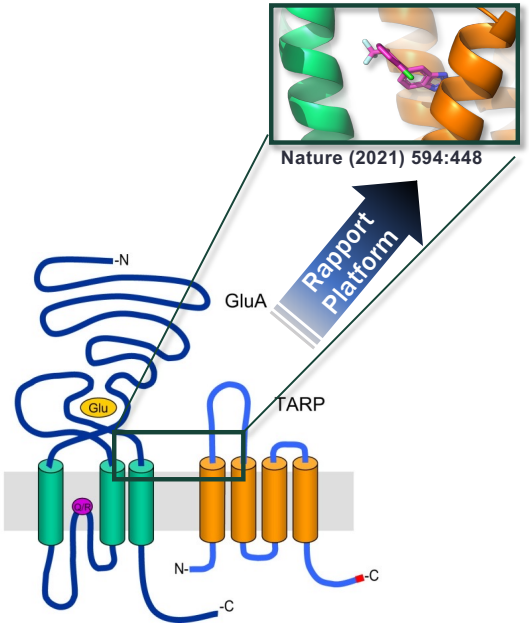
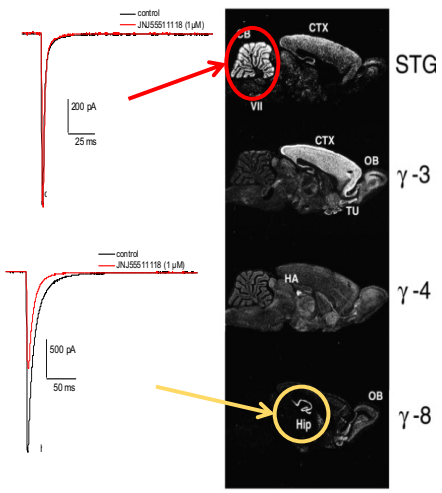
RAP-219 targets AMPA Receptors Expressing TARPγ8

Rapport's Platform Discovery



Most Enriched in Hippocampus, Cortex, Amygdala



JPET 2016 **657**:394

Highly-potent and γ-8 specific

TARPγ8-containing AMPA receptors (IC_{50})	~100 pM
vs. AMPA receptors (GluA1) lacking TARPs	>100,000x
vs. AMPA receptors containing other TARPs (γ2, γ3, γ4, γ7)	>4,000x
vs. NMDA receptors (2A, 2B, 2D)	>500,000x
vs. GPCRs/ion channels/enzymes (panel of 52)	>10,000x
vs. kinases (panel of 373)	>100,000x

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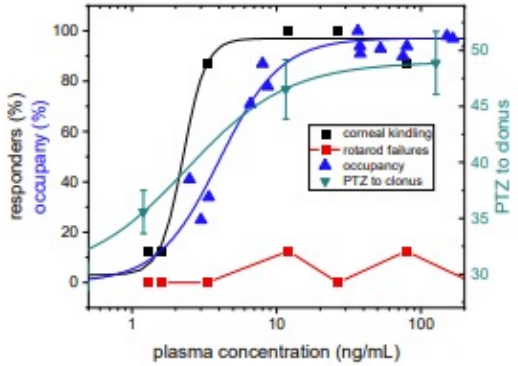
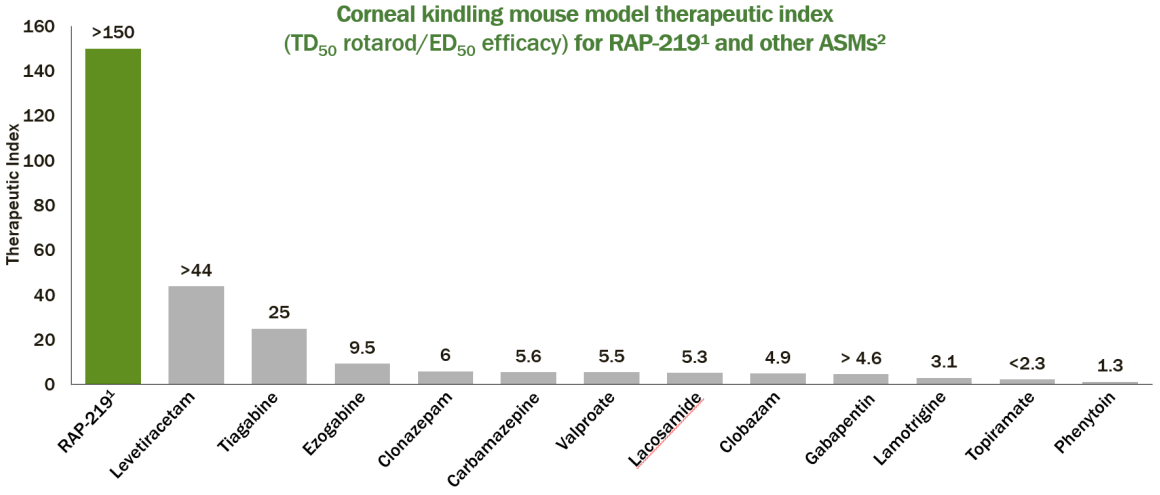
RAP-219 Exhibits Precision Neuromedicine Profile

Non-Sedating Anticonvulsant



- Effective at levels corresponding to 70% receptor occupancy
- Selective Targeting = Potential Differentiated TI

Advantageous Therapeutic Index (TI) vs. Common ASMs



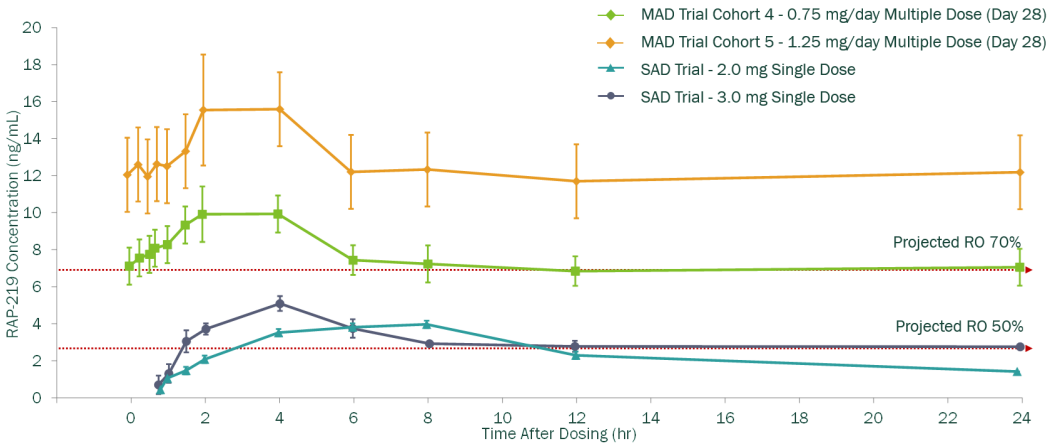
Therapeutic Index = TD_{50} (toxic dose) on Rotarod/ED_{50} (effective dose) for efficacy

[1] Data on file, Rapport Therapeutics; https://panache.ninds.nih.gov/

[2] Data are based on published reports from different preclinical studies at different points in time, with differences in preclinical study design and subject population. As a result, cross-study comparisons cannot be made. No head-to-head studies have been conducted.

RAP-219 Phase 1 Studies in Healthy Volunteers

- RAP-219-101
  - Single ascending dose study – Completed
- RAP-219-102
  - First multiple ascending dose study, up to 4 weeks of dosing – Completed
- RAP-219-103
  - PET imaging study to determine brain target receptor occupancy – Ongoing
- RAP-219-104
  - Continuation of multiple ascending dose study to explore additional dosing regimen – Ongoing



[1]Based on unaudited blinded data from Cohort 5 of the MAD trial, as compared to the highest single doe (3mg) in the Phase 1 SAD trial

RAP-219 MAD Unblinded Safety Summary

At highest dose, no TEAEs above Grade 1 and no treatment-related TEAEs

Treatment Emergent Adverse Events (TEAEs) in Phase 1 RAP-219-102 (MAD) Trial by Cohort and Pooled Placebo	Pooled Placebo (N=10)	Cohort 1 (0.25 mg × 2 weeks) (N=6)	Cohort 2 (0.25 mg × 1 week; 0.5 mg × 1 week) (N=6)	Cohort 3 (0.5 mg × 4 weeks) (N=6)	Cohort 4 (0.75 mg × 4 weeks) (N=6)	Cohort 5 (0.75 mg x 5 days; 1.25 mg x 23 days) (N=6)
Any TEAEs	4 (40.0%)	5 (83.3%)	6 (100%)	3 (50.0%)	5 (83.3%)	2 (33.3%)
Grade 1 (Mild) Related[1]	2 (20.0%)	3 (50.0%)	3 (50.0%)	2 (33.3%)	0	0
Grade 2 (Moderate) Related[1]	0	0	0	0	0	0
Grade 1 (Mild) Unrelated	2 (20.0%)	2 (33.3%)	4 (66.7%)	2 (33.3%)	4 (66.7%)	2 (33.3%)
Grade 2 (Moderate) Unrelated	0	3 (50.0%)	3 (50.0%)	0	2 (33.3%)	0
Grade 3 (Severe)	0	0	0	0	0	0
Grade 4 (Potentially Life Threatening)	0	0	0	0	0	0
Grade 5 (Death Related to AE)	0	0	0	0	0	0

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RAP-219 Phase 2a PoC Trial in Focal Epilepsy

Principal Investigator: Jacqueline French, MD

Trial Goal:

- Evaluate efficacy of RAP-219 using Long Episode biomarker
  - Organized epileptiform activity exceeding a specified duration, typically 30 sec
  - Often represent electrographic seizures (EES)

Design Overview:

- Adult drug-resistant focal epilepsy patients with implanted RNS® System (NeuroPace, Inc.)
- Multi-center open-label trial to enroll approximately 20 patients
- MAD Cohort 5 dose: 0.75 mg/day for 5 days followed by 1.25 mg/day

Eligibility Criteria:

- 18-65 years old
- Implanted RNS System:
  - Implanted ≥ 15 mos. prior to screening
  - Stable configuration, detection, & stimulation settings including LE duration
  - ≥ 8 LEs per 4-wk period during combined retrospective/prospective baseline
  - ≥ 50% concordance between LE & EES
  - No anticipated need for setting changes during trial
- ≥ 1 clinical seizure during retrospective baseline

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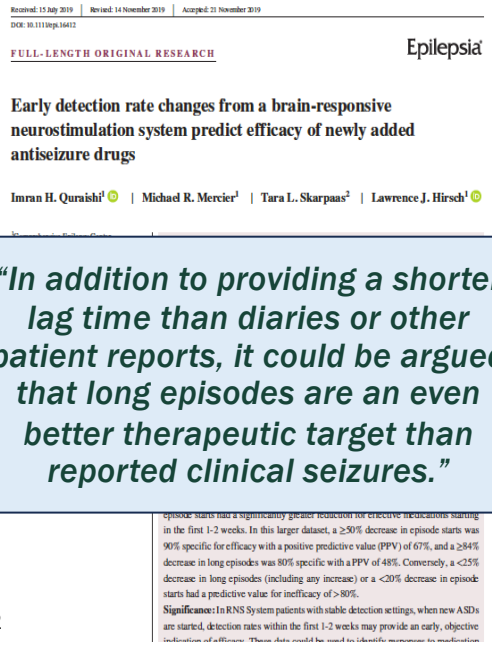
Long Episodes – a Biomarker-based Endpoint Demonstrated to Predict Clinical Response

Change in seizure activity recorded through intracranial EEG (iEEG) **predicted ASM clinical response**



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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Early detection rate changes from a brain-responsive neurostimulation system predict efficacy of newly added antiseizure drugs

Imran H. Quraishi[1] | Michael R. Mercier[1] | Tara L. Skarpaas[2] | Lawrence J. Hirsch[1]

in the first 1-2 weeks. In this larger dataset, a ≥50% decrease in episode starts was 90% specific for efficacy with a positive predictive value (PPV) of 67%, and a ≥84% decrease in long episodes was 80% specific with a PPV of 48%. Conversely, a <25% decrease in long episodes (including any increase) or a <20% decrease in episode starts had a predictive value for inefficacy of >80%.

Significance: In RNS System patients with stable detection settings, when new ASDs are started, detection rates within the first 1-2 weeks may provide an early, objective

"In addition to providing a shorter lag time than diaries or other patient reports, it could be argued that long episodes are an even better therapeutic target than reported clinical seizures."

Epilepsy & Behavior 83 (2018) 192–200

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical and electrocorticographic response to antiepileptic drugs in patients treated with responsive stimulation

Tara L. Skarpaas [a,*], Thomas K. Tcheng [a], Martha J. Morrell [a,b]

ARTICLE INFO ABSTRACT

must be repeated with each dose adjustment. A physiological biomarker that provides a rapid assessment of a medication's effect on cortical excitability could quickly and objectively establish whether a given medication and dose are likely to be clinically effective. Chronic

regardless of the AED used. Farther, Meisel et al. [9] demonstrated that the effect of AEDs could be quantified in a graded manner using intrinsic measures of cortical excitability recorded during intracranial monitoring. However, neither evoked nor intrinsic measures of cortical excitability have been available outside of the clinic or hospital.

The aim of this retrospective study was to explore whether chronic ambulatory ECoG data recorded by a closed-loop neurostimulation system (the RNS® System, NeuroPace Inc.) could reveal potential biomarkers

"Long Episode rates had the strongest correlation with changes in clinical seizure rates. These data suggest that these measures may provide an objective assessment of cortical excitability and response to AEDs."

- 30-40% reduction in LEs within 1-4 weeks of new ASM was associated with a ≥50% seizure reduction
- No decrease in LEs predicts ASM will not be clinically efficacious

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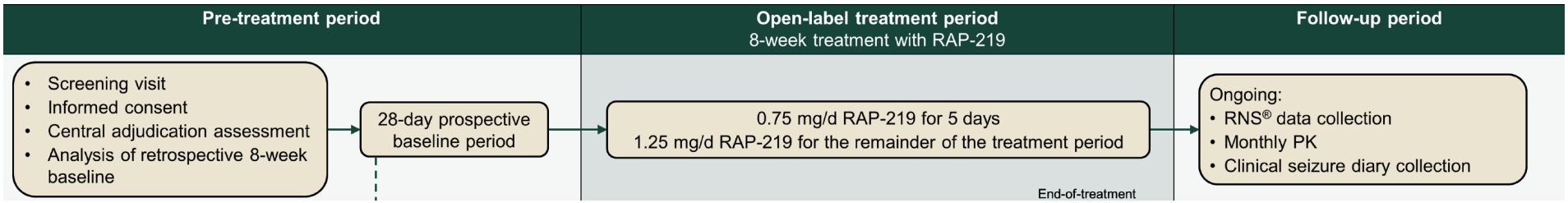
RAP-219 Phase 2a PoC Trial Schema in Focal Epilepsy

Trial schema



Key Endpoints:

- LE frequency responder analysis (% of patients that demonstrate ≥30% reduction in LEs)
- Change in LE frequency, estimated EES, clinical seizure frequency, and additional iEEG biomarkers
- Clinically meaningful improvements in global ratings (PGIC/CGIC)
- Incidence TEAEs

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