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Corporate overview

May 2024

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This presentation contains forward-looking statements of Rapport Therapeutics, Inc. ("Rapport," the "Company," "we," "us," or "our") that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potentially" "predict," "should," "will" or the negative of these terms or other similar expressions. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: our ability to identify, develop, and commercialize current and future product candidates based on our receptor associated protein ("RAP") technology platform; the initiation, timing, progress, and results of our research and development programs, preclinical studies and clinical trials; the translation of endpoints in our current and planned clinical trials to future registrational trials; our ability to replicate positive results from earlier preclinical studies or clinical trials conducted by us or third parties in current or future clinical trials; our ability to demonstrate that our current and future product candidates are safe and effective for their proposed indications; the implementation of our business model and strategic plans for our business, programs, future product candidates and RAP technology platform; our ability to advance any product candidates through applicable regulatory approval processes; our ability to comply with our obligations under our intellectual property licenses with third parties; our ability to maintain, expand and protect our intellectual property portfolio; general economic, industry, and market conditions, including rising interest rates and inflation; our ability to obtain additional cash and the sufficiency of our existing cash, cash equivalents, and short-term investments to fund our future operating expenses and capital expenditure requirements; and the accuracy of our estimates regarding expenses, future revenue, capital requirements, and needs for additional financing. These risks are not exhaustive. New risk factors emerge from time to time and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

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This presentation discusses product candidates that are investigational only and have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of these product candidates for the use for which such product candidates are being studied.

Leadership with track record of innovation and expertise

Management Team

David Bredt, M.D., Ph.D.[1,2]
Founder, Chief Scientific Officer

20 years neuroscience drug discovery experience; Former Global Head of Neuroscience Discovery, Janssen Global Services

Johnson&Johnson Lilly

Abe Ceesay[1]
Chief Executive Officer

15+ years commercial and executive leadership experience; Former President, Cerevel Therapeutics

cerevel Ironwood genzyme TIBURIO THERAPEUTICS scPharmaceuticals

Brad Galer, M.D.
Chief Medical Officer

20+ years biopharma development experience; Former CMO, Zogenix

ZOGENIX NUVO endo

Cheryl Gault
Chief Operating Officer

20+ years corporate strategy and corporate development experience

cyclerion Ironwood genzyme

Troy Ignelzi
Chief Financial Officer

20+ years financial leadership experience in biotech and pharma sectors

KARUNA THERAPEUTICS scPharmaceuticals Lilly CINCOR ESPERION

Kathy Wilkinson
Chief People Officer

15+ years of human resources experience in biotech

bluebirdbio 2seventybio Bristol Myers Squibb

Swamy Yeleswaram, Ph.D.
Chief Development Officer

25+ years drug discovery experience; Founding scientist of Incyte

Incyte Bristol Myers Squibb

Board of Directors

Steve Paul, M.D.
Board Chair

Partner, Third Rock Ventures

Terry-Ann Burrell, M.B.A.
Director

CFO, Beam Therapeutics

James Healy, M.D., Ph.D.
Director

Managing Partner, Sofinnova Investments

Reid Huber, Ph.D.
Director

Partner, Third Rock Ventures; CEO, Merida Biosciences

Raymond Kelleher, M.D., Ph.D.[2]
Director

Managing Director, Cormorant Asset Management

John Maraganore, Ph.D.
Director

Former Founding CEO, Alnylam

Jeff Tong, Ph.D.
Director

Partner, Third Rock Ventures

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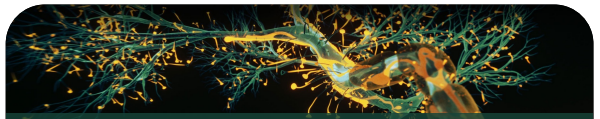
[1]Employee directors
[2]Resigning from Board upon effectiveness of registration statement for contemplated offering

Ushering in a new era of precision neuroscience

Vision: To become a leader in precision neuroscience through the discovery and development of transformational small molecule medicines for patients suffering from central nervous system (CNS) disorders



Potential for differentiated approach to generate precision small molecule medicines

Road-tested capability of identifying **key mediators of receptor function**

Differentiated pharmacology we believe promotes **high selectivity and specificity**

Potential to transform the treatment of neurological disorders with **differentiated profile**

Accomplished scientific innovators & company builders

Pioneering discovery team

Company builders with industry-proven leadership

THIRD ROCK VENTURES

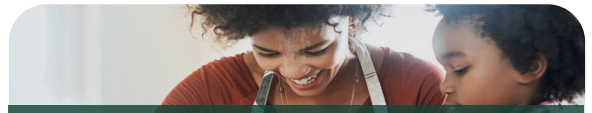
Janssen Neuroscience
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Robust clinical & discovery pipeline

Potential for first-in-class programs leveraging receptor associated protein (RAP) science

RAP-219 clinical program
Non-sedative forebrain restricted TARPγ8 AMPAR[1] modulator – significant opportunity in initial indication in focal epilepsy

Discovery programs
Medicinal chemistry-enabled portfolio with potential in additional indications



Historically well financed

$100M Series A

$150M Series B

PERCEPTIVE ADVISORS · LOGOS CAPITAL · CORMORANT ASSET MANAGEMENT · SOFINNOVA INVESTMENTS · SURVEYOR · ARCH VENTURE PARTNERS · T.RowePrice · Fidelity

Financing to-date funds **RAP-219 through Phase 2 proof-of-concept** (PoC) in focal epilepsy, early clinical work for indication expansion, and discovery efforts

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[1]AMPAR α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors

We believe the current state and limitations of neuromedicine compels the creation of Rapport

RAPs are components of the broader neuronal receptor complexes and play critical roles in regulating receptor assembly and function

Conventional CNS drug discovery

- Drugs interact with receptors that are ubiquitous in the brain and body
- Drugs not designed with precision for disease-specific neuroanatomic sites / receptors
- Drug interactions and adverse events lead to noncompliance and discontinuation
- Drug discovery with conventional approaches (lacking RAPs) can miss high potential, previously unexplored targets

The potential of RAPs

- RAPs serve as unique binding sites targetable by novel pharmacophores designed for increased selectivity
- RAP targeting can provide tissue / neuroanatomical specificity
- RAPs enable differentiated pharmacology and potentially provide optimal efficacy, safety, and administration profiles
- RAPs can “unlock” drug targets previously inaccessible to study in vitro, allowing for potentially first-in-class drug discovery programs

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Advancing our precision neuroscience pipeline to potentially address large market opportunities

Category	Program	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Next Expected Milestone
TARPγ8 AMPAR Programs	RAP-219 *Focal Epilepsy**						Ph1 MAD results 2Q 2024 Ph2a: Trial initiation Mid-2024 Topline results Mid-2025
	RAP-219 *Peripheral Neuropathic Pain**						Ph2a trial initiation 2H 2024
	RAP-219 *Bipolar Disorder**						Ph2a trial initiation 2025
	RAP-199 *Indications to be announced*						Ph1 trial initiation 1H 2025
nAChR Discovery Programs	*α6* *Chronic Pain*						Nominate Development Candidate
	α9α10 *Hearing Disorders*						Nominate Development Candidate

Strong intellectual property with worldwide rights to all programs

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Note: "Mid" defined as Q2 or Q3

* We have conducted two Phase 1 trials supportive of multiple RAP-219 indications

Focal epilepsy is a large market with high unmet need

Key highlights of U.S. focal epilepsy market

3.0M — ***U.S. Epilepsy Patients (ages 18+)***

60% — ***% Focal Epilepsy***

1.8M — ***Focal Epilepsy Patients***

30-40% — ***% Drug-Resistant[1]***

Limitations of current therapies

- **Limited Efficacy:** Despite over >20 FDA approved anti-seizure medications (ASMs), 30-40% of patients are drug-resistant[1]
- **Tolerability Issues:** Especially CNS side-effects, such as sedation, ataxia, and cognitive problems
- **Potential for Serious Adverse Events:** Such as severe cutaneous reactions, serious hematological disorders, and hepatic failure
- **Complicated Administration:** Long titration, drug-drug interactions, and lab monitoring

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[1] Drug-resistant patients are those who continue to experience recurring seizures despite taking two or more ASMs
Internal Market Research, 2023

RAP-219 is a “pipeline in a product” opportunity

Expanding the potential of RAP-219

Focal epilepsy
U.S. patients: 1.8 million[1]

Peripheral neuropathic pain
U.S. patients: ~5.6 million[2]

Bipolar disorder
U.S. patients: ~7 million[3]

TARPγ8 is a preclinically and clinically validated target for epilepsy, which RAP-219 is designed to selectively target

Strong mechanistic data in both peripheral neuropathic pain and bipolar disorder, and compelling preclinical data in peripheral neuropathic pain

Once daily (QD) dosing | No evidence of sedation or motoric impairment | No observed drug-drug interactions (DDI)

Evaluating long acting injectable (LAI)

Potency and metabolic profile positions RAP-219 as the first potential ASM in a depot formulation, which enables appealing administration alternative

Opportunity for improving patient adherence

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Internal Market Research, 2023. [1] Diagnosed prevalence. [2] Diagnosed prevalence across diabetic peripheral neuropathy (~2.8 million), post-herpetic neuralgia (~1.8 million), trigeminal neuralgia (~1.0 million). [3] True prevalence (diagnosed prevalence divided by the diagnosis rate)

RAP-219 overview

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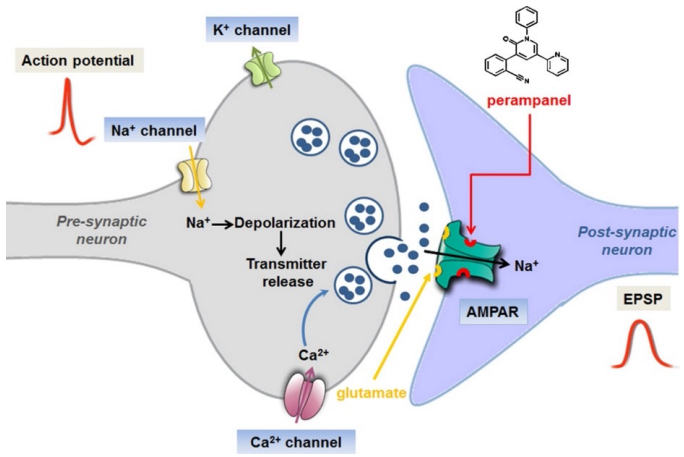
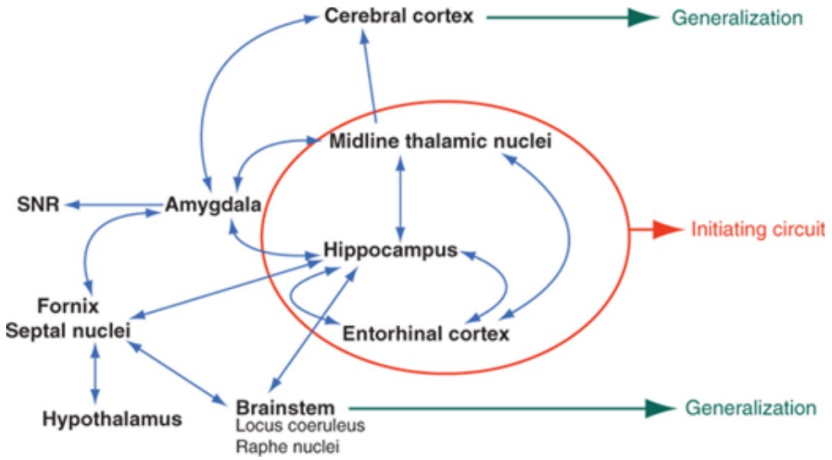
AMPAR inhibition is a clinically validated approach for epilepsy

AMPA receptors (AMPAR) in epilepsy



- AMPA type glutamate receptors at excitatory synapses can mediate seizure initiation and spread
- AMPAR target is clinically validated - perampanel (FYCOMPA®) is an FDA/EMA approved pan-AMPAR antagonist for the treatment of focal onset and generalized seizures

Hippocampus and cortex are important sites of focal onset seizure origination



ISBN 978-0-07-129621-6

- Hippocampus is a common seizure initiation site, with approximately 50% of all seizures originating in or around this area
- Cerebral cortex, which expresses abundant TARPγ8, is another common site of FOS initiation, originating up to 50% of all seizures
- Seizures originating in the cerebral cortex often spread into and are propagated by the hippocampus

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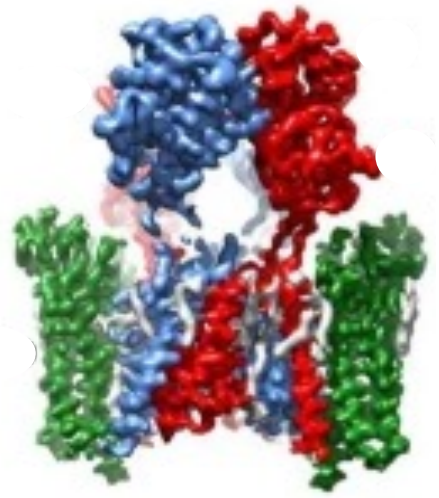
Molecular science of transmembrane AMPA regulatory proteins (TARPs)

TARPs: Auxiliary subunits that associate with AMPA receptors in the brain
Crucial for regulating the trafficking, subcellular localization and gating of AMPA receptors

- TARPs display distinct regional expression profiles, offering opportunity for precision neuromedicine targets
- TARPγ8 is most enriched in the hippocampus and present in other forebrain structures

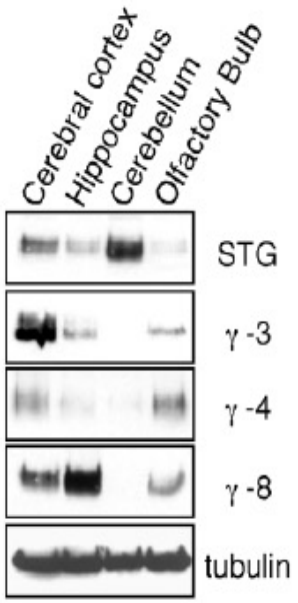
Cryogenic electron microscopy of GluA1/2 + TARPγ8 complex

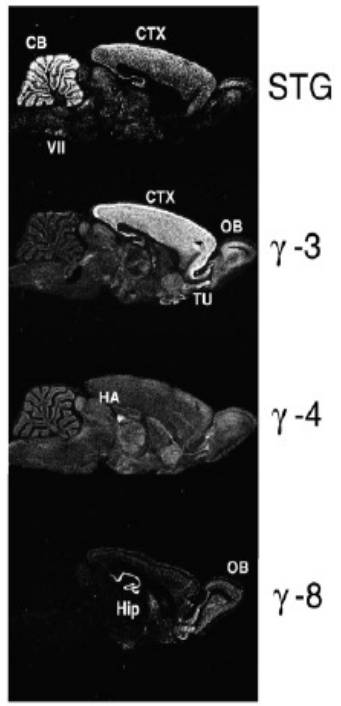


GluA1
GluA2
TARPγ8

NatComm 2022 13:734

TARPs in rat brain





JCB 2003 161:805

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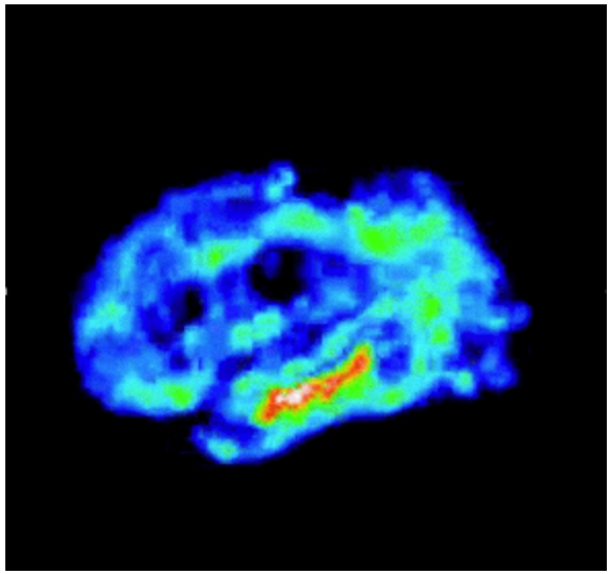
Observed to be highly potent and selective TARPγ8 AMPAR NAM

RAP-219 potency and selectivity	
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

TARPγ8 clinical PET in human



ACNP 2018 27.6: 536

Selective for hippocampus and other forebrain structures

Minimal or no expression in the cerebellum and brainstem

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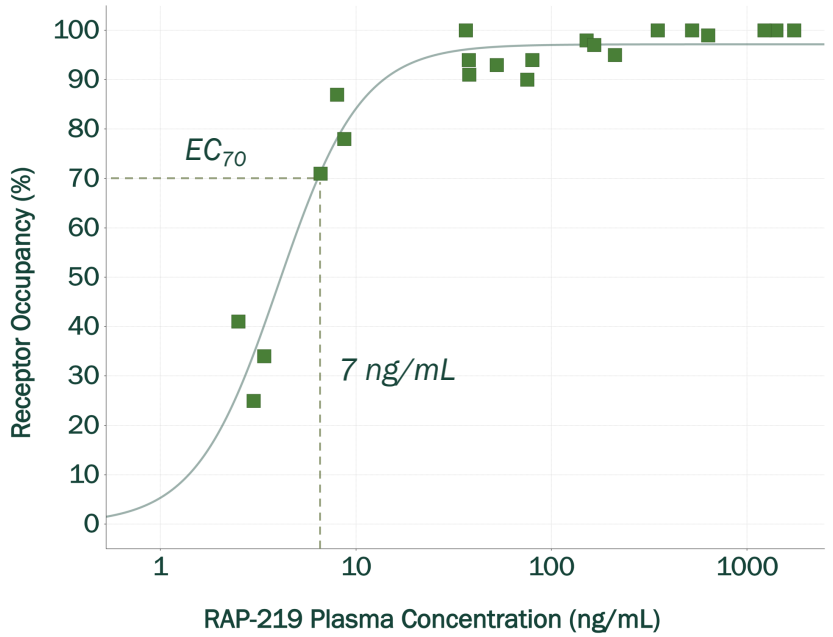
NAM = Negative allosteric modulator

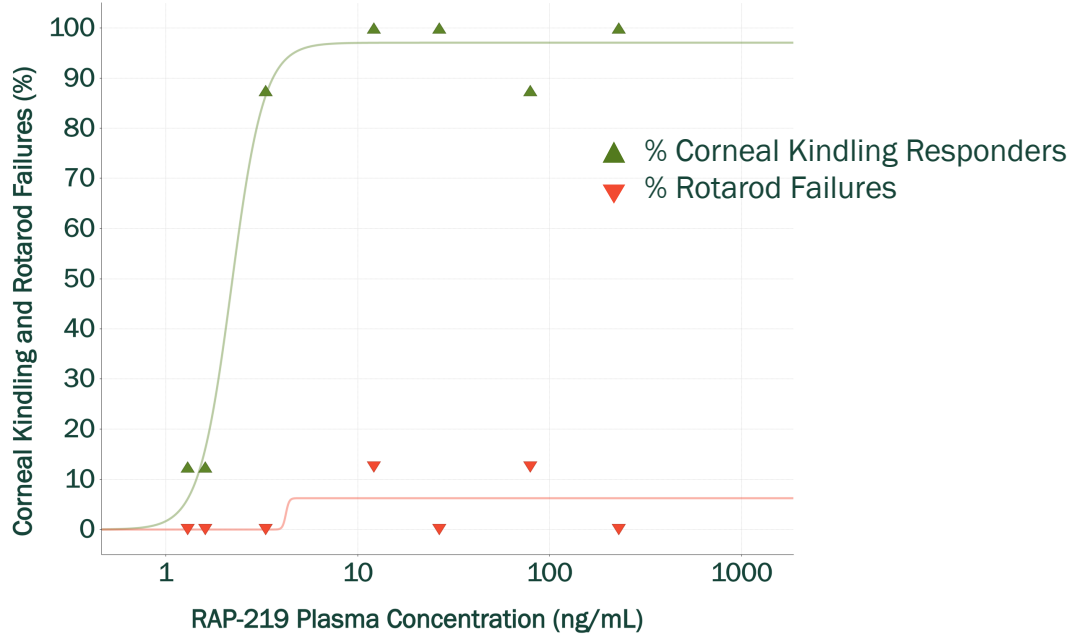
Differentiated precision preclinical profile of RAP-219

Receptor occupancy (%) in rats



- Oral administration of RAP-219 (0.001-10 mg/kg)
- Plasma EC_{70}'s of 7 ng/mL in rats (shown above) and plasma EC_{70}'s of 3 ng/mL in mice

Corneal kindling responders and rotarod failures in mice



- Valid model in focal epilepsy
- Oral administration of RAP-219 resulted in significant seizure reduction in kindled mice at low plasma levels (<7 ng/mL) corresponding to a projected 50-70% receptor occupancy
- No motoric impairments observed at highest doses tested

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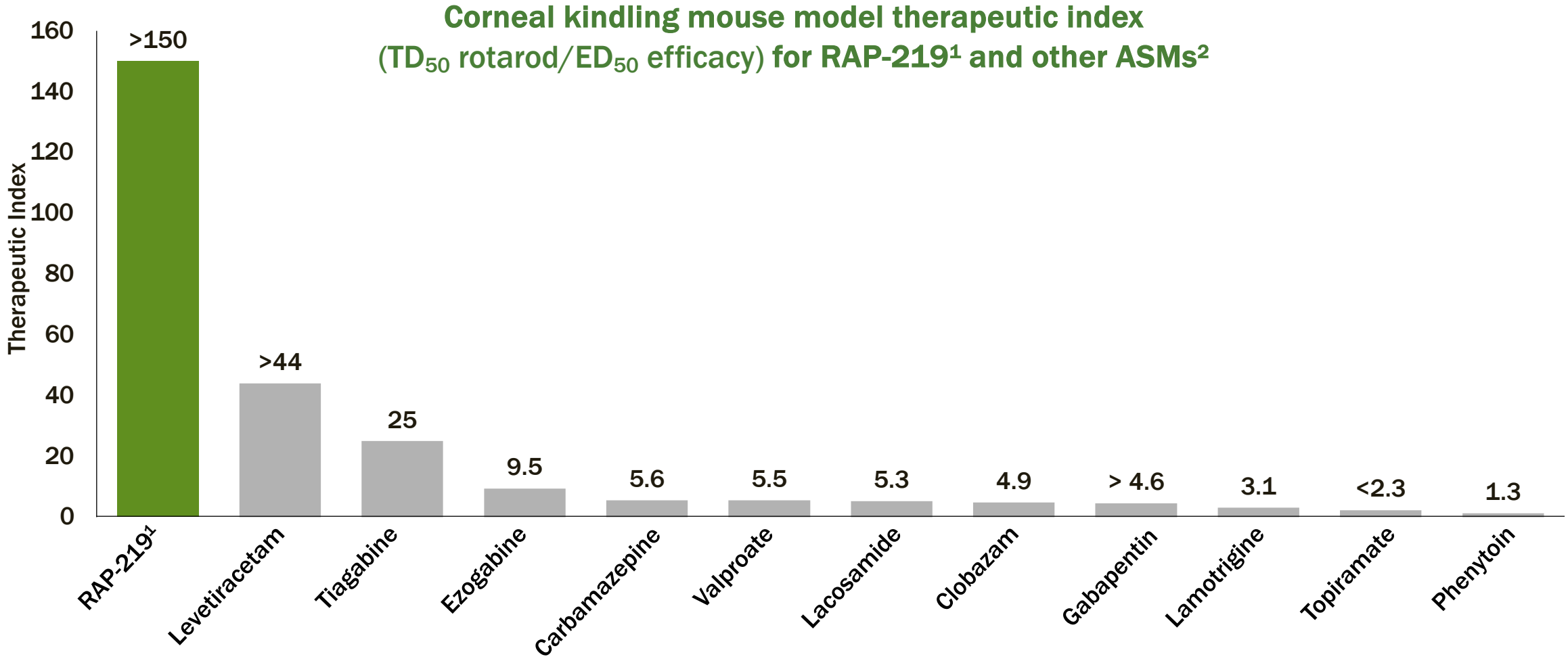
EC_{70} = effective concentration achieving 70% occupancy of target receptor

RAP-219 precision has the potential to significantly improve the therapeutic index



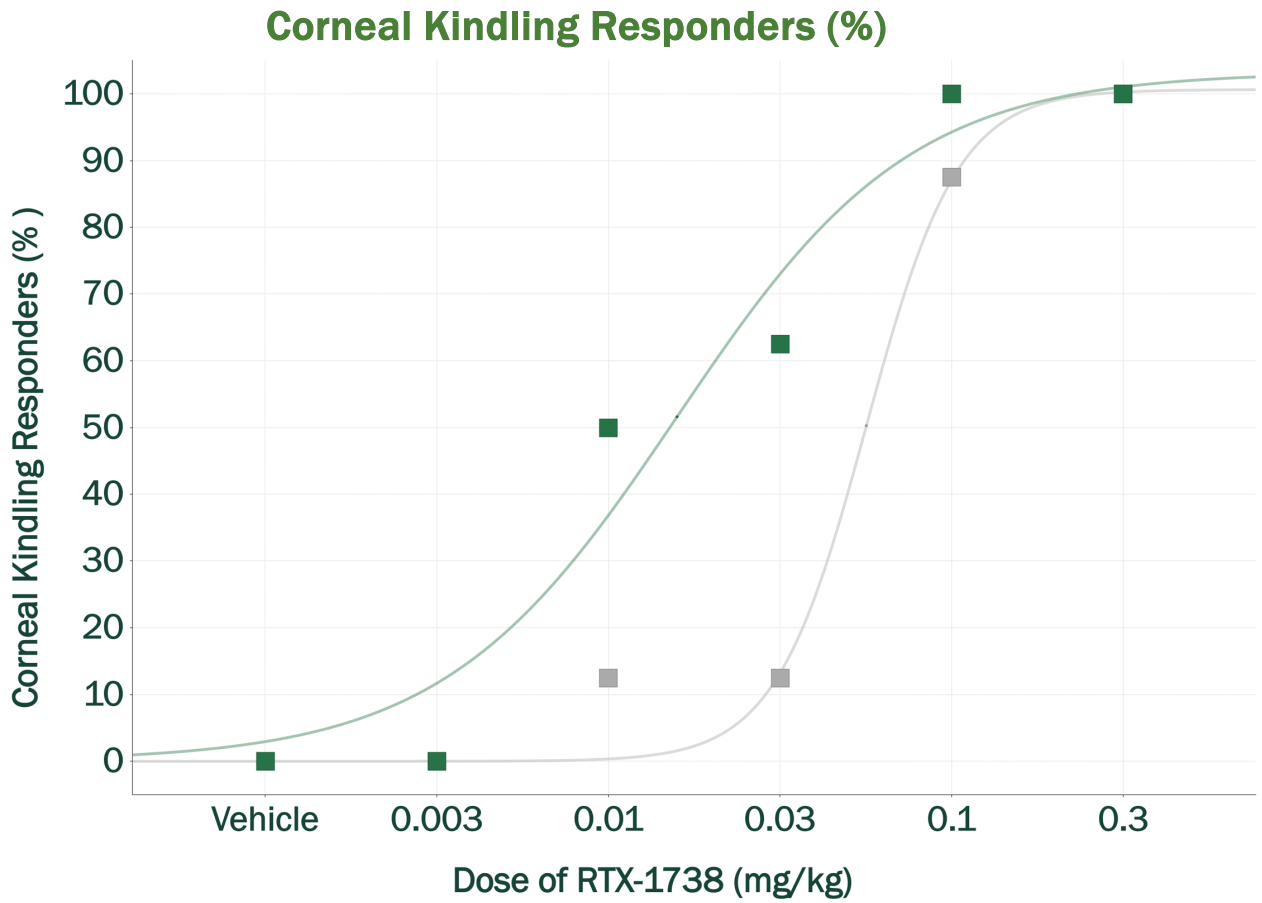
Therapeutic Index = TD_{50} (toxic dose) on Rotarod/ED_{50} (effective dose) for efficacy

[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.

TARPγ8 NAM effectiveness persists with repeat dosing

Antiseizure activity maintained after prolonged exposure



- Efficacy in corneal kindling used to evaluate RTX-1738 (an analog of RAP-219)
- RTX-1738 (3 mg/kg) tested following either single day or seven consecutive days of oral administration
- Antiseizure activity was maintained or became more potent after 7-day dosing

Single oral administration, tested 2 hours post dose
Seven-day oral administration, tested 2 hours after last dose

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TARPγ8 AMPAR NAMs active in preclinical epilepsy models

Preclinical epilepsy models are highly translatable, with probabilities of clinical success up to 70%, according to epileptologist Jackie French

Model	
Corneal Kindling – mouse*	✅
PTZ - mouse*	✅
Rotarod*	✅
Amygdala kindling – mouse	✅
Hippocampal kindling – mouse	✅
6Hz stimulation – mouse	✅
Frings audiogenic seizure – mouse	✅
GAERS absence epilepsy – rat	✅

- Robust efficacy across a broad array of preclinical focal and generalized seizure models
- Potent activity in kindling model has been observed to predict efficacy in focal epilepsy
- Activity not seen in maximal electroshock (MES) model, consistent with performance of levetiracetam and some other effective ASMs

"Chronic seizure models [like corneal kindling] offer the most etiologically relevant platform on which to accurately replicate clinical epilepsy and are thus deserving of more use earlier in ASD identification." – Barker-Haliski, Expert Opinion on Drug Discovery

* Used RAP-219; where not noted, used other TARPγ8 NAM

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CNS & Neurological Disorders - Drug Targets (2017) 16:1099; J Pharmacol Exp Ther (2016) 357:394; J Amer Soc for Exper NeuroTherapeutics (2007) 4:12; Jackie French AES Presentation, Professor, Neurology, NYU Grossman School of Medicine; Director, The Epilepsy Study Consortium (TESC); Barker-Haliski, M. (2019) Expert Opinion on Drug Discovery, 14(10), 947–951.

RAP-219 overview

A. Mechanism of action and preclinical development
B. Phase 1 SAD/MAD trials
C. Phase 2a proof-of-concept trial in focal epilepsy
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RAP-219 Phase 1 SAD/MAD trials

- In Phase 1, RAP-219 was generally well tolerated
  - No serious adverse events were reported
  - No clinically meaningful abnormal changes in labs, ECGs, or vital signs
- In SAD trial, treatment related TEAEs were generally consistent with the effects seen in non-clinical toxicology studies
  - All treatment related TEAEs were Grade 1 or Grade 2
  - At the highest doses of 2 mg and 3 mg, CNS pharmacology was observed to be generally consistent with non-clinical studies
- In MAD trial, no treatment related TEAEs above Grade 1 were reported
  - Highest dose evaluated (Cohort 5: 0.75 mg x 5 days → 1.25 mg x 23 days) had no treatment related TEAEs
  - The MAD trial indicated exposures up to 3-fold higher than those achieved in the SAD trial, exceeding projected target RO

Phase 2a trial in focal epilepsy expected to be initiated in mid-2024; topline results expected in mid-2025

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TEAE = Treatment emergent adverse events

RAP-219 first-in-human Phase 1 trials

Single ascending dose (SAD) trial: RAP-219-101

Part 1

- Randomized, double-blind, placebo-controlled single ascending dose trial
- 5 cohorts, N=8 per cohort (6 active & 2 placebo)
- 0.25 mg to 3 mg doses

Part 2

- Open label food effect study, 1 mg with food, N=6

Multiple ascending dose (MAD) trial: RAP-219-102

- Randomized, double-blind, placebo-controlled multiple ascending dose trial
- 5 cohorts, N=8 per cohort (6 active & 2 placebo)
- 0.25 mg QD to 1.25 mg QD
- 2 weeks (Cohorts 1 & 2) or 4 weeks (Cohorts 3-5) of QD dosing

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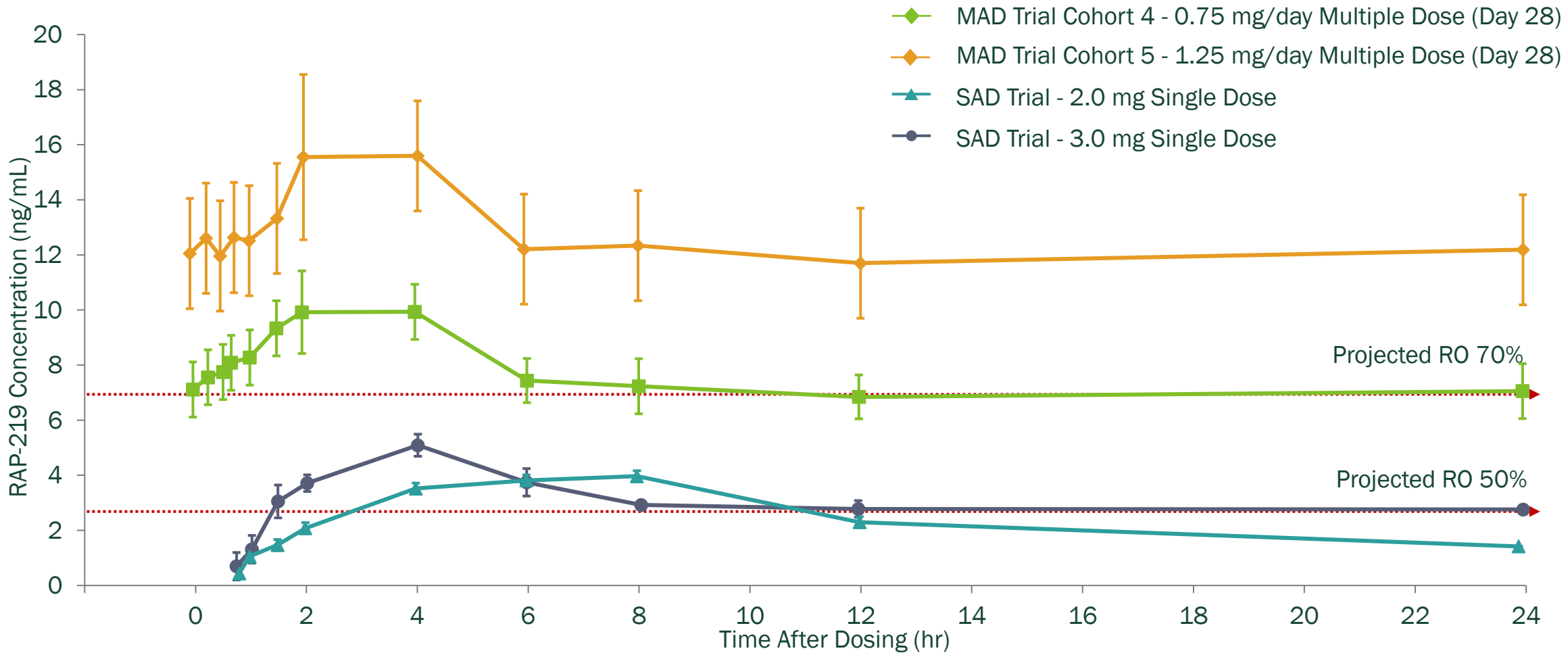
RAP-219 SAD vs. MAD exposures

MAD trial achieved 3-fold higher Cmax than SAD trial[1]



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

RAP-219 MAD blinded trial results

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	Cohort 1 0.25 mg × 2 weeks or placebo (N=8)		Cohort 2 0.25 mg × 1 week; 0.5 mg × 1 week or placebo (N=8)		Cohort 3 0.5 mg × 4 weeks or placebo (N=8)		Cohort 4 0.75 mg × 4 weeks or placebo (N=8)		Cohort 5 0.75 mg for 5 days, 1.25 mg for 23 days or placebo (N=8)	
Toxicity Grade of TEAE	n (%)	M	n (%)	M	n (%)	M	n (%)	M	n (%)	M
Grade 1 (Mild) Related[1]	3 (37.5%)	3	4 (50.0%)	7	3 (37.5%)	3	1 (12.5%)	1	0	0
Grade 2 (Moderate) Related[1]	0	0	0	0	0	0	0	0	0	0
Grade 1 (Mild) Unrelated	3 (37.5%)	4	4 (50.0%)	6	2 (25.0%)	2	5 (62.5%)	17	2 (25.0%)	2
Grade 2 (Moderate) Unrelated	3 (37.5%)	3	3 (37.5%)	4	0	0	2 (25.0%)	4	0	0
Grade 3 (Severe)	0	0	0	0	0	0	0	0	0	0
Grade 4 (Potentially Life Threatening)	0	0	0	0	0	0	0	0	0	0
Grade 5 (Death Related to AE)	0	0	0	0	0	0	0	0	0	0

Dose for Phase 2a focal epilepsy trial

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[1] Possibly related or probably related

Potentially optimal target profile emerging for RAP-219 in focal epilepsy

Ideal Product Profile	RAP-219 Emerging Profile
Reduces seizures potently without evidence of sedation	• At low dose, reduced seizures in validated preclinical epilepsy models
Displays no dose limiting toxicities	• Highest dose evaluated in IND-enabling studies were considered to be generally well tolerated
Potential for reduced drug-drug interactions	• Low DDI potential as RAP-219 not observed to interact with CYP enzymes • Well suited for polypharmacy as no dose adjustments anticipated when combined with other ASMs
Generally well tolerated	• Achieved exposures exceeding projected target RO • No SAEs and no abnormal laboratory or ECGs reported • No treatment related TEAEs above Grade 1 reported in the MAD trial
Potential for greater therapeutic index	• RAP-219 exposure achieved with planned Phase 2a dose exceeded targeted therapeutic levels with no apparent treatment related AEs
Convenient administration	• QD dosing • Single step up dosing

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Phase 2a proof-of-concept trial in focal epilepsy

Key design considerations for an ideal trial

- Same population to be used in registrational trials – refractory FOS patients
- Informs dose selection and effect size
- Utilizes a recognized seizure biomarker
- Enables rapid progression into registrational trials

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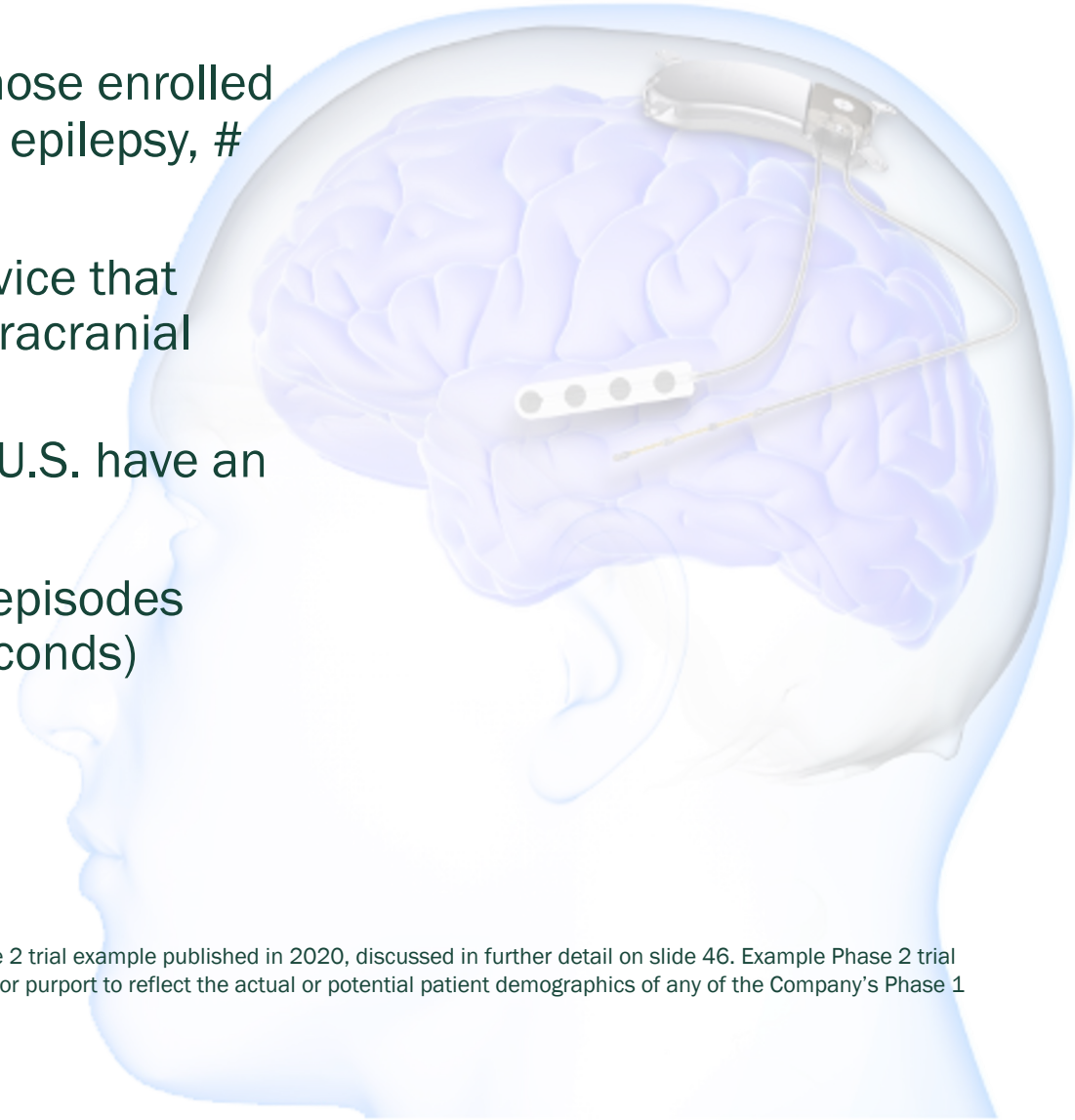
Focal epilepsy patients with a responsive neurostimulation (RNS) system

- RNS system patients had similar demographics to those enrolled in a third-party registrational FOS study[1] (duration of epilepsy, # of seizures, # of ASMs)
- The RNS system is an FDA-approved implantable device that continually monitors and records seizure activity (intracranial EEG, or iEEG data) in patients with FOS
  - >5,000 refractory focal epilepsy patients in the U.S. have an implanted RNS device[2]
- RNS detects[3] a biomarker of clinical seizures - long episodes (LEs) exceeding a specified duration (typically 30 seconds)



[1]Based on a comparison of NeuroPace's long-term treatment retrospective study and a Phase 2 trial example published in 2020, discussed in further detail on slide 46. Example Phase 2 trial patient demographic information does not include patients with the RNS system implanted, nor purport to reflect the actual or potential patient demographics of any of the Company's Phase 1 clinical trials or any planned Phase 2 clinical trials.
[2]As of December 31, 2023
[3]The RNS system is also a therapeutic device for adults with drug-resistant focal epilepsy

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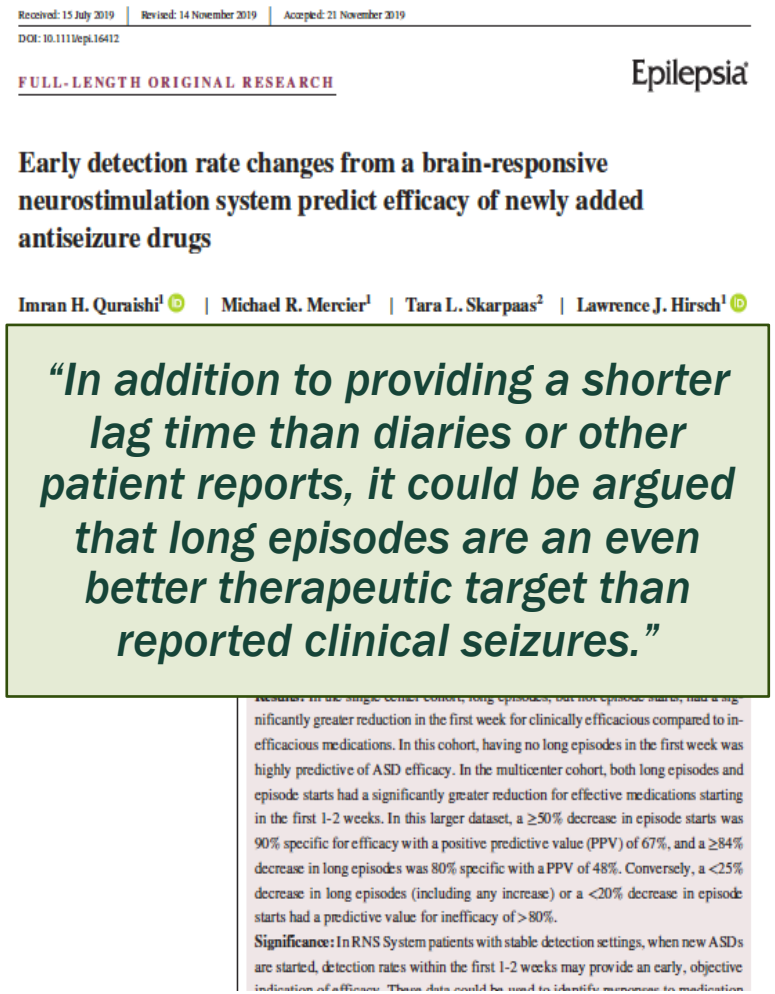
Long episodes – a biomarker-based endpoint demonstrated to predict clinical response

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



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DOI: 10.1111/epi.16412

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

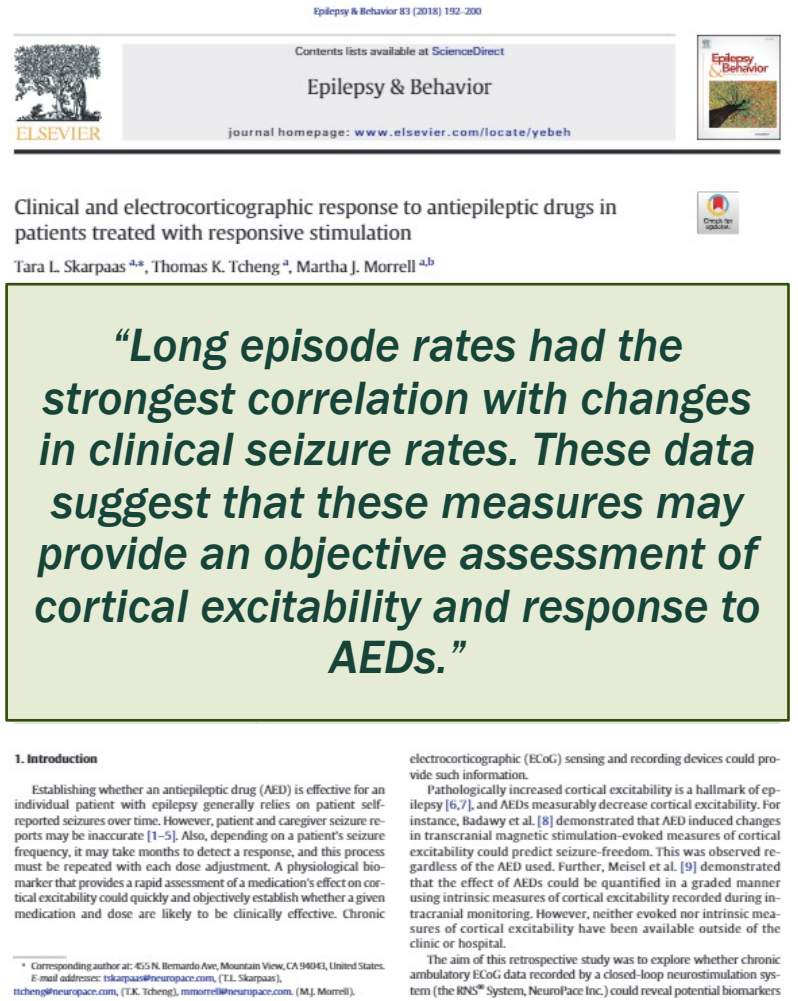
Early detection rate changes from a brain-responsive neurostimulation system predict efficacy of newly added antiseizure drugs

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

nificantly greater reduction in the first week for clinically efficacious compared to inefficacious medications. In this cohort, having no long episodes in the first week was highly predictive of ASD efficacy. In the multicenter cohort, both long episodes and episode starts had a significantly greater reduction for effective medications starting 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

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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]

1. Introduction

Establishing whether an antiepileptic drug (AED) is effective for an individual patient with epilepsy generally relies on patient self-reported seizures over time. However, patient and caregiver seizure reports may be inaccurate [1–5]. Also, depending on a patient's seizure frequency, it may take months to detect a response, and this process 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 electrocorticographic (ECoG) sensing and recording devices could provide such information.

Pathologically increased cortical excitability is a hallmark of epilepsy [6,7], and AEDs measurably decrease cortical excitability. For instance, Badawy et al. [8] demonstrated that AED induced changes in transcranial magnetic stimulation-evoked measures of cortical excitability could predict seizure-freedom. This was observed regardless of the AED used. Further, 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

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"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[1]
- No decrease in LEs predicts ASM will not be clinically efficacious

Epilepsy & Behavior. 2018; 83: 192-200; Epilepsia. 2020; 61:138-148.

[1]Based on internal analysis of data from third-party studies

RAP-219 Phase 2a PoC trial in focal epilepsy

Principal Investigator:

Jacqueline French, M.D.

Professor, Neurology, NYU Grossman School of Medicine

Trial Goal:

Evaluate efficacy of RAP-219 using LE biomarker

Design Overview:

- Signal detection trial in adult drug-resistant focal epilepsy patients with implanted RNS systems
- 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

Primary endpoint:

- Change in LE frequency during the final 4-week interval of the treatment (weeks 5-8) compared to baseline frequency (determined across 8-week retrospective and 4-week prospective baseline)

Secondary endpoints:

- Change in clinical seizure frequency (measured using the RNS system and patient-recorded paper diaries)
- Change in electrographic biomarkers, including episode duration, saturation frequency, spike frequency, spectral power)

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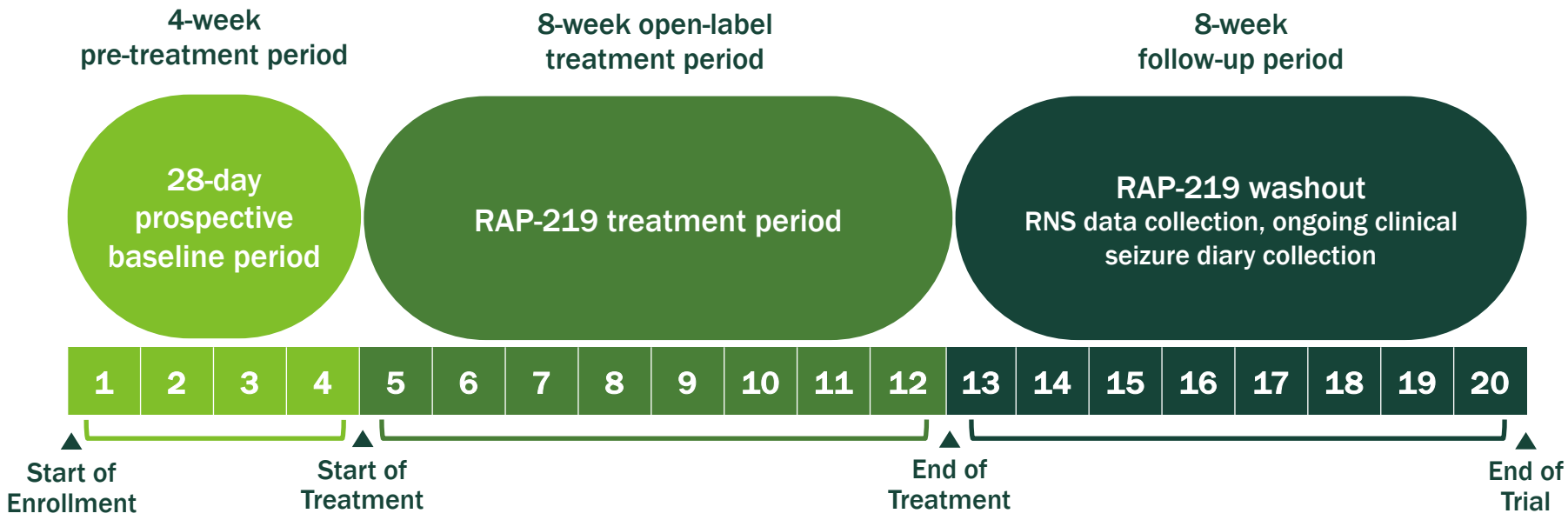
[1]As of December 31, 2023

RAP-219 Phase 2a PoC trial schema in focal epilepsy

Trial schema



1. Confirm localization of seizure onset zone and electrode placement
2. Confirm stability of RNS system settings and therapies
3. Provide historical iEEG data with at least an average of 8 LEs per 4-week interval
4. At least 1 clinical seizure during 8-week retrospective period

Establish baseline iEEG and clinical seizure frequency

Evaluate the effect of RAP-219 on long episodes and other iEEG biomarkers and biomarker event frequency (RNS measured long episodes) as well as establish PK/PD relationship

Follow-up to allow for washout and potential return to baseline iEEG measures and evaluate PK/PD relationship

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RNS PoC comparability to Phase 2b/3 trial

RNS system patients similar to those enrolled in third-party Phase 2b/3 trials

NeuroPace long-term-treatment retrospective study

Clinical characteristic	Value
Age at enrollment, mean ± SD (range)	33.9 ± 11.5 (18-58)
Duration of epilepsy, years at enrollment, mean ± SD (range)	19.4 ± 11.5 (2-54)
Number of clinical seizures at *Preimplant Baseline,* median (range)	11 (0-338)
Number of AEDs at enrollment, mean ± SD (range)	2.9 ± 1.2 (1-8)
Female, % (n/N)	46% (61/132)

Phase 2 trial example published in 2020 (Cenobamate)*

Clinical characteristic	Study Drug	Placebo
Age, mean (range)	36 (18-61)	38 (18-59)
Median time since diagnosis, years (range)	20 (2-53)	21 (2-61)
Number of seizures at Baseline, median (range)	7.5 (0,187)	5.5 (2, 237)
Number of AEDs at enrollment, mean (range)	2.19 (1-3)	2.3 (1-3)
Female, % (n/N)	51% (58/113)	47% (51/109)

* Patient demographic information for a Phase 2 trial of cenobamate in patients with uncontrolled focal (partial-onset) seizures is provided for informational purposes only and does not purport to reflect the actual or potential patient demographics of any of the Company's Phase 1 clinical trials or any planned Phase 2 clinical trials.

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Skarpaas et al., Epilepsy and Behavior, 2018; Neurology, 2020

Focal epilepsy PoC model comparison

Ideal Model	RNS	Photosensitivity (PPR)	Transcranial Magnetic Stimulation (TMS)
Uses focal epilepsy patient population	✓ Yes	✗ No	✗ No
Recognized seizure biomarker	✓ Long episode reduction shown to predict clinical seizure reduction	✗ Generalized photoparoxysmal EEG responses	✗ TMS-evoked EEG potentials (TEPs)
Obtains data on effect size	✓ Measures drug effect on FOS biomarker of focal onset seizure	? Measures evoked generalized epileptiform discharges	? Measures provoked cortical hyperexcitability in normal healthy volunteers
Informs dose selection for registrational trials	✓ PK/PD data will allow direct measure of degree of efficacy at different exposure levels	? Indirect dose response readout for non-FOS seizure	? Indirect dose response readout of cortical hyperexcitability in HNV
Enables rapid progression into registrational trial	✓ Expect translatable data that can inform dose and effect size for future registrational trials	? Does not provide dosing or effect size for FOS registration trials	? Does not provide dosing or effect size for FOS registration trials

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Source: Porter et al. (2016); Biondi et al. (2022)

RAP-219 overview

A. Mechanism of action and preclinical development
B. Phase 1 SAD/MAD trials
C. Phase 2a proof-of-concept trial in focal epilepsy
D. **RAP-219 in peripheral neuropathic pain and bipolar disorder**

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Chronic peripheral neuropathic pain

Strong mechanistic and compelling preclinical data for RAP-219

Peripheral neuropathic pain

- Diagnosed prevalence of ~5.6 million[1] in the U.S.
- Conditions include painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, and idiopathic sensory polyneuropathy
- Caused by injury or dysfunction of peripheral nerves → CNS maladaptive changes
- Significant unmet need for new drugs with:
  - Novel MOA
  - Once per day dosing
  - Improved tolerability
  - Minimal or no drug-drug interactions
  - No abuse or cardiovascular liabilities

Rationale for RAP-219

- TARPγ8 is expressed in areas of the CNS associated with pain
  - Spinal cord dorsal horn, where the sensation of pain (nociception) enters the CNS
  - The anterior cingulate cortex, where the affective or emotional aspects of pain resides
- Positive results observed in multiple animal models of pain, including neuropathic pain

Phase 2a trial in peripheral neuropathic pain expected to be initiated in 2H 2024

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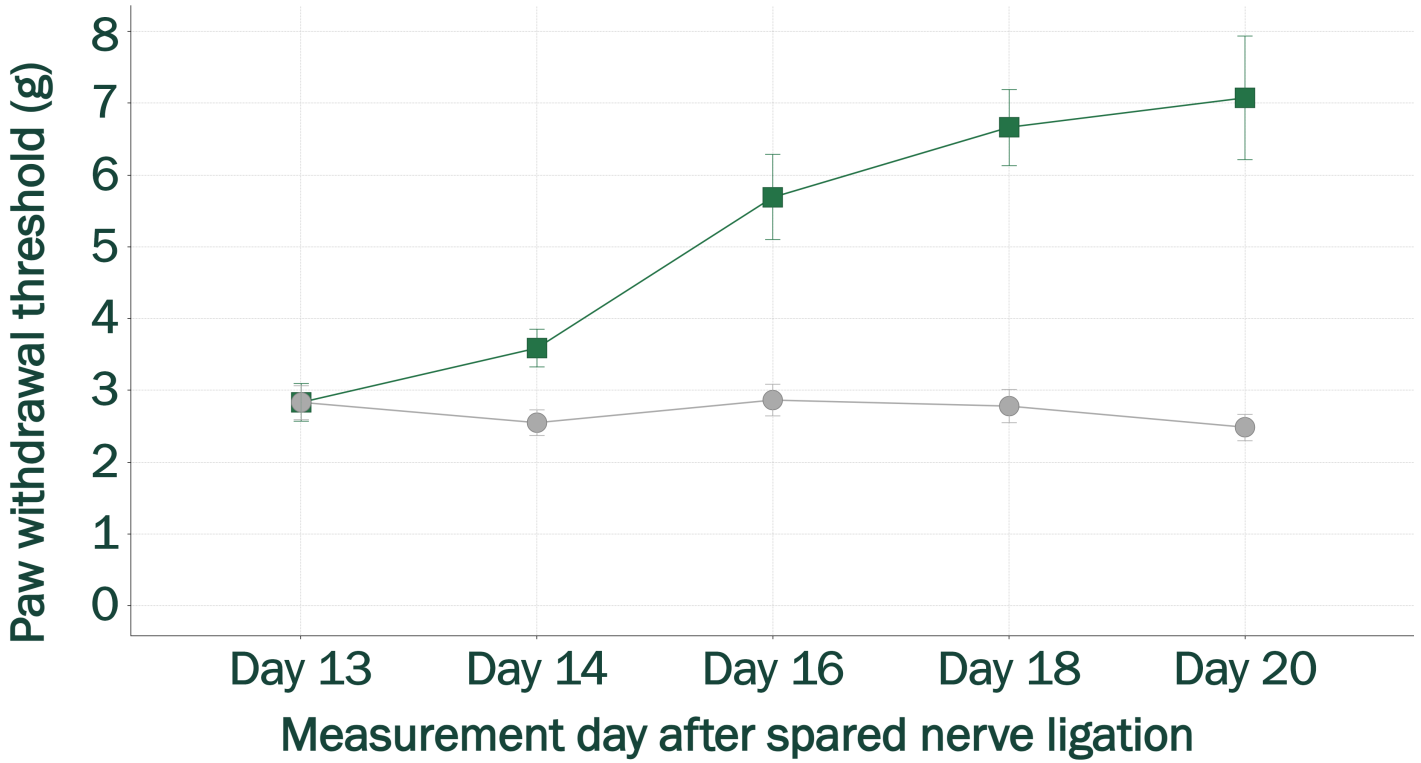
[1]Diagnosed prevalence across diabetic peripheral neuropathy (~2.8 million), post-herpetic neuralgia (~1.8 million), and trigeminal neuralgia (~1.0 million).

Preclinical evidence supporting RAP-219 in chronic pain

Study of RTX-1738, TARPγ8 NAM (RAP-219 analog)

RTX-1738 attenuates tactile allodynia in spinal nerve ligation (SNL) rat model

Starting on Day 16 (third day of dosing) and continuing through Day 20, paw withdrawal thresholds were elevated, reflecting decreased pain behavior



*p<0.001 RTX-1738 vs. Vehicle group by two-way ANOVA followed by Dunnett's Multiple Comparison Test (n=10)

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Bipolar disorder acute mania

Strong mechanistic data for RAP-219

Bipolar disorder

- Affects 2.8 percent of the adult population in the US (approximately 7 million adults)
- Extreme shifts in mood – “manic-depressive”
- Manic episodes characterized by feelings of over-excitement, irritability, impulsivity, grandiose beliefs and racing thoughts
- Typically treated with antipsychotic medications as either monotherapy or in combination therapy with mood stabilizers
- Drug treatments often poorly tolerated with safety risks

Rationale for RAP-219

- Bipolar disorder is associated with hyperactivity in the hippocampus, where TARPγ8 is enriched
- Bipolar risk alleles overrepresented in genes encoding synaptic signaling proteins with high specificity of expression in neurons of the prefrontal cortex and hippocampus
- Other ASMs (such as valproate, lamotrigine, and carbamazepine) are FDA approved to treat bipolar disorder
- The corneal kindling model of epilepsy is believed by some experts to be predictive of bipolar treatments

Phase 2a trial in bipolar disorder patients with acute mania expected to be initiated in 2025

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Ongoing research of RAP-219 to inform future development

MAD 2 & PET studies to evaluate escalation pace and receptor occupancy

RAP-219-104 (MAD Trial 2)

- Objective: Assess dosing regimens that may enable reaching therapeutic exposure more quickly
- Double-blind, placebo controlled
- Two cohorts with option to add up to three additional cohorts
- Results expected 2H 2024, which will help determine dosing for Phase 2a in bipolar disorder

Positron Emission Tomography (PET) Trial

- Objective: Confirm human brain target receptor occupancy across a range of RAP-219 dosing and exposure levels
- Results expected 1H 2025

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nAChR discovery programs

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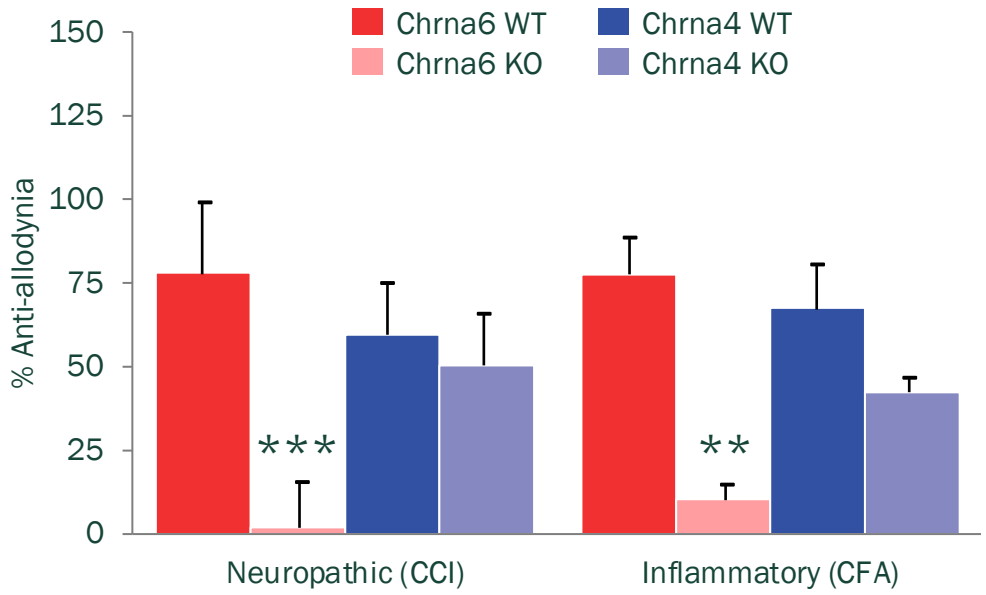
α6 nAChR program

Preclinically-validated approach to neuropathic pain

- nAChR agonists have been observed to be efficacious in third-party preclinical and clinical neuropathic pain studies; preclinical evidence in acute, inflammatory, and neuropathic pain
- Abbott's pan-nAChR agonist demonstrated significant improvements in patients with diabetic neuropathic pain, but up to 66% of patients withdrew from the trial due to AEs such as nausea, dizziness, vomiting, abnormal dreams, and asthenia
- Evidence shows that α6 is a potential target for chronic pain



Genetic knockout (KO) mice demonstrate requirement of α6- but not α4-containing nicotinic receptors for anti-allodynia mediated by intrathecal nicotine administration

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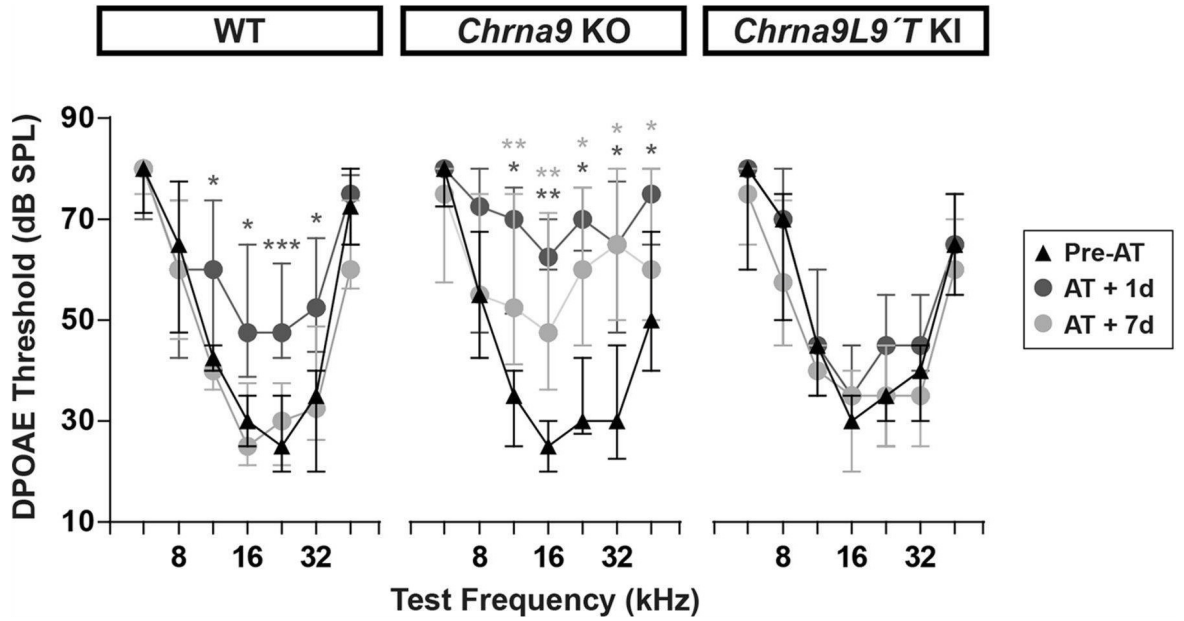
www.ScienceTranslationalMedicine.org 13 May 2015 Vol 7 Issue 287 287ra72

α9α10 nAChR program

Potential for first-in-class approach to hearing disorders

- Potential for α9α10 nAChRs in hearing disorders demonstrated in preclinical studies
- Engagement of α9α10 has been observed to mitigate hearing loss in preclinical models
- Our RAP platform technology enabled Rapport to identify potentially first-in-class orally-delivered agonists that are selective for α9α10 nAChRs



- (Left) Auditory brainstem responses (ABRs) are elevated at 1 day but not at 7 days following acoustic trauma (AT).
- (Middle) α9 KO elevates ABR thresholds at 1 and 7 days after acoustic trauma.
- (Right) α9 gain of function knock-in (L9'T KI) completely prevents acoustic trauma hearing deficits.

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PNAS 2020 117: 11811-9

Rapport Therapeutics: Charting new paths in neuroscience with groundbreaking precision design

Experienced leadership

Proven track record of building companies, novel therapies, and development platforms

Proprietary program

Pioneered discoveries of receptor associated proteins (RAPs); IP expiration in 2036 + potential PTE

Neuroanatomical specificity

Technology designed to create precisely targeted neuromedicines, potentially overcoming limitations of conventional treatments

Lead asset in clinical development for treatment of focal epilepsy

Data support initiating Phase 2a proof-of-concept trial for RAP-219

Therapeutic potential across multiple indications

Significant markets, including epilepsy, peripheral neuropathic pain, and bipolar disorder

Steady cadence of milestones anticipated

Robust clinical and discovery pipeline with multiple anticipated upcoming milestones

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Thank you