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Corporate overview

March 2025

Disclaimer

This presentation contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, each as amended. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, but are not limited to, express or implied statements regarding: the clinical development of RAP-219 for the treatment of drug-resistant focal epilepsy, peripheral neuropathic pain and bipolar disorder, including the initiation, timing, progress and results of our ongoing and planned clinical trials; Rapport's ability to resolve a clinical hold with the FDA; the potential activity and tolerability of RAP-219; the potential of Rapport's RAP technology platform; the ongoing and planned development of RAP-199 and Rapport's discovery-stage programs; and expectations for Rapport's uses of capital, expenses and financial results, including its cash runway through the end of 2026.

Forward looking statements are based on management's current expectations and are subject to risks and uncertainties that could negatively affect Rapport's business, operating results, financial condition and stock value. Factors that could cause actual results to differ materially from those currently anticipated include: risks relating to Rapport's research and development activities; Rapport's ability to execute on its strategy including obtaining the requisite regulatory approvals on the expected timeline, if at all; uncertainties relating to preclinical and clinical development activities; Rapport's dependence on third parties to conduct clinical trials, manufacture its product candidates and develop and commercialize its product candidates, if approved; Rapport's ability to attract, integrate and retain key personnel; risks related to Rapport's financial condition and need for substantial additional funds in order to complete development activities and commercialize a product candidate, if approved; risks related to regulatory developments and approval processes of the U.S. Food and Drug Administration and comparable foreign regulatory authorities; risks related to establishing and maintaining Rapport's intellectual property protections; and risks related to the competitive landscape for Rapport's product candidates; as well as other risks described in "Risk Factors," in Rapport's Registration Statement on Form S-1 and most recent Quarterly Report on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in Rapport's subsequent filings with the Securities and Exchange Commission. Rapport expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in its expectations or any changes in events, conditions or circumstances on which any such statement is based, except as required by law, and claims the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

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Leadership with track record of innovation and expertise

Management Team

David Bredt, M.D., Ph.D.
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

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

Jeff Sevigny, M.D.
Chief Medical Officer
15+ years translational and clinical drug development

Lilly Prevail THERAPEUTICS Biogen
NOVARTIS MERCK

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.
Founder and Board Chair
Partner, Third Rock Ventures

James Healy, M.D., Ph.D.
Director
Managing Partner, Sofinnova Investments

Reid Huber, Ph.D.
Director
Partner, Third Rock Ventures; CEO, Merida Biosciences

John Maraganore, Ph.D.
Director
Former Founding CEO, Alnylam

Robert Perez
Director
Operating Partner, General Atlantic
Former CEO, Cubist Pharmaceuticals
Founder and Chairman, Life Science Cares

Raymond Sanchez, M.D.
Director
Senior Advisor, Bain Life Sciences; Former CMO, Cerevel Therapeutics

Paul Silva
Director
Former Chief Accounting Officer, Vertex Pharmaceuticals

Wendy Young, Ph.D.
Director
Former Head of Small Molecule Drug Discovery, Genentech

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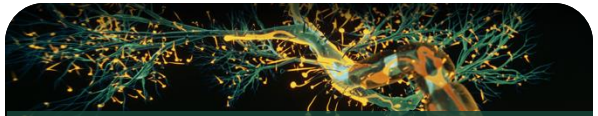
[1]Employee director

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

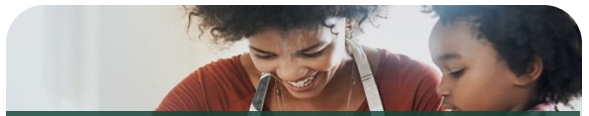
Janssen Neuroscience
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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



Well financed

$305.3 million as of December 31, 2024[2]

Cash runway expected to fund operations **through end of 2026**, including multiple development catalysts

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[1]AMPAR α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors
[2]Includes cash, cash equivalents, and short-term investments, excluding restricted cash

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
RAP-219 TARPγ8 AMPAR Programs	*Refractory Focal Epilepsy*	Trial Underway					Topline Results Q3 2025
	Bipolar Mania						Trial Initiation Q3 2025 Topline Results 1H 2027
	Diabetic Peripheral Neuropathic Pain						Trial Initiation*
nAChR Discovery Programs	*α6* *Chronic Pain*						Development Candidate
	α9α10 *Hearing Disorders*						Development Candidate

Strong intellectual property with worldwide rights to all programs

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

*Subject to resolution of clinical hold with the FDA

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

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

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

Compelling data supporting potential in peripheral neuropathic pain and bipolar disorder

Long acting injectable (LAI) opportunity

Potency and metabolic profile positions RAP-219 as the first potential ASM in a depot formulation

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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

A. Mechanism of action and preclinical development
B. Phase 1 trials
C. Phase 2a proof-of-concept trial in refractory focal epilepsy
D. Bipolar mania and diabetic peripheral neuropathic pain

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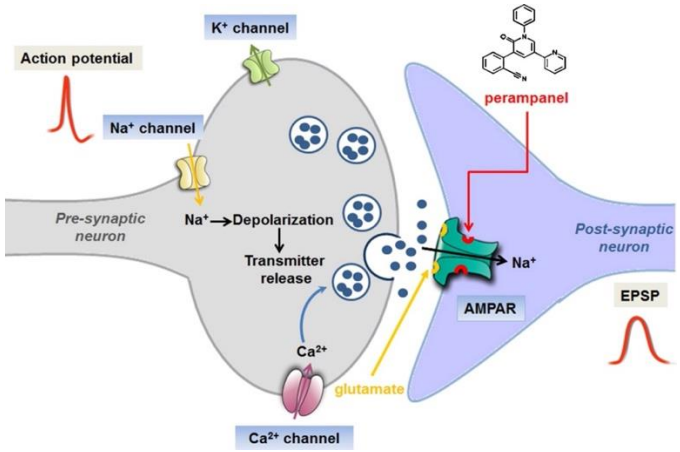
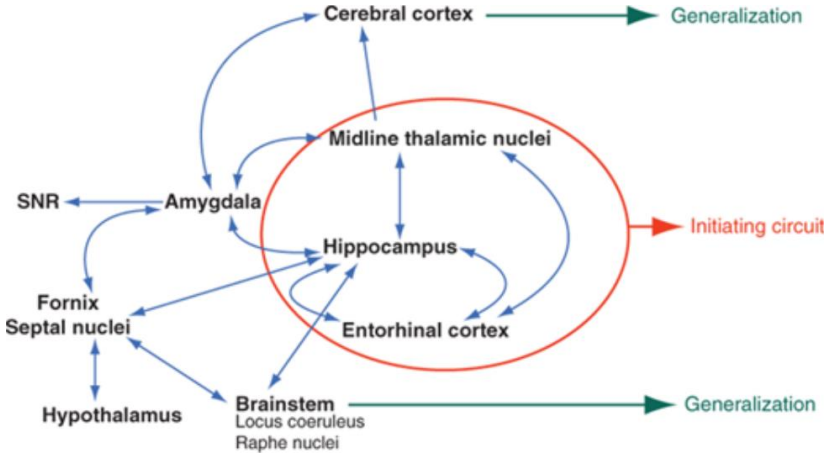
AMPAR inhibition is a clinically validated approach for epilepsy

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

- Approximately 50% of all focal onset seizures originate in the mesial temporal lobe, which includes the hippocampus and amygdala
- Most of the remaining 50% originate in the cerebral neocortex and often spread into and are propagated by the mesial temporal structures

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Transmembrane AMPA regulatory proteins (TARPs)

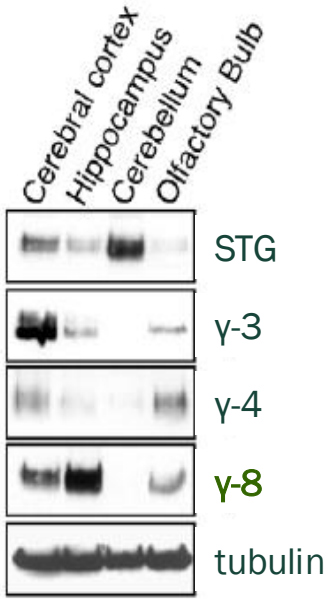
TARPs: Auxiliary subunits that associate with AMPA receptors in the brain
Crucial for regulating the trafficking, subcellular localization and gating of AMPA receptors

Cryogenic electron microscopy of GluA1/2 + TARPγ8 complex

GluA1
GluA2
TARPγ8

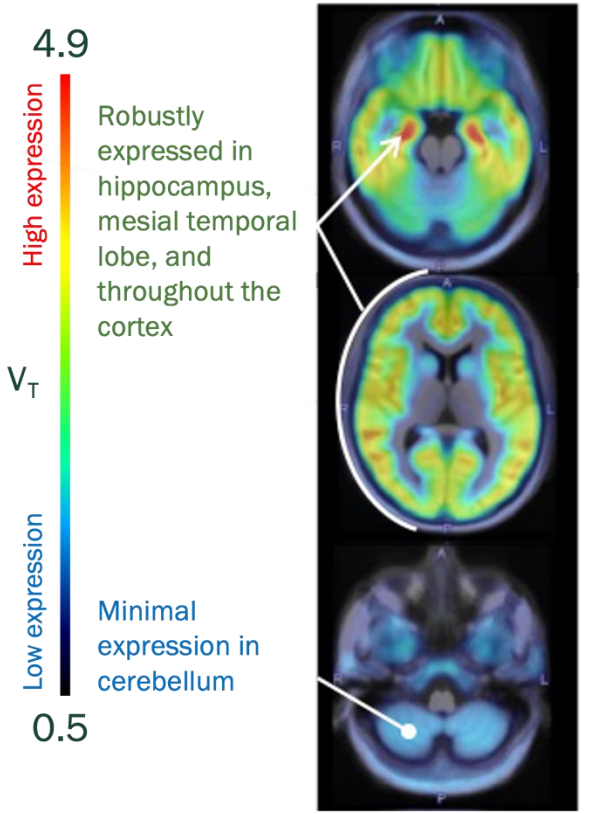
NatComm 2022 13:734

Western Blot



JCB 2003 161:805

TARPγ8 clinical PET



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RAP-219 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

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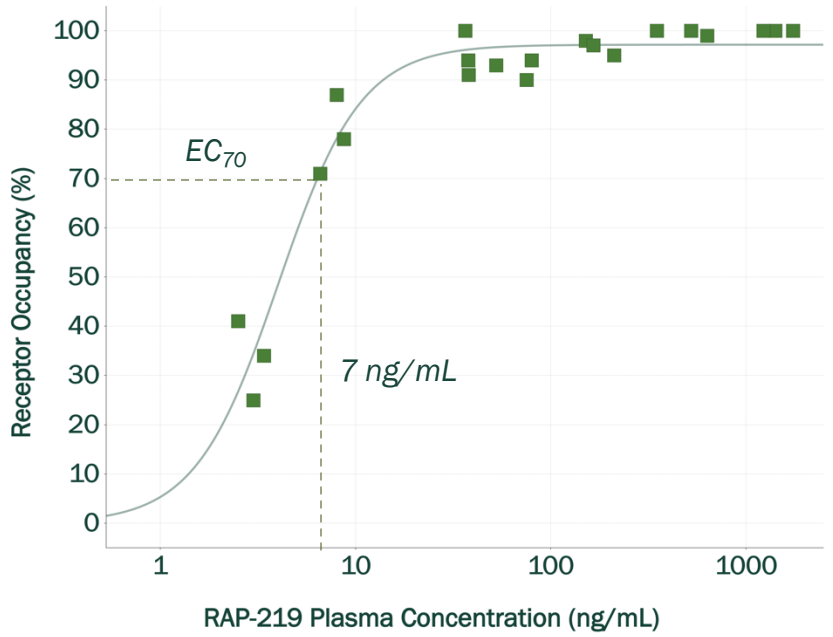
NAM = Negative allosteric modulator

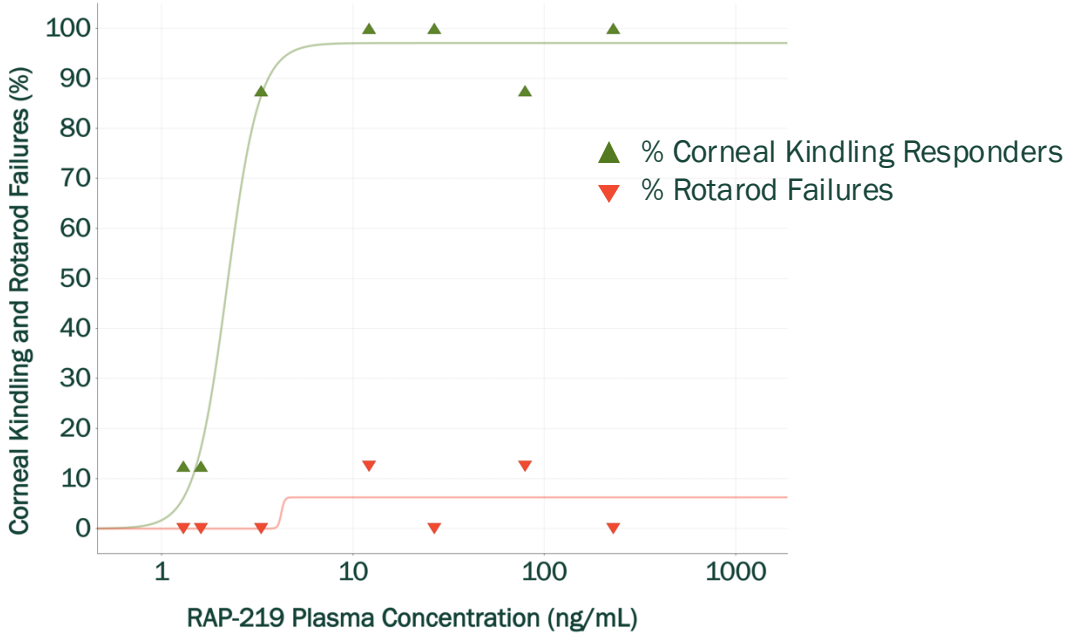
Differentiated precision preclinical profile of RAP-219

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 (RO)
- No motoric impairments observed at highest doses tested

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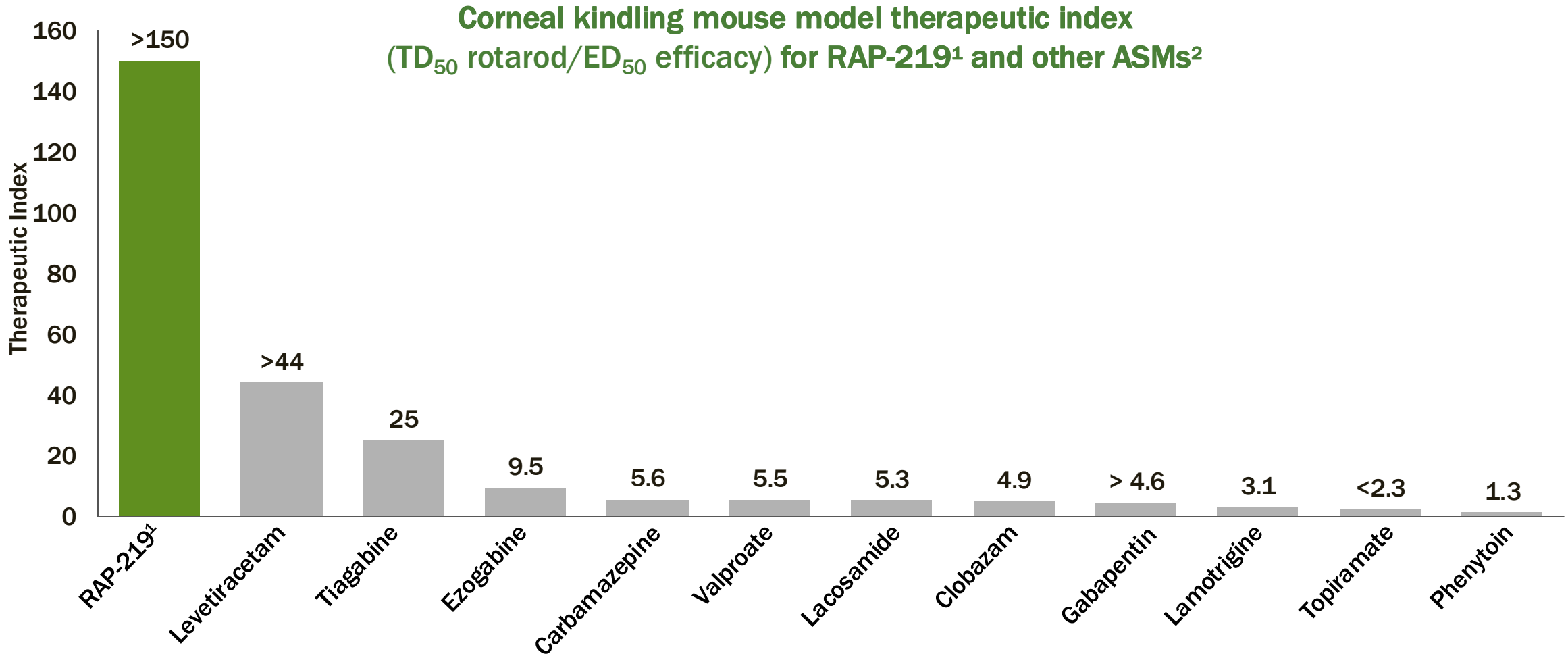
EC_{70} = effective concentration achieving 70% occupancy of target receptor

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



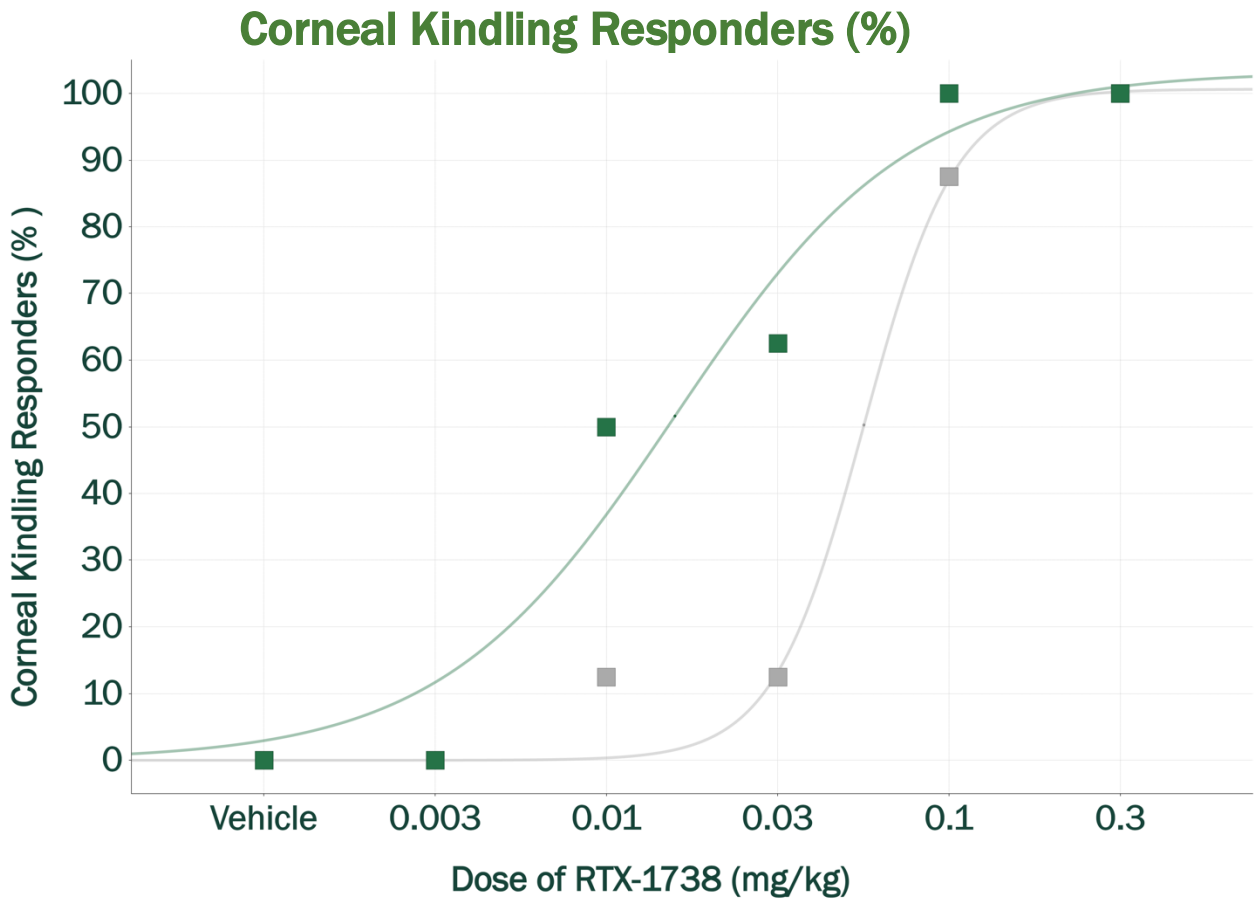
Therapeutic Index = TD_{50} (toxic dose) on Rotarod/ED_{50} (effective dose) for efficacy

[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

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 trials
C. Phase 2a proof-of-concept trial in refractory focal epilepsy
D. Bipolar mania and diabetic peripheral neuropathic pain

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RAP-219 first-in-human Phase 1 trials

PET receptor occupancy trial (RAP-219-103)

- Open label, multiple dose trial in healthy volunteers
- Objective: confirm neuroanatomical expression of TARPγ8 and establish relationship between PK and brain target receptor occupancy (RO)
- 3 cohorts, n=3-6 per cohort
- 0.25 mg QD to 1.25 mg QD doses; over 14 days

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

- Randomized, double-blind, placebo-controlled SAD and open label food effect study
- Objective: evaluate safety and tolerability
- 5 cohorts, n=8 per cohort (6 active & 2 placebo)
- 0.25 mg QD to 3 mg QD doses

Multiple ascending dose trial (MAD-1) (RAP-219-102)

- Randomized, double-blind, placebo-controlled MAD
- Objective: evaluate safety and tolerability with dose escalation
- 5 cohorts, n=8 per cohort (6 active & 2 placebo)
- Up to 1.25 mg QD doses; over 2 to 4 weeks

Multiple ascending dose trial (MAD-2) (RAP-219-104)

- Randomized, double-blind, placebo-controlled MAD
- Objective: evaluate safety and tolerability with continued dose escalation and shorten time to reach predicted therapeutic levels
- 3 cohorts, n=8 per cohort (6 active & 2 placebo)
- Up to 1.75 mg QD doses; up to 28 days

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RAP-219 Phase 1 experience

100 healthy volunteers exposed to RAP-219

Data underscore the potential broad therapeutic index, differentiated tolerability profile, and dosing flexibility of RAP-219

RAP-219 tolerability

- RAP-219 was generally well tolerated with no SAE's and no TEAEs greater than Grade 2
- Three treatment discontinuations occurred (3%) that were attributed to TEAEs, none of which were greater than Grade 2
- No clinically significant laboratory, electrocardiogram (ECG), or vital sign abnormalities were reported in the SAD or two MAD trials
- Among the 48 participants exposed to RAP-219 in the two MAD trials, the most common TEAEs were headache (n=5), sinus tachycardia (n=4), and brain fog, insomnia, bowel movement irregularity, dry mouth, and medical device site reaction (n=3 each). Among the 16 participants exposed to placebo, the most common TEAEs were abdominal pain, brain fog, constipation, cough, decreased appetite, dizziness, medical device site reaction, and second-degree atrioventricular block (n=1 each)
- While the final study report is in progress, PET trial TEAEs are generally consistent with other Phase 1 trials

RAP-219 receptor occupancy

- PET trial confirmed restricted neuroanatomical expression of TARPγ8
- RAP-219 achieved and exceeded target RO associated with maximal efficacy in preclinical models (50%-70%), while maintaining a differentiated tolerability profile
- Target RO can be achieved within five days of dosing

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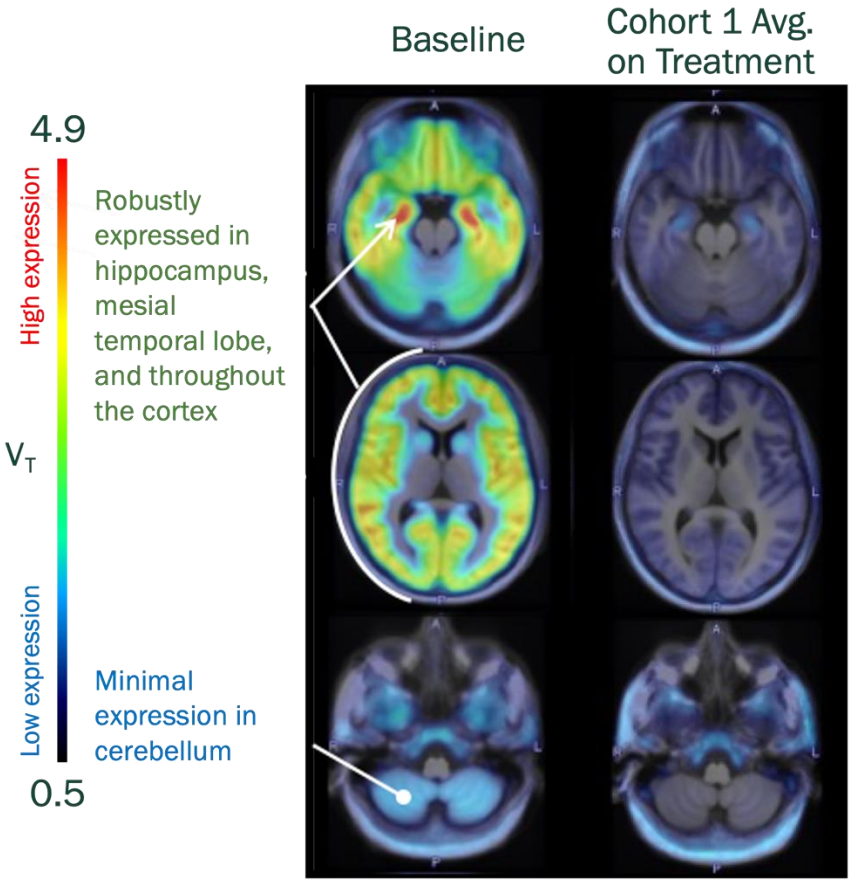
SAE = Serious adverse event; TEAE = Treatment emergent adverse events; ECG= electrocardiogram

RAP-219 Phase 1: PET trial results

RAP-219 achieved and exceeded target RO and was generally well tolerated
Restricted neuroanatomical expression of TARPγ8 was confirmed

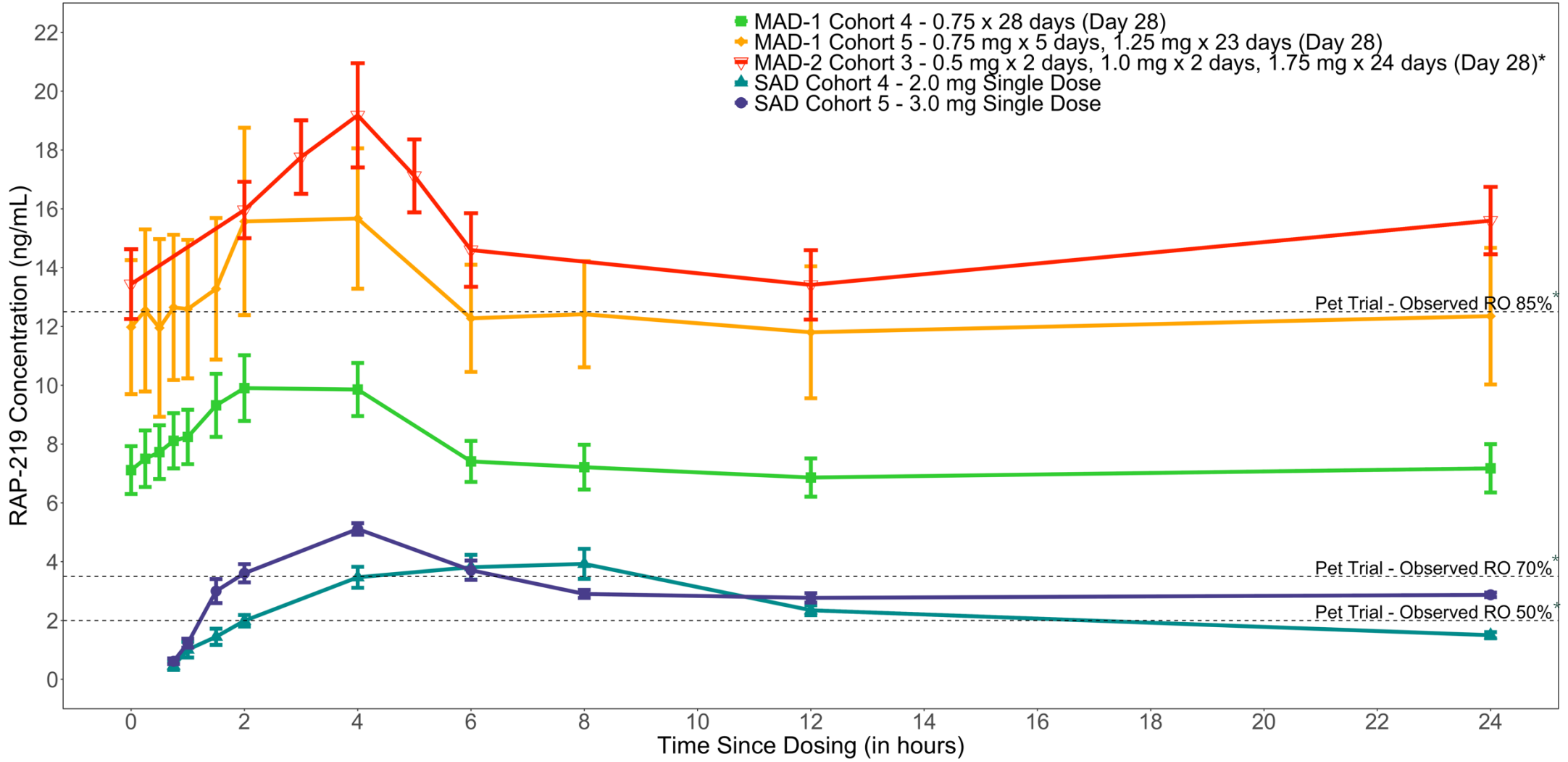
- TARPγ8-containing AMPA receptors were enriched in the hippocampus and neocortex, and expression was minimal in the cerebellum and brain stem
- Cohort 1 (Phase 2a focal epilepsy trial dosing regimen) exceeded the target RO range associated with maximal efficacy in preclinical models (50%-70%) while maintaining tolerability
- Collectively, PET and MAD-2 trials demonstrated that target plasma concentrations and associated RO could be achieved within 5 days

TARPγ8 clinical PET



Note: Results are based on preliminary analysis of the data. Clinical conduct of the PET and MAD-2 trials is complete, and the clinical study reports for both are in progress.

RAP-219 Phase 1: SAD vs. MAD exposures



*Pending finalization

RAP-219 Phase 1: MAD-1 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 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

Dose in 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 was 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
Generally well tolerated	No treatment related TEAEs above Grade 2 in Phase 1 trials
Potential for greater therapeutic index	Target RO achieved and exceeded while maintaining differentiated tolerability profile
Convenient administration	QD, single step-up dosing

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RAP-219 overview

A. Mechanism of action and preclinical development
B. Phase 1 trials
C. **Phase 2a proof-of-concept trial in refractory focal epilepsy**
D. Bipolar mania and diabetic peripheral neuropathic pain

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

Key design considerations

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

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

iEEG-recorded clinical seizure biomarker used to evaluate efficacy

Principal investigator

Jacqueline French, M.D.
Professor, Neurology
NYU Grossman School of Medicine

Trial overview

- Multi-center open-label trial
- Approximately 20 adult drug-resistant focal epilepsy patients
- MAD-1 Cohort 5/PET Cohort 1 dose: 0.75 mg/day for 5 days followed by 1.25 mg/day

RNS System

- FDA-approved implantable device continually monitors and records seizure activity (intracranial EEG) in patients with FOS
- RNS system patients (>6,500 patients in the U.S.[1]) are demographically similar to those enrolled in a third-party registrational FOS study[2] (duration of epilepsy, # of seizures, # of ASMs)

Phase 2a trial ongoing; topline results expected in Q3 2025

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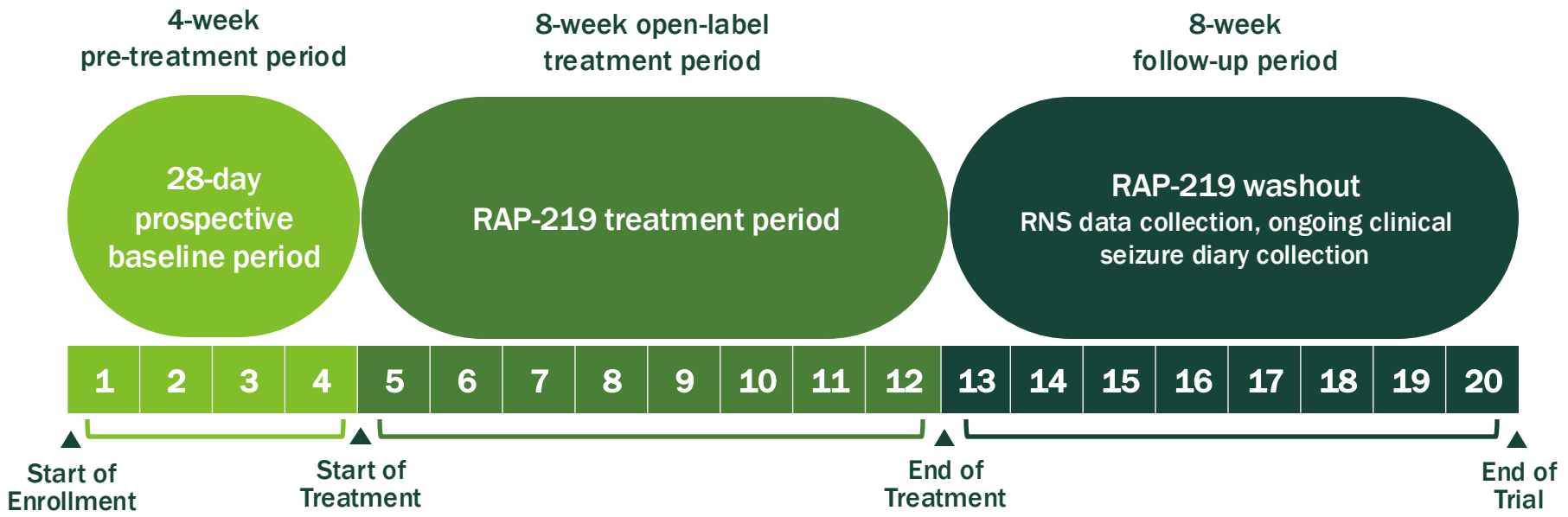
[1]Source: NeuroPace, January 2025
[2]Based on a comparison of NeuroPace's long-term treatment retrospective study and a Phase 2 trial example published in 2020. Example Phase 2 trial patient demographic information does not include patients with the RNS system implanted, nor purport to reflect the actual or potential patient demographics of any of the Company's Phase 1 clinical trials or any planned Phase 2 clinical trials.

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

Eligibility criteria review
Including review of 8 weeks of retrospective RNS system data

[estimated time: 1-2 weeks]

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

Key endpoints:

- Change in LE frequency on treatment compared to baseline
- LE frequency responder analysis (% of patients that demonstrate ≥30% reduction in LEs)
- Change in estimated electrographic seizure frequency, CS frequency, and additional iEEG biomarkers
- Clinically meaningful improvements in global ratings (PGIC/CGIC)

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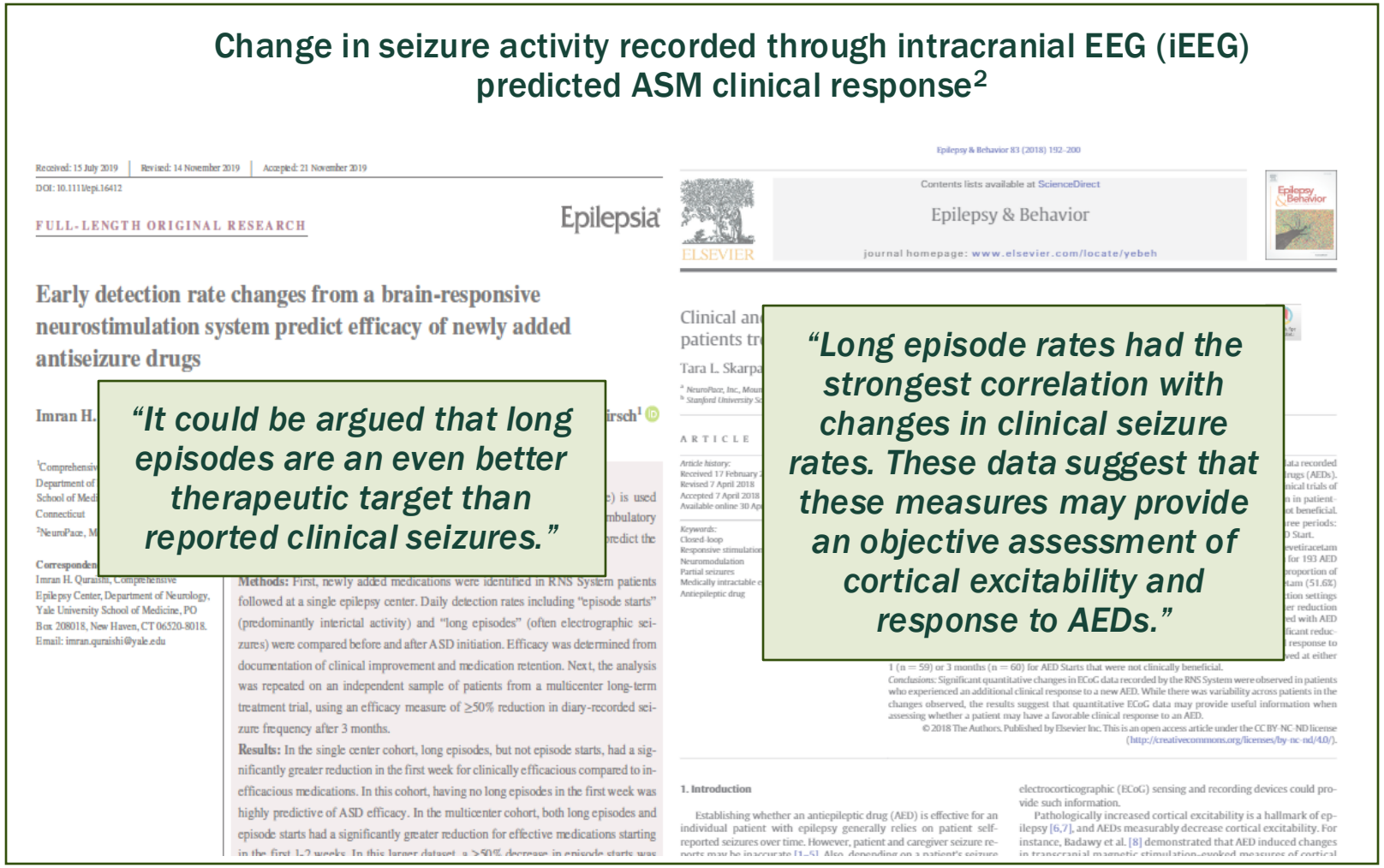
Source: Porter et al. (2016); Biondi et al. (2022)

Long episodes (LEs)

Objective and translatable biomarker for clinical seizure frequency

- RNS[1] detects a biomarker of clinical seizures – long episodes (LEs), which are considered subclinical seizures
- LEs are runs of ictal or interictal epileptiform activity exceeding a specified duration (typically 30 seconds)
- LEs avoid common seizure diary challenges -- memory impairments, nocturnal or amnesic seizures, and inaccurate reporting
- All Phase 2a FOS study patients must have a high correlation between their LEs and electrographic seizures

Change in seizure activity recorded through intracranial EEG (iEEG) predicted ASM clinical response[2]



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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.

"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 an
patients tr

Tara L. Skarpa

ARTICLE

"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."

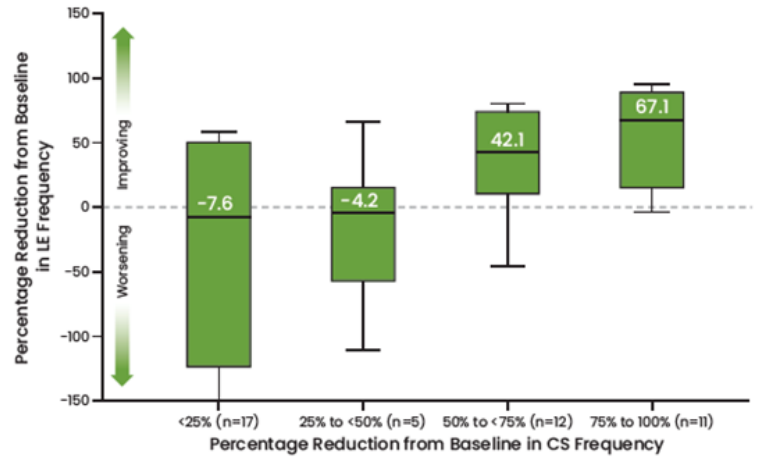
[1]The RNS system is also a therapeutic device for adults with drug-resistant focal epilepsy
[2]Epilepsy & Behavior. 2018; 83: 192-200; Epilepsia. 2020; 61:138-148.

Optimal cut point for reduction in LE frequency to predict meaningful change in CS frequency

- A 30% reduction in LEs was associated with a 50% or greater reduction in CS in a post-hoc analysis, regardless of the antiseizure medication initiated
- High positive predictive value -- LEs correlate with patient diary-reported seizures and CS are always associated with the presence of LEs
- High negative predictive value -- the absence of a LE indicates that no epileptic seizure occurred

LE & CS exhibit linear relationship (i.e. move in the same direction)

Percentage of LE Frequency Reduction by CS Responder Group



A ≥30% reduction in LE frequency correlates with a ≥50% reduction in CS

Clinical Seizure Reduction & Correlated LE Frequency Reduction

CS frequency reduction	AUC	Reduction cut point in LE frequency (%)	Sensitivity (%)	Specificity (%)	Positive predictive ability[a]
≥25%	0.725	25.6	64.3	64.7	64.4
≥50%[b]	0.765	**30.0**	69.6	68.2	68.9
≥75%[c]	0.735	49.6	63.6	64.7	64.4

Source: Gammaitoni et al, American Epilepsy Society (AES) 2024 Annual Meeting, Poster #1.494

RAP-219 overview

A. Mechanism of action and preclinical development
B. Phase 1 SAD/MAD trials
C. Phase 2a proof-of-concept trial in refractory focal epilepsy
D. **Bipolar mania and diabetic peripheral neuropathic pain**

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Bipolar mania

Strong mechanistic data for RAP-219

Bipolar disorder

- Diagnosed prevalence is ~2.8 percent of the adult population in the U.S. (~7 million adults)
- Condition is characterized extreme shifts in mood, referred to as “manic-depressive”
- Bipolar mania is 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 mania expected to be initiated in Q3 2025; topline results expected 1H 2027

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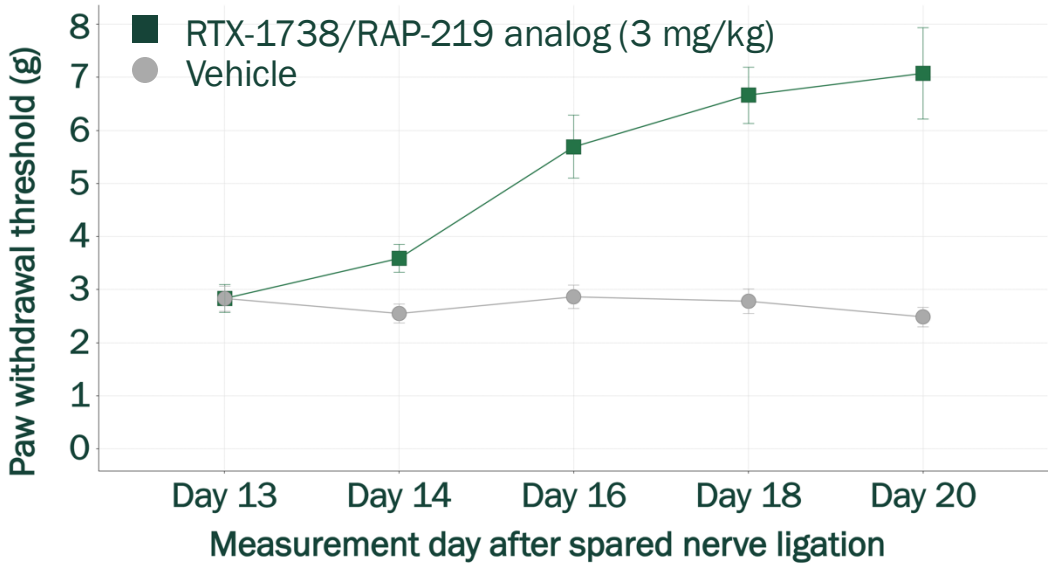
Diabetic peripheral neuropathic pain

Strong mechanistic and compelling preclinical data for RAP-219

- Diagnosed U.S. prevalence: ~5.6 million[1]
- Incl. diabetic peripheral neuropathic pain, postherpetic neuralgia, trigeminal neuralgia, and idiopathic sensory polyneuropathy
- Caused by injury or dysfunction of peripheral nerves
- 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
- TARPγ8 is expressed in the spinal cord dorsal horn, where the sensation of pain (nociception) enters the CNS, and the anterior cingulate cortex, where the affective or emotional aspects of pain resides

RTX-1738 (*TARPγ8 NAM/RAP-219 analog*) 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



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

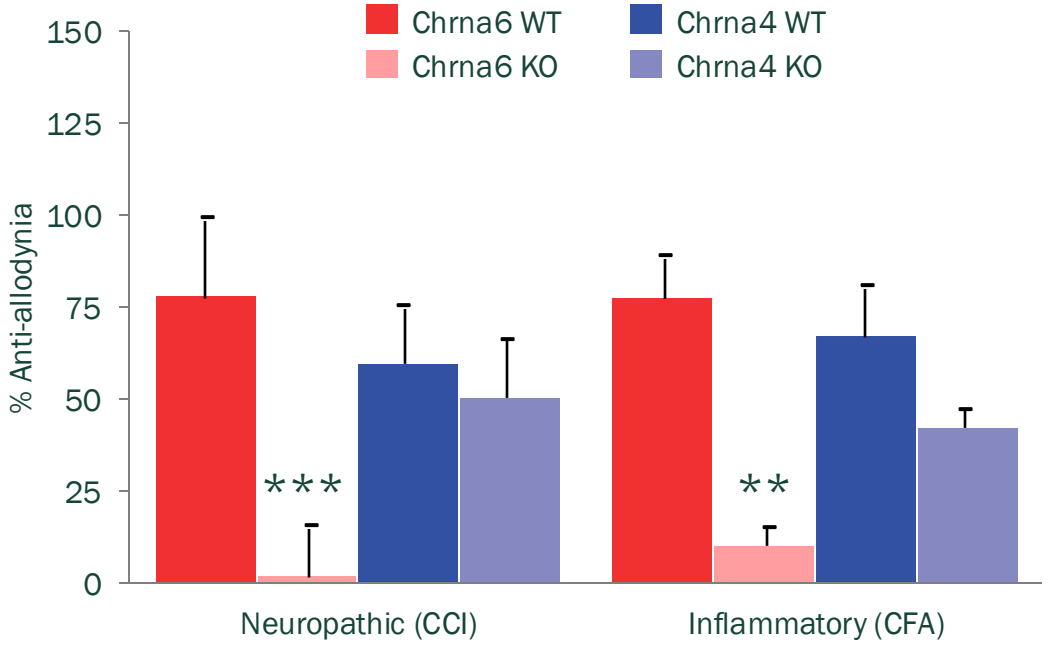
*p<0.001 RTX-1738 vs. Vehicle group by two-way ANOVA followed by Dunnett's Multiple Comparison Test (n=10)

nAChR discovery programs

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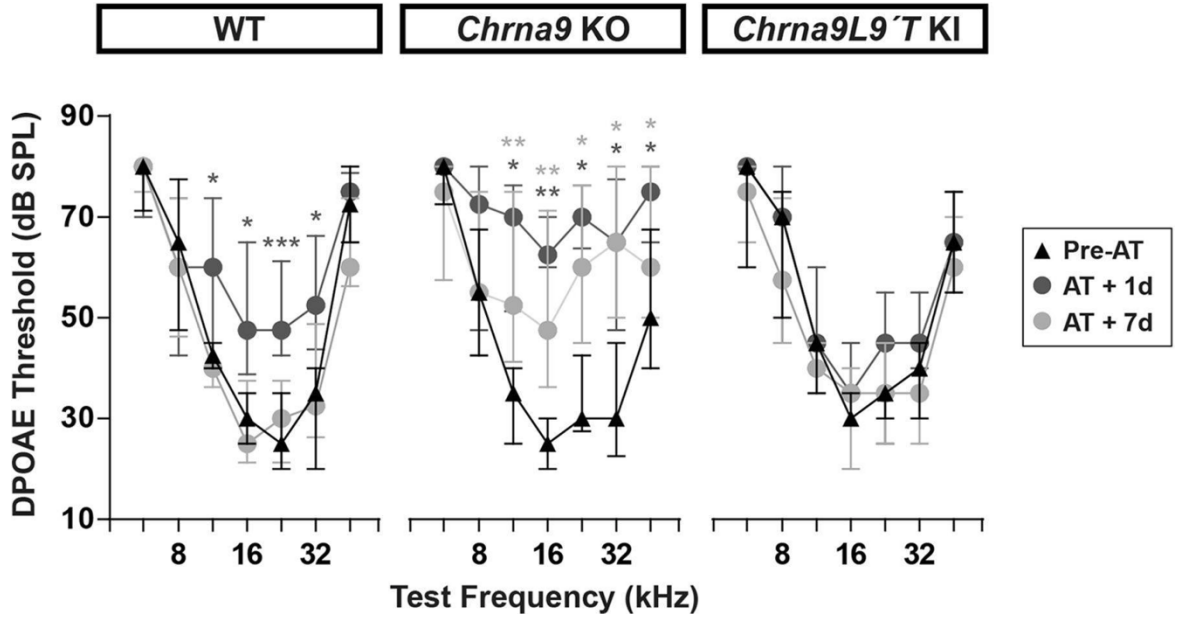
www.ScienceTranslationalMedicine.org 13 May 2015 Vol 7 Issue 287 287ra72

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

Experienced leadership

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

Proprietary program

Pioneered discoveries of 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 the treatment of refractory focal epilepsy

Data demonstrate RAP-219's potential to deliver transformative outcomes for patients

Therapeutic potential across multiple indications

Significant markets, including focal 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