

# Evolution of RAP-219 for the Treatment of Epilepsy

## 1990s through Early 2000s

An increase in  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors is identified in patients with epilepsy. AMPA receptors are found to be absent from cerebellar cells of stargazer mice but are still intact in the forebrain.

Stargazin ( $\gamma$ 2) is the first transmembrane AMPA receptor regulatory protein (TARP) discovered to interact with AMPA receptors.

### 2000s through 2020s

Additional work on receptor-associated proteins (RAPs) reveals that targeting a specific TARP subunit of AMPA receptors (eg, TARPy8) can selectively affect excitability initiated in the forebrain and therefore can be used to treat certain conditions while also avoiding some adverse events observed with nonselective AMPA receptor inhibitors.

### 2022

Rapport Pharmaceuticals launches as a biotechnology

## Purpose for Development

• There is an unmet need for precision-targeted therapies for epilepsy that offer novel mechanisms of action, deliver optimal efficacy with an improved safety and tolerability profile, and provide a differentiated profile with the potential to shift the treatment paradigm

## **AMPA Receptors**

• α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are glutamate-gated ion channels that primarily mediate excitatory signaling in the central nervous system (CNS)<sup>1,2</sup>

- Hippocampal AMPA receptor subunit mRNAs and their proteins were increased in brain tissue of autopsied patients with epilepsy compared with autopsied patients who did not have seizures<sup>3</sup>
- AMPA receptor inhibition or negative modulation has been studied in various neurological and psychiatric conditions, including epilepsy, pain, and disorders associated with cognitive deficits<sup>4-6</sup>

• Transmembrane AMPA receptor regulatory proteins (TARPs), which include stargazin (γ2), γ3, γ4, and γ8, mediate surface expression of AMPA receptors<sup>7</sup>

- The first TARP discovered to interact with AMPA receptors was stargazin  $(\gamma 2)^1$
- Stargazer mutant mice exhibit seizures and cerebellar ataxia, attributed to a lack of functional surface AMPA receptors<sup>1,7-9</sup>

- However, AMPA receptors in the stargazer mouse forebrain neurons were intact,<sup>7</sup> indicating specificity by isoform to brain regions

- David S. Bredt, MD, PhD, and Professor Roger A. Nicoll, MD, recognized that stargazin and related TARPs regulate the synaptic targeting, gating, and pharmacology of AMPA receptors
- TARPs increase the trafficking of AMPA receptors to both the plasma membrane and synapses<sup>5</sup>
- TARP isoforms are generally expressed in distinct yet overlapping patterns in the brain<sup>4,10</sup>



David S. Bredt, MD, PhD



Professor Roger A. Nicoll, MD



Steve Paul, MD

## Targeting TARPy8

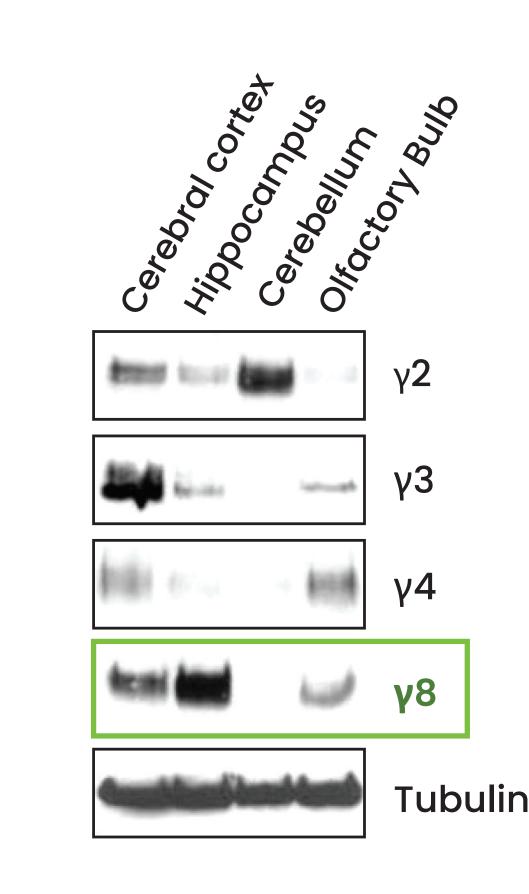
#### TARPy8 Expression

- High expression in the neocortex and mesial temporal lobe, the brain regions where seizures originate and propagate<sup>4,7,10,11</sup> (Figure 1A)
- AMPA receptors are selectively depleted in the hippocampus of TARPγ8 knock-out (KO) mice<sup>11</sup>
- The hippocampus and cortex are important sites of focal onset seizure (FOS) generation
- There is minimal TARPy8 expression in the hindbrain or midbrain

#### TARPy8 Function

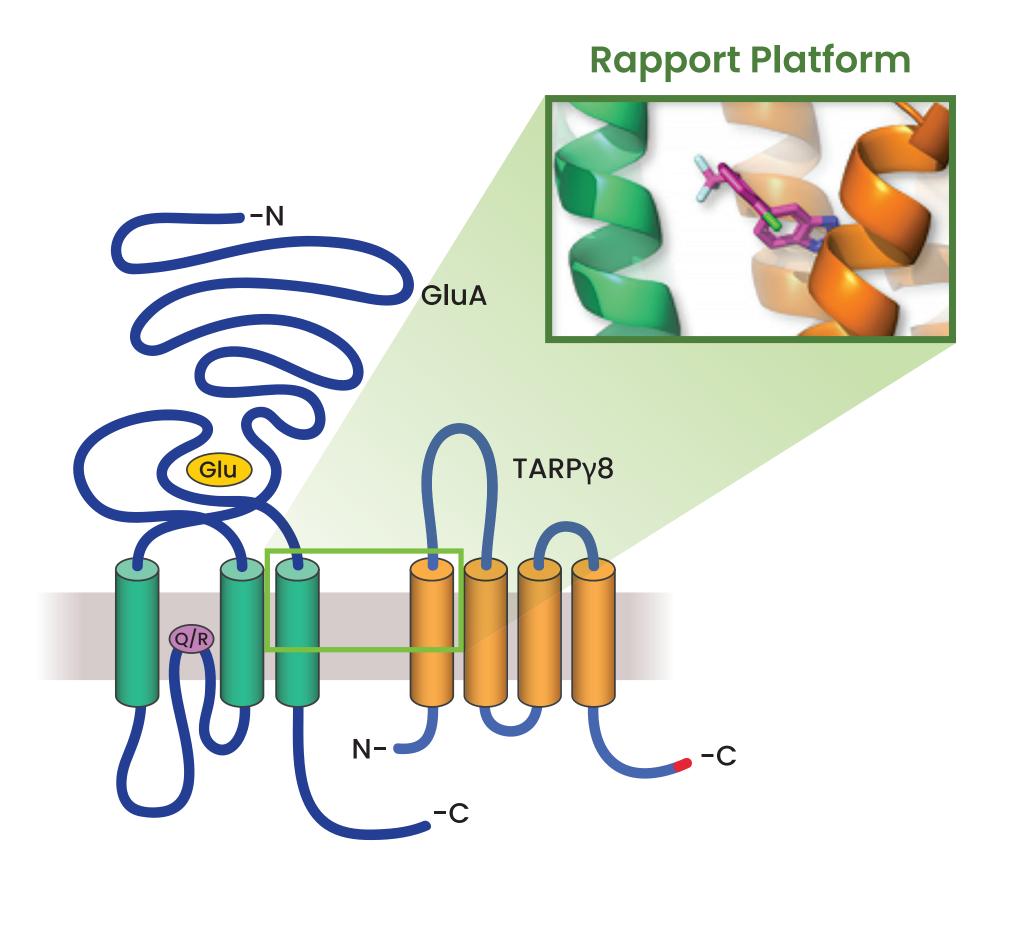
- Regulates AMPA receptor levels and extrasynaptic surface expression, which plays a key role in long-term potentiation 1
- Has long-range effects on the receptors, even though interactions are primarily seen in transmembrane segments and the ligandbinding domain<sup>12</sup>
- AMPA receptor resensitization, a gating characteristic, is also seen with TARPγ8 and contributes to inhibiting neuronal excitability in epilepsy<sup>12,13</sup>
- Nonspecific AMPA receptor antagonists are associated with adverse events (AEs) such as ataxia, motor impairment, dizziness, falling, and sedation<sup>4,14,15</sup>
- Selectively targeting TARPγ8 (Figure 1B) may reduce excitatory transmission in the forebrain while improving the therapeutic index seen with nonspecific AMPA receptor antagonists<sup>16-18</sup>

#### Figure 1A.



define a family of transmembrane AMPA receptor regulatory proteins. *J Cell Biol*. 2003;161(4):805-16; permission conveyed through Copyright Clearance Center, Inc.

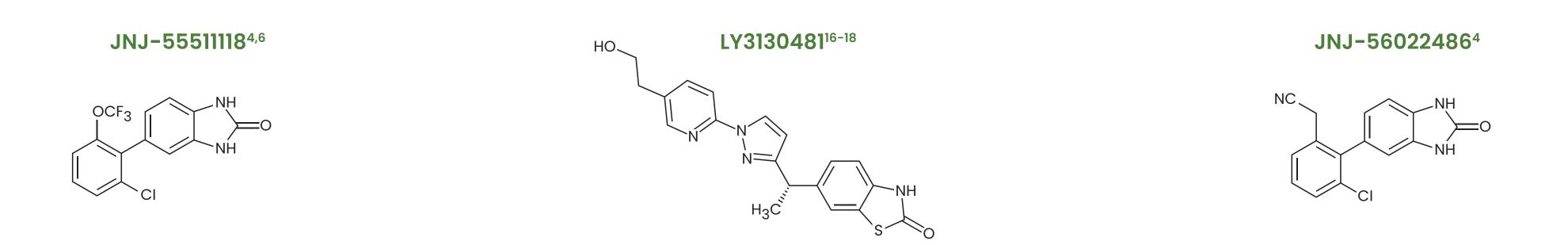
#### Figure 1B.



#### Developing a New Class of Medications

- In 2016, TARPγ8-specific compounds were discovered by Janssen and Lilly (**Figure 2**)<sup>19</sup>
- All these compounds, including RAP-219 (formerly known as JNJ-64300912), have broad-ranging antiseizure effects without motor side effects because they do not block AMPA signaling in the cerebellum

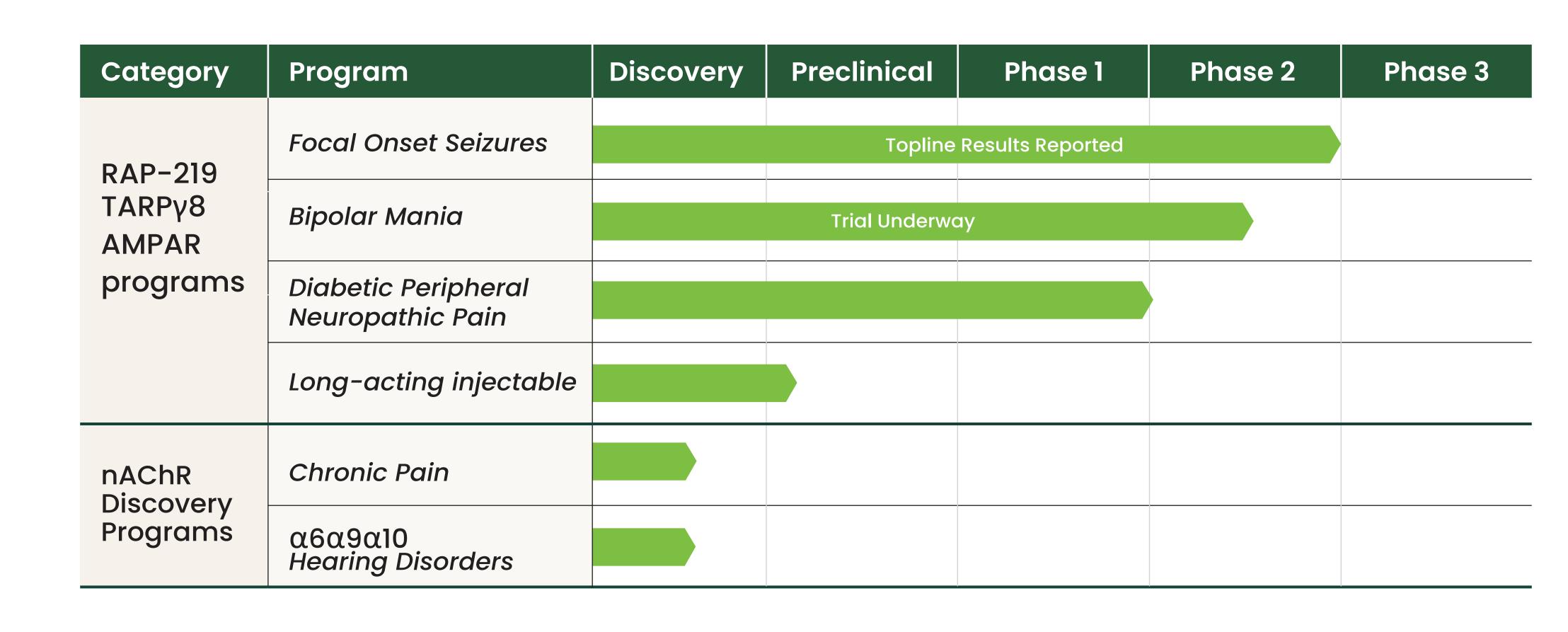
#### Figure 2.



#### Launch of Rapport Therapeutics with a Focus on Precision Medicine

- Founded by David Bredt, MD, PhD and Steve Paul, MD
- Dr. Bredt, Co-founder and Chief Scientific Officer, led groundbreaking receptor-associated protein research at Janssen
- Dr. Paul, Co-founder and Chairman of the Board of Directors, has over 40 years of experience in neuroscience, molecular neuropharmacology, and CNS drug discovery and development
- Funded through collaboration between Third Rock Ventures and Johnson & Johnson (specifically, Janssen) in February 2022
- A clinical-stage biopharmaceutical company focused on the discovery and development of a portfolio of small molecule product candidates that we believe have the potential to transform the standard of care of many CNS disorders (see Pipeline in Figure 3)

#### Figure 3. Rapport Therapeutics Pipeline



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# Evolution of RAP-219 for the Treatment of Epilepsy

2023-2024

Single ascending dose (SAD) and multiple ascending dose (MAD) studies initiated. NeuroPace partnership established. Phase 2 proof-of-concept (POC) study in focal onset seizures initiated.

#### 2025-2026

Phase 2A study meets primary endpoint, supporting advancement into Phase 3 studies.

## Focal Onset Seizures (FOS)

• Over 30% of people with epilepsy experience drug-resistant FOS despite the existence of multiple treatment options

- Probability of achieving seizure freedom decreases with each unsuccessful treatment
- Central nervous system adverse events (AEs) are observed with most antiseizure medications<sup>2</sup>
- Nonspecific AMPA receptor antagonists, in particular, are associated with AEs such as ataxia, motor impairment, dizziness, falling, and sedation<sup>3-5</sup>

## Preclinical Efficacy of NAMs Targeting TARPy8

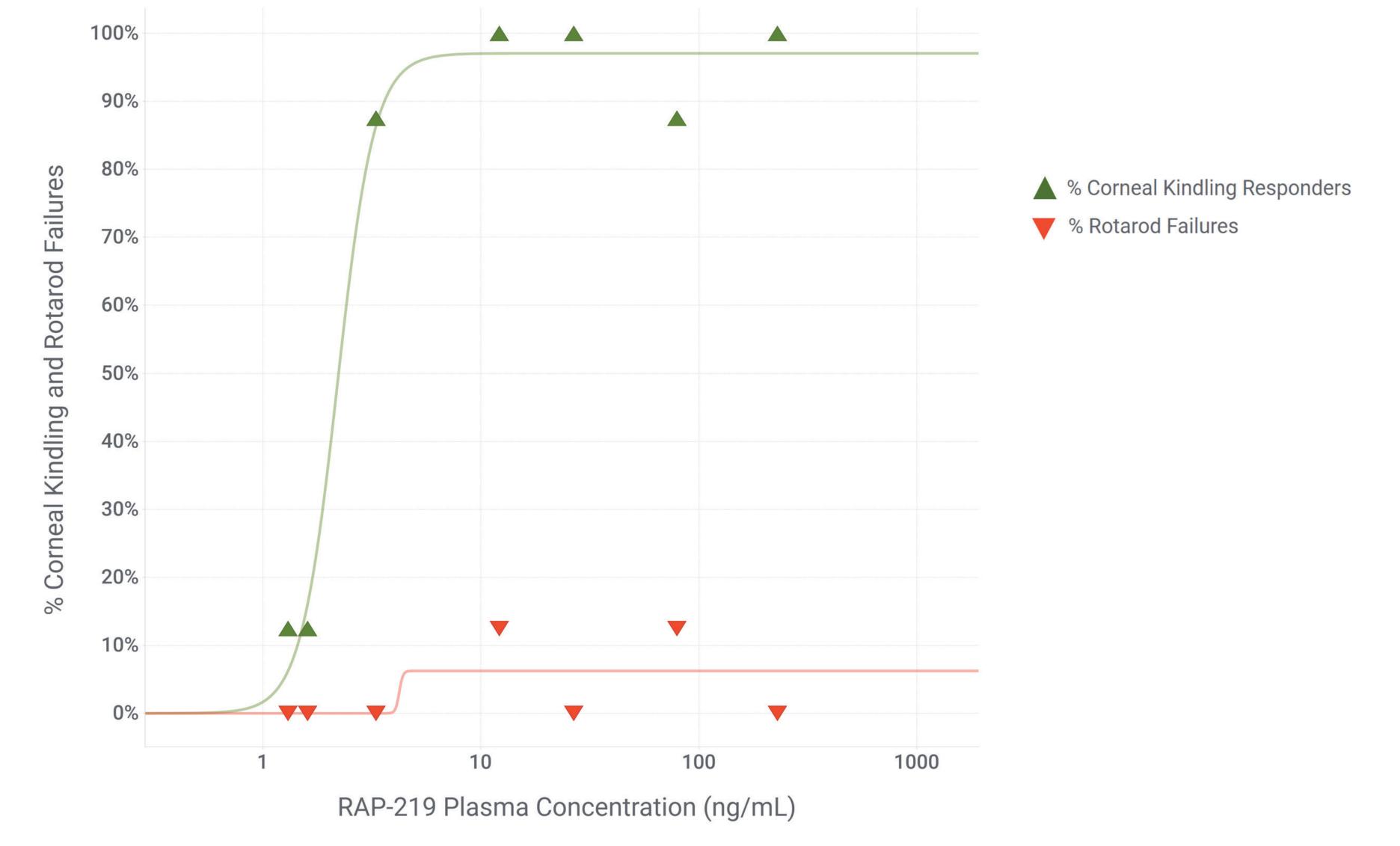
- Targeting RAPs provides cell-type and/or neuroanatomical specificity and allows optimal efficacy with a tolerable safety profile
- RAP-219 is an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor negative allosteric modulator selective for TARPγ8
- TARPγ8-specific compounds have shown robust efficacy across a broad array of preclinical focal and generalized seizure models (Table 1)
- RAP-219 specifically has demonstrated efficacy in pentylenetetrazol (PTZ) and corneal kindling (CK) models without motoric impairment on a rotarod (Table 1, Figure 1)
- In mice, seizures were prevented following oral administration of RAP-219 at a receptor occupancy of 70%

#### Table 1. TARPy8 Compounds in Preclinical Pharmacology

Validated	γ8-TARP Compounds Tested
<b>✓</b>	RAP-219, JNJ'118, RAP-482, and LLY'481 active
<b>√</b>	RAP-219, JNJ'118, RAP-482, and LLY'481 active
<b>√</b>	JNJ'118, RAP-482, and LLY'481 active   RAP-219 not tested
<b>√</b>	LLY'481 active   JNJ compounds not tested
<b>√</b>	LLY'481 active   JNJ compounds not tested
<b>√</b>	LLY'481 active   JNJ compounds not tested
<b>√</b>	RAP-219, JNJ '118, RAP-482, and LLY'481 = wide safety margin
	Validated  ✓  ✓  ✓  ✓  ✓  ✓  ✓

GAERS – genetic absence epilepsy rats from Strasbourg; JNJ – Johnson & Johnson; PTZ – pentylenetetrazol; TARP – transmembrane AMPA receptor regulatory protein.

#### Figure 1. RAP-219 Corneal Kindling Responders and Rotarod Failures as Functions of Plasma Concentration



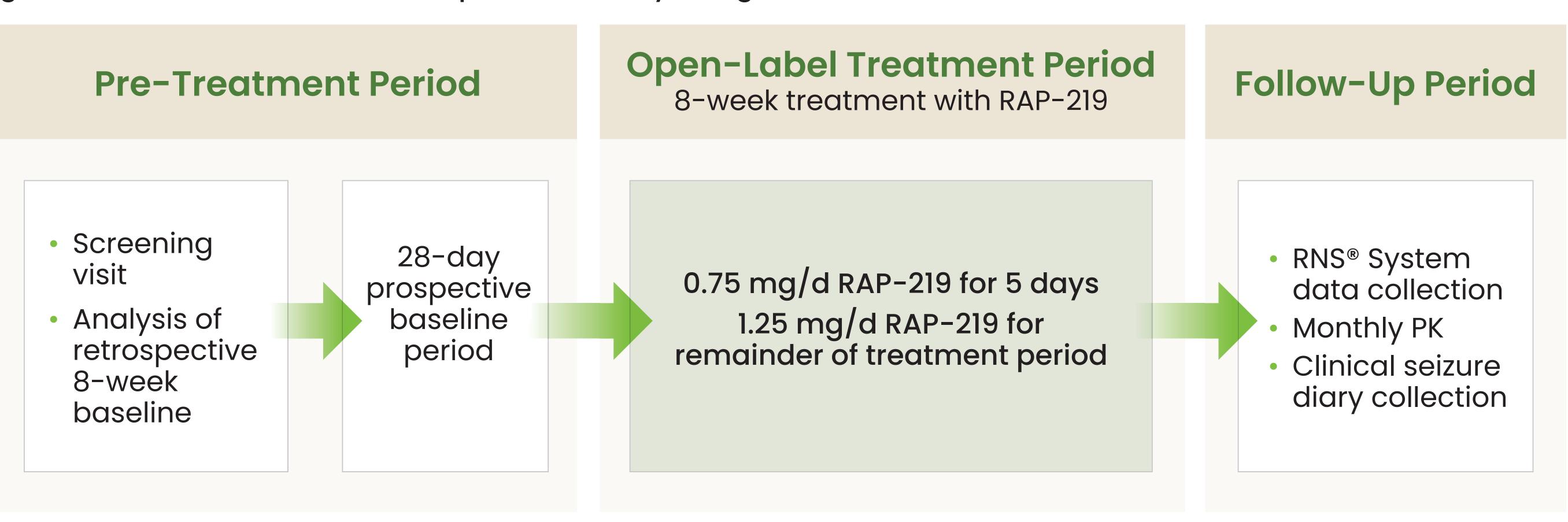
Receptor occupancy as a function of plasma concentration in rat at t=4h was used as a surrogate for this analysis, as potency in mouse vs rat was nearly identical (mouse plC50=9.8; rat plC50=9.9). PTZ threshold, corneal kindling, and rotarod were assessed in mouse.

## RAP-219 Clinical Program

- Phase 1 studies characterizing single and multiple dose PK/tolerability
- Results from the Phase 1 trials conducted have revealed that RAP-219 is associated with:
- Long terminal half-life
- ->95% protein binding
- Metabolism via UGT1A4
- Low risk of drug-drug interactions with other ASMs metabolized by CYP450 enzymes
- No abnormalities observed in vital signs, laboratory values, or electrocardiograms in single-ascending dose (SAD) and multiple ascending dose (MAD) studies; all TEAEs in SAD/MAD studies were Grade 1 or 2
- Results of PET receptor occupancy study confirmed the expression and distribution of TARPy8 in the cortex and mesial temporal lobes, the brain regions where seizures originate and propagate<sup>6</sup>

- The Phase 2A study of RAP-219 for the treatment of drug-resistant FOS uses a novel POC design in partnership with NeuroPace (NCT06377930; **Figure 2**)
- The responsive neurostimulator (RNS) POC study paradigm offers new methodologies and outcome measures while also reducing timelines and yielding scientifically valid results
- Using quantitative intracranial EEG (iEEG) biomarker outputs from implanted RNS® System (NeuroPace, Inc.) as a surrogate biomarker for reduction in clinical seizure frequency, the aim is to establish POC for RAP-219 in the treatment of drug-resistant FOS

#### Figure 3. Phase 2A Proof-of-Concept (POC) Study Design



PK – pharmacokinetic; RNS® – responsive neurostimulator.

#### Topline Results of Phase 2A POC Study

- 30 adult patients enrolled: mean age 40.1 y, baseline median 10 clinical seizures (CSs) per 28 days, and baseline 48 long episodes (LEs) per 28 days
- Patients achieved median 71.0% and 77.8% reductions in LEs and CSs, respectively; 24% of patients achieved seizure freedom for the entire 8-week treatment period
- ≥1 treatment-emergent AE (TEAE) was reported in 25 (83.3%) patients treated with RAP-219
- TEAEs reported in >10% of patients were dizziness (26.7%), headache (16.7%), and fatigue (13.3%)
- 3 (10%) patients discontinued treatment due to TEAEs
- RAP-219 FOS Phase 3 studies to begin in Q3 2026



For information on Rapport's Phase 3 focal onset program, please contact: RAP-219-FOS@rapportrx.com

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