

\$RAPP Rapport Therapeutics Long Suggestion

By Snaking

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Executive Summary

At a market capitalization of \$380m, with a cash balance of \$305m (EV of 75 million US\$) and quarterly spending of ~\$20m, I believe that the market is underestimating the potential of RAP-219 as a major player in the focal epilepsy market.

I expect RAP-219 to show competitive efficacy in its Phase 2a Proof of Concept trial for Focal Epilepsy (expected to happen in Q3 2025) due to the previous success of the mechanism of action in epilepsy from other compounds with related, and even the same mechanisms of action.

I expect RAP-219 to show a comparable safety profile to that of perampanel (and in general other Anti-Epileptic Medications), with the possible improvement of not including serious psychiatric and behavioral changes in the list of expected adverse events due to the higher selectivity of targeted brain regions derived from mechanistic differences.

Additional positive indicators such as recent insider buying and a great management team full of vastly experienced professionals are not mentioned in this thesis but may be taken into account.

Bull Case (35% Probability) >\$17.5, +>75%: >70% reduction in absolute seizure frequency, >50% reduction in the iEEG “long episodes” biomarker, no unexpected adverse events of grade higher than 2

Base Case (55% Probability) \$13 - \$17.5, +30 - 75%: 45-70% reduction in absolute seizure frequency, 40%-50% reduction in the iEEG “long episodes” biomarker, no major unexpected adverse events

Bear Case (10% Probability) \$6.5, -35%: <45% reduction in absolute seizure frequency, <40% reduction in the iEEG “long episodes” biomarker or major unexpected adverse events

Context

Rapport was formed in February 2022, with founding support from Third Rock Ventures and Johnson & Johnson Innovation-JJDC.

Its scientific founder and Chief Scientific Officer, David Bredt, M.D., Ph.D., pioneered the discovery of RAPs (Receptor Associated Proteins) and their targeting by small molecules while serving as Global Head of Neuroscience Discovery at Janssen Pharmaceutica NV (“Janssen”) and prior to that as Vice President of Neuroscience at Eli Lilly and Company and as a Professor of Physiology at the University of California, San Francisco.

Dr. Bredt was subsequently joined at Rapport by additional scientists who previously worked on the RAP platform at Janssen.

In August 2022, Rapport Therapeutics entered into a license agreement with Janssen (the “Janssen License”) for the research, development and commercialization of certain TARPγ8 products, including RAP-219 and RAP-199, and nAChR products created by Dr. Bredt and his colleagues at Janssen.

Some of the pre-clinical studies that will be mentioned were completed by Janssen prior to the License agreement. In many cases, these efforts were made by certain of the same personnel who have since joined Rapport.

The most notorious asset in the licensing agreement, Rapport Therapeutics’ most advanced investigational small molecule, was **RAP-219**: an investigational small molecule that is designed to inhibit TARPγ8-containing AMPARs with picomolar affinity, in development for its potential to be a differentiated therapy for focal epilepsy and other CNS disorders (including neuropathic pain and bipolar disorder).

AMPA Receptors are glutamate-gated cation channels that mediate fast excitatory neurotransmission throughout the central nervous system. Malfunction of these receptors is associated with a variety of neurological and psychiatric disorders, rendering them a strategic drug target.

AMPA inhibition is a clinically validated approach for the treatment of epilepsy, with perampanel (marketed as FYCOMPA) approved by the FDA in 2012 for the treatment of both focal and generalized epilepsy. TARPγ8, an AMPA RAP (Receptor Associated Protein), is expressed in specific brain regions, being most enriched in the hippocampus and other forebrain structures, which are key sites associated with focal onset seizures.

As brain regions with TARPγ8 expression closely overlay with the brain sites most often involved with the pathophysiology of focal epilepsy, Rapport believes

that RAP-219, which has been shown in preclinical studies to bind to TARPγ8, has potential to provide a differentiated profile.

Furthermore, preclinical studies have demonstrated that TARPγ8 expression is enriched in the hippocampus, amygdala, cerebral cortex and striatum and has minimal or no expression in certain other areas that are critical for normal brain functions, including the cerebellum and brainstem.

In contrast to the precision mechanism of RAP-219, most Anti-Seizure Medications (ASMs), including perampanel, bind their target receptors throughout the brain, and it is worth hypothesizing that this lack of anatomical specificity may contribute to their side effect profiles.

Rapport Therapeutics has an ongoing Proof of Concept clinical trial of RAP-219 in patients with refractory focal epilepsy (with topline results expected in Q3 2025 as of the company's last quarterly report), and plans to start other 2 Proof of Concept studies of this drug for the treatment of Bipolar Mania in the third quarter of 2025 and of Diabetic Peripheral Neuropathic Pain.

Johnsson & Johnsson (JNJ) owns 6.8% of the shares outstanding.

In this work, a higher emphasis will be placed in RAP-219 for Epilepsy. A value of 0\$ will be attributed to the company's Bipolar Mania and Diabetic Peripheral Neuropathic Pain programs, for the sake of conservativeness.

RAP-219, TARPy8, AMPA Receptors and Glutamate

RAP-219

RAP-219 is an AMPA Receptor (AMPA) negative allosteric modulator (NAM) designed to achieve neuroanatomical specificity through its selective targeting of a RAP (Receptor Associated Protein) known as TARPy8 (Transmembrane AMPAR Regulatory Protein γ 8), associated with neuronal AMPAR.

TARPy8 Ligands are Highly Selective Inhibitors of AMPAR

TARPs are AMPA receptor auxiliary subunits.

Structural analyses performed by a third party using cryogenic electron microscopy (“Cryo-EM”) have shown that a TARPy8 AMPAR NAM, JNJ-55511118 (an earlier generation TARPy8 NAM), binds to an interface between TARPy8 and AMPAR, which leads to alterations in the structure of the AMPAR, thereby negatively modulating receptor function and its ability to respond to glutamate. Third-party structural studies indicated that all TARPy8 AMPAR NAMs tested bind in a similar mode, suggesting the potential for RAP-219 to also bind in this pocket between GluA (Glutamate ionotropic receptor AMPA-type subunit) and TARPy8 (as depicted in Picture 1).

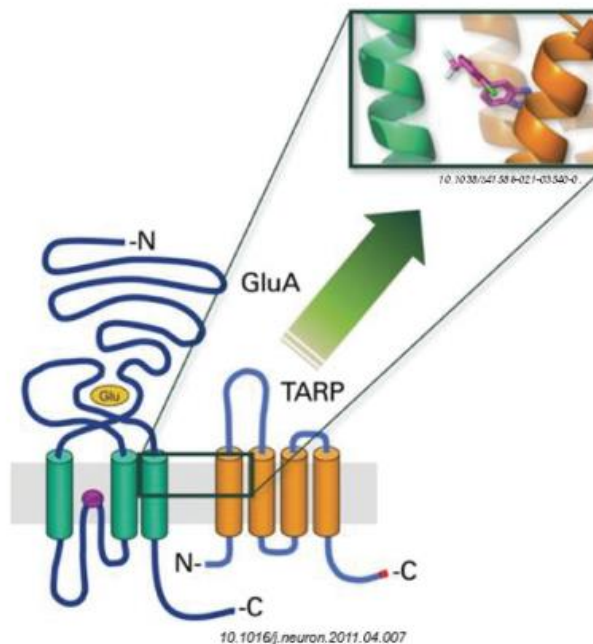


Figure 1. TARPy8 ligands bind to the interface between TARPy8 and AMPAR.

TARPy8 Expression is Localized

TARPy8 is expressed in specific brain regions, being most enriched in the hippocampus, and also present in the amygdala and cortex. In a study completed by Janssen, radiolabeled TARPy8 ligands, such as JNJ-56022486 (an earlier generation TARPy8 NAM), were shown to bind selectively to regions of the mouse brain in a distribution that overlapped TARPy8 protein expression.

The highest radioactive JNJ-56022486 density occurred in the hippocampus, which is also the region where the majority of focal seizures originate and the brain region where focal seizures originating in the cortex often spread. Radioligand binding of JNJ-56022486 also occurred in other brain regions that contain TARPy8, including the amygdala, cerebral cortex and striatum, which can also be involved in seizure initiation and propagation.

Importantly, the spread of seizures from the hippocampus into the amygdala has been shown in a third-party study to increase the risk of Sudden Unexpected Death in Epilepsy (SUDEP) in patients.

Figure 2 illustrates the enrichment of TARPy8 in mouse hippocampus. The left image derives from the Allen Brain Atlas, a publicly available database of gene expression in the brain, and depicts in red high levels of TARPy8 messenger ribonucleic acid detected by in situ hybridization. The right image depicts with yellow and orange high levels of JNJ-56022486 binding detected by autoradiography.

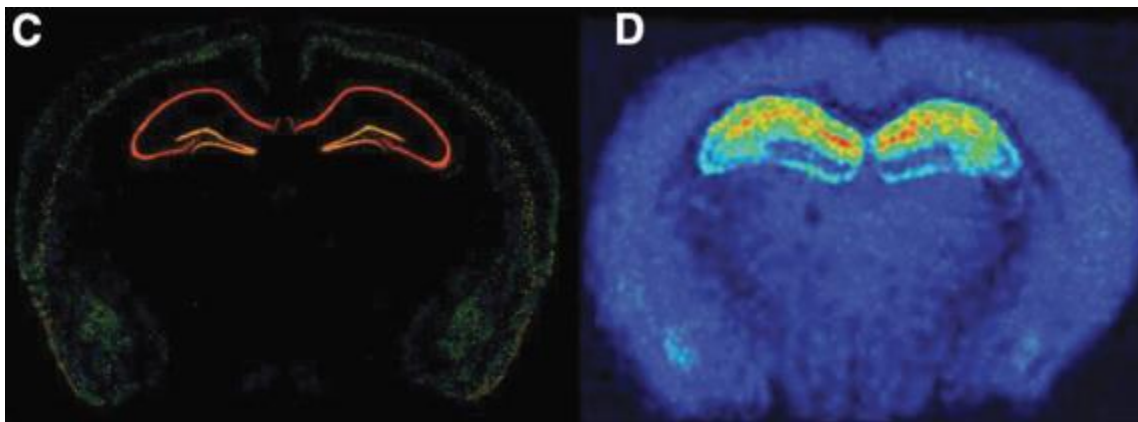


Figure 2. TARPy8 is expressed in the mouse hippocampus.

Glutamate, Antiseizure Therapy Through Modulation of Glutamate Signaling

Glutamate is the major excitatory neurotransmitter in the brain. Both glutamate's release from presynaptic nerve terminals and its activation of postsynaptic receptors are critical for neurotransmission.

Glutamate mediates most excitatory synaptic transmission in the CNS by activating AMPA- and NMDA-type ionotropic neurotransmitter receptors. AMPA receptors mediate much of the moment-to-moment transmission, whereas NMDA receptor activation initiates both long-term potentiation (LTP) and long-term depression (LTD).

Correspondingly, processes associated with glutamate release and its downstream signaling are highly regulated. Elevation in extracellular glutamate levels can lead to seizures, and many Anti-Seizure Medications (ASMs) target this pathway.

ASMs can blunt glutamate-dependent signaling through diverse mechanisms. Drugs such as phenytoin, carbamazepine, lamotrigine and lacosamide molecule voltage-gated sodium channels and inhibit action potentials from reaching the glutamate release machinery within the presynaptic nerve terminal. Other drugs such as ethosuximide and ezogabine modulate voltage-gated calcium and potassium channels, respectively, which also can prevent the presynaptic release of glutamate.

After being released into the synaptic cleft, glutamate can bind to AMPA Receptors on postsynaptic neurons. This process permeates sodium and other cations, triggering a series of events that can ultimately lead to the generation of an action potential and the propagation of neuronal signals. Perampanel directly blocks the gating of all AMPARs, while other drugs, such as phenobarbital and tiagabine, oppose glutamate signaling by increasing the activity of inhibitory synaptic signaling driven by the GABAA receptors.

In-Vitro and Pre-Clinical Data

Janssen tested RAP-219's effect on recombinant human GluA1-TARPy8 complexes in mice and rats. The study found that RAP-219 inhibited the function of GluA1-TARPy8 receptors with half maximal effect, referred to as the IC₅₀, at a concentration of approximately 100 pM, demonstrating RAP-219's potency. By contrast, as exemplified in Figure 3 below, RAP-219 was found to be far less potent on complexes of GluA1 with other relevant TARP isoforms, including g2, g3, g4 or g7 or on other receptor types, such as NMDA receptors, G protein-coupled receptors (GPCRs), enzymes or and kinases.

RAP-219 selectivity

TARPy8-containing AMPA receptors (IC ₅₀)	~100 pM
vs. AMPA receptors (GluA1) lacking TARPs	>100,000x
vs. AMPA receptors containing other TARPS (γ 2, γ 3, γ 4, γ 7)	>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

Figure 3. RAP-219 observed to be a highly selective inhibitor of TARPy8 AMPAR.

RAP-219 has shown robust efficacy across a broad array of preclinical focal and generalized seizure models: Corneal kindling in mice, PTZ in mice, Rotarod, Amygdala kindling in mice, Hippocampal kindling in mice, 6Hz stimulation in mice, Frings audiogenic seizure in mice, GAERS absence epilepsy in rats.

In-Human Data (Phase 1 Clinical Trials)

A total of four Phase 1 trials have been conducted to date, with 100 healthy volunteers exposed to RAP-219. In these trials, RAP-219 was generally well tolerated in multiple repeat-dose studies with up to 28 days of dosing, with no serious adverse events (SAEs), no treatment emergent adverse events (TEAEs) greater than Grade 2, and no clinically relevant laboratory or electrocardiogram (ECG) abnormalities.

These four Phase 1 Trials were:

- Single-Ascending Dose (SAD) Study, n=41, RAP-219-101
- Multi-Ascending Dose (MAD) Study 1, n=40, RAP-219-102
- Multi-Ascending Dose (MAD) Study 2, RAP-219-104
- Positron Emission Tomography (PET) Study, RAP-219-103

All, with the exception of the PET Study, were double-blind and placebo-controlled.

SAD Study

In this Phase 1 trial, RAP-219 exhibited biphasic elimination, with a mean half-life ($t_{1/2}$) of 278 ± 200 h (~8-14 d).

In total, 51 TEAEs were reported by 19 (46%) subjects. No Grade 3 or worse TEAEs, SAEs, or dose-limiting toxicity events were observed. Most (82.4%) TEAEs were Grade 1 (mild); 9 events (17.6%) in 3 subjects were Grade 2 (moderate). Most common TEAEs at any dose: sinus tachycardia (n=5, 16.7%), anxiety (n=4, 13.3%), dizziness, paresthesia, and palpitations (n=3 each, 10%). All AEs resolved during the study, with no clinically significant changes in laboratory parameters, vital signs, or ECGs following RAP-219 treatment.

MAD-1 Study

In this Phase 1 trial, RAP-219 showed the following safety profile. It is important to highlight the first 2 cohorts were analyzed over 2 weeks vs 4 weeks for the last 3 cohorts.

	Pooled placebo n=10	14 Days of Treatment		28 Days of Treatment		
		0.25 mg/d RAP-219 n=6	0.25 mg/d → 0.5 mg/d RAP-219 n=6	0.5 mg/d RAP-219 n=6	0.75 mg/d RAP-219 n=6	0.75 mg/d → 1.25 mg/d RAP-219 n=6
Subjects with ≥1 TEAE, n (%)	4 (40.0)	5 (83.3)	6 (100.0)	3 (50.0)	5 (83.3)	2 (33.3)
Sinus tachycardia	0	1 (16.7)	3 (50.0)	0	0	0
Medical device site reaction	1 (10.0)	2 (33.3)	1 (16.7)	0	0	0
Headache	0	1 (16.7)	0	0	2 (33.3)	0
Insomnia	0	0	2 (33.3)	0	1 (16.7)	0
Subjects with ≥1 Grade 2 TEAE, n (%)	0	3 (50.0)	3 (50.0)	0	2 (33.3)	0
Subjects with ≥1 Grade 3 or above TEAE, n (%)	0	0	0	0	0	0

TEAEs listed include those with ≥10% incidence in all subjects who received RAP-219 treatment (n=30); Toxicity grades of TEAEs: Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=potentially life threatening, Grade 5=death related to AE.

TEAE – treatment-emergent adverse event.

Figure 4. Safety and Disposition Following Multiple Dosing of RAP-219 in Healthy Subjects

RAP-219 MAD Unblinded Safety Summary

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

Treatment Emergent Adverse Events (TEAEs) in Phase 1 RAP-219-102 (MAD) Trial by Cohort and Pooled Placebo	Pooled Placebo (N=10)	Cohort 1 (0.25 mg × 2 weeks) (N=6)	Cohort 2 (0.25 mg × 1 week; 0.5 mg × 1 week) (N=6)	Cohort 3 (0.5 mg × 4 weeks) (N=6)	Cohort 4 (0.75 mg × 4 weeks) (N=6)	Cohort 5 (0.75 mg × 5 days; 1.25 mg × 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

Figure 5. Safety and Disposition Following Multiple Dosing of RAP-219 in Healthy Subjects

MAD-2 Study

In this Phase 1 trial, RAP-219 was generally well-tolerated. All TEAEs were Grade 1 or Grade 2 and generally consistent with tolerability observed in prior Phase 1 trials. Unlike with many anti-seizure medications, no sedation or motoric impairments were observed with RAP-219, consistent with target biology and preclinical observations.

MAD Studies

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).

PET Study

In this trial, RAP-219 maintained a differentiated tolerability profile generally consistent with prior Phase 1 trial findings.

This Study confirmed that the expression of TARP γ 8-containing AMPA receptors is enriched in the hippocampus and cerebral cortex and is minimal in the cerebellum and brain stem.

Cohort 1 (being used in the Phase 2a Proof of Concept trial) exceeded the target Receptor Occupation (RO) range associated with maximal efficacy in pre-clinical studies (50%-70%) within 5 days of dosing.

Highlights from these Phase 1 Studies

The achievement of target Receptor Occupation further validates the mechanism of action while also validating management's choice of dosing regimen.

It is only logical that a comparison between RAP-219's safety profile and that of other epileptic drugs (perampanel in particular) be made.

Safety Profile Comparison

XENE1101

XENE1101 is Xenon Pharmaceuticals' promising Kv7.2/7.3 activator, in late-stage clinical trials for Focal Epilepsy, valued at ~\$2B as of the company's current share price.

In its phase 2 proof-of-concept double-blind, randomized, placebo-controlled X-TOLE trial, XENE1101 displayed its safety profile in 325 patients.

Overall, there was little difference between Serious Adverse Events between patients treated with the drug vs placebo (3.3% XEN1101 vs 2.63% Placebo). However, there were cases of Psychiatric disorders consistent with the current Anti-Epileptic Drugs: 1 occurrence each of Psychogenic seizure, Psychotic disorder and Somatic Delusion vs 0 in the placebo arm.

Non-Serious AEs were much more common in patients treated with XEN1101 than placebo (77% vs 49.12%). Of note were the prevalence of the following adverse events:

- Dizziness (24.6% vs 7.02%)
- Somnolence (15.6% vs 7.02%)
- Balance Disorder (9% vs 1.75%)
- Tremor (8.5% vs 1.75%)
- Memory Impairment (4.2% vs 0.88%)
- Disturbance in Attention (3.5% vs 0.88%)
- Hallucinations (1.4% vs 0%)
- Confusional State (4.7% vs 0.88%)

ES-481

ES-481 is ES Therapeutics' Novel TARP-γ8 Inhibitor, it should provide the best comparison of efficacy and safety to RAP-219. Unfortunately, ES Therapeutics isn't known for being the most transparent company in the space, and hasn't made much of their data available. ES-481 was formerly known as LY-3130481 (from Eli Lilly), but was then purchased by Avalo Therapeutics which rebranded it to CERC-611 and subsequently sold it to ES Therapeutics, finally becoming ES-481.

The rate of Serious Adverse Events in ES-481's 4 week long Phase 2 trial (n=22) was higher in the placebo arm than in patients treated with the drug (14.3% vs 4.8%). Adverse events of special interest (AESI) were, however, more common while taking ES-481 (52.4% vs. 19.0%). No further safety data was provided by the company.

Perampanel

Finally, it is only reasonable that RAP-219 be compared to perampanel, the only AMPAR antagonist to receive FDA approval for its clinical use in the treatment of partial seizures and generalized tonic-clonic seizures for people older than twelve years.

Perampanel's label has a black box warning noting that some people taking the drug have undergone serious psychiatric and behavioral changes. These events occurred in people who had no history of such issues, as well as people who had such a history. The psychiatric changes included mood changes like euphoric mood, anger, irritability, aggression, belligerence, agitation, and anxiety, as well as psychosis (acute psychosis, hallucinations, delusions, paranoia) and delirium (delirium, confusional state, disorientation, memory impairment). Behavioral changes included physical assault and homicidal ideation and/or threats.

Other serious side effects include suicidal thoughts or behavior (like all anti-epileptic drugs), dizziness and gait disturbance, somnolence and fatigue, risk of falls, and increased risk of seizures if the drug is quickly withdrawn.

In a randomized, double-blind, placebo-controlled study of the adjunctive use of parempanel for refractory partial-onset seizures (n=706), with a treatment duration of approximately 14 weeks parempanel displayed the following safety profile:

- Lower rate of Serious Adverse Events in the perampanel cohorts than in the placebo population (3.50% vs 4.86%)
 - o Of note is that one case of each of the following happened in the perampanel population (none of them occurred in placebo-treated patients): aggression, confusional state, delirium

	Placebo (n = 185)	Patients, n (%)		
		2 mg/day (n = 180)	4 mg/day (n = 172)	8 mg/day (n = 169)
AnyTEAE	101 (54.6)	111 (61.7)	111 (64.5)	121 (71.6)
Any treatment-related TEAE	59 (31.9)	67 (37.2)	77 (44.8)	96 (56.8)
Any TEAE leading to discontinuation ^a	7 (3.8)	12 (6.7)	5 (2.9)	12 (7.1)
Any TEAE leading to dose reduction/ interruption	6 (3.2)	3 (1.7)	12 (7.0)	29 (17.2)
Any serious TEAE	9 (4.9)	6 (3.3)	6 (3.5)	6 (3.6)
TEAEs in ≥5% (any treatment group)				
Dizziness	18 (9.7)	18 (10.0)	28 (16.3)	45 (26.6)
Somnolence	12 (6.5)	22 (12.2)	16 (9.3)	27 (16.0)
Headache	16 (8.6)	16 (8.9)	19 (11.0)	18 (10.7)
Fatigue	5 (2.7)	8 (4.4)	13 (7.6)	9 (5.3)
Upper respiratory tract infection	5 (2.7)	11 (6.1)	6 (3.5)	3 (1.8)
Nasopharyngitis	3 (1.6)	7 (3.9)	9 (5.2)	3 (1.8)
Gait disturbance	2 (1.1)	1 (<1)	2 (1.2)	9 (5.3)

Final Safety Remarks

I expect RAP-219 to show a comparable safety profile to that of perampanel (and in general other Anti-Epileptic Medications), with the possible improvement of not including serious psychiatric and behavioral changes in the list of expected adverse events due to the higher selectivity of targeted brain regions derived from mechanistic differences.

RAP-219 has had 2 of its clinical trials put on hold, which after careful investigation (of the reasons for each clinical hold) can be determined not to be indicative of safety concerns. This is likely part of the reason may currently be underappreciated, creating an opportunity. If Phase 2a reveals a safety profile in accordance with previous Phase 1 trials, a convergence between price and value is to be expected.

Efficacy Comparison

Although there are multiple endpoints that would allow for a comparison between the efficacy of different Anti-Seizure Medications (with the objective of defining and evaluating the worth of RAP-219), the one that is common to all trials of all drugs under comparison in this document is the mean reduction in seizure frequency, which is very logically representative of efficacy.

Because of the lack of efficacy data regarding RAP-219, best practice is that we analyze the efficacy of a drug with the same mechanism of action (ES-481) and compare it against a highly anticipated drug in the same realm (so as to establish a high bar).

XEN1101

In the first 4 weeks of evaluation in a Phase 2 randomized, double-blind, placebo-controlled trial of XEN1101 as an adjunctive therapy in Focal Epilepsy (X-TOLE), the population treated with the drug displayed a 55.3% reduction in focal seizure frequency, whereas placebo registered a 14.9% reduction. In the second 4 weeks, the reduction in both arms increased to 64.7% and 21.8%, respectively.

ES-481

In a 4 week Phase 2 randomized, double-blind, placebo-controlled study of ES-481 in patients with Drug-Resistant Epilepsy, the population treated with the drug showed a 68-80% reduction, while subjects on placebo showed a 38-49% reduction (this was all data made available by the ES Therapeutics, who conducted the study).

Final Efficacy Remarks

Available data is not enough to draw major conclusions for many reasons, namely the fact that Drug-Resistant Efficacy is inherently harder to treat. XEN1101's trial design might appear to suggest a higher rate of use of other Anti-Seizure Drugs (AEDs) concomitantly, due to being tested as an "adjunctive therapy". However, ES-481's trial inclusion criteria includes the following sentence: "The subject must be taking 1 to 4 antiepileptic drugs (AED)", making the two trials more comparable, and ES-481's result more impressive, if representative of the drug's true effect.

Despite the comparability-issues previously mentioned, I expect RAP-219 to show similar efficacy in its Phase 2a Proof of Concept trial to that of ES-481 in the above mentioned clinical trial, in which case it would have to be considered a drug with immense potential.

Design of the Phase 2a Proof-of-Concept Study (Topline Data Q3 2025)

This will be the first evidence of RAP-219's efficacy in the treatment of patients with Focal Epilepsy. The trial is multi-center (US exclusive, with 14 locations) and open-label.

The activity of approximately 20 adult participants with refractory focal epilepsy with the RNS® system will be assessed. RNS® is an FDA approved responsive neurostimulator that continually monitors electrographic activity from electrodes (intracranial encephalogram; iEEG) placed directly into the seizure focus or foci and is programmed by the patient's physician to detect epileptiform activity of significance including long episodes (LEs).

iEEG measures (i.e., LEs, detection counts, spike rate) have been shown to correlate with clinically meaningful seizure frequency reduction ($\geq 50\%$ reduction). LE frequency reduction demonstrated the strongest correlation of the iEEG measures, and a 30-40% reduction in LEs within 1-4 weeks of new Anti-Seizure Medication (ASM) initiation was associated with $>50\%$ seizure reduction.

After a pre-treatment period of 28 days, participants that match the inclusion criteria and not the exclusion criteria described below will be enrolled in the 8 week Open-Label treatment period, in which they will receive a 0.75mg oral tablet of RAP-219 daily for 5 days, followed by 1.25mg RAP-219 daily for the remainder of the 8 week treatment period.

Approximately 20 patients meeting the following key inclusion criteria:

18-65 years old

Medically refractory FOS

An implanted RNS® device and:

- RNS® implanted ≥ 15 months before screening
- Stable device configuration, stimulation, and detection settings, including LE duration
- An average of ≥ 8 LEs per 4-week interval during the combined retrospective/prospective baseline periods
- Concordance of $\geq 50\%$ between LEs and EES
- No anticipated need for device setting changes during the study period

≥ 1 clinical seizure(s) during the retrospective baseline period

Key exclusion criteria:

Use of perampanel within 12 weeks before screening

Figure 6. Key Inclusion and Exclusion Criteria

The company's reasoning for this study design is summarized by the following table:

Model Attributes	Responsive neurostimulator (RNS® System)	Photosensitivity	Transcranial magnetic stimulation (TMS)
Uses focal epilepsy patient population	Yes	No	No
Direct measure of drug activity	Yes Reduction in LEs	No Evoked generalized epileptiform discharges	No Provoked cortical hyperexcitability
Informs dose selection for registrational trials	Yes PK/PD data can provide measure of efficacy degree at different exposure levels	No Indirect dose response readout	No Indirect dose response readout
Enables rapid progression into registrational trials	Yes Biomarker data to inform dose and effect size	No Does not inform dose or effect size	No Does not inform dose or effect size

FOS, focal onset seizures; LE, long episode; PK/PD, pharmacokinetic/pharmacodynamic; POC, proof-of-concept.

Figure 7. Focal Epilepsy Model Attributes

The following list of key endpoints will be assessed:

Key endpoints
LE frequency responder analysis (% of patients that demonstrate ≥30% reduction in LEs)
Change in LE frequency per 28 days during the second 4-week interval of open-label treatment period compared to frequency across retrospective and prospective baselines
Change in estimated EES, clinical seizure frequency, and additional iEEG biomarkers per 28 days during the second 4-week interval of open-label treatment period compared to frequency across retrospective/prospective baseline periods
Number of patients with clinically meaningful improvement in PGIC and/or CGIC measures
Incidence of TEAEs and SAEs
CGIC, Caregiver Global Impression of Change; EES, electrographic seizures; iEEG, intracranial electroencephalogram; LE, long episode; PGIC, Patient Global Impression of Change; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events.

Figure 8. Key Endpoints being Assessed

The bar for success of this trial is, in my view, very explicitly defined by a mixture of absolute seizure frequency reduction and efficacy in reducing RNS-recorded long episodes (listed as the primary endpoint on clinicaltrials.gov).

Assessing the Associated Risks

The novel design choice for the Phase 2a Proof of Concept (POC) Study represents an increased risk due to the unpredictability of outcomes and lack of comparison. This shouldn't be a major issue as the connection between the proposed biomarkers and absolute seizure reduction have been established in recent studies, but it is something to consider.

The appearance of side effects related to psychiatric and behavioral changes could limit the upside, as it would suggest that the targeting of TARPγ8 (as opposed to directly targeting AMPA Receptors, like perampanel) has limited to non-existent safety benefit.

Even if Phase 2a shows impeccable efficacy, there is a risk that the market reads it as uninterpretable, given there is no control to compare against. I don't expect this to be a major issue, given prior examples in the epilepsy space.

Estimating RAP-219's Value in the Focal Epilepsy market (NPV)

In order to estimate the potential value of RAP-219 in the Epilepsy Market, a couple assumptions ought to be made (reasonably conservatively):

- Year of Approval: 2028
- Reasonable Discount Rate: 12%
- Peak Sales: \$350M
- Years to Peak Sales: 4
- Expenses undertaken in the development of said drug: \$300M

Some observations also ought to be made:

- Patent Expiry: 2036

The Net Present value given these inputs comes off to about \$650M, and therefore \$350M of added value (accounting for the expenses to take RAP-219 from Phase 2a to FDA Approval), representing a double from \$RAPP's current share price.

Of course, this is a very simplistic calculation and is not representative of a good method, the point of this valuation estimation exercise is to set a reasonable expectation of what the market should read into this trial given good enough results.

References

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[IPO of shares of common stock of Rapport Therapeutics, Inc](#)

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