Proof-of-concept phase 2a trial of a novel septin modulator reveals EEG pharmacodynamic effects in Alzheimer's disease.

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INTRODUCTION

- Individuals with Alzheimer's disease (AD), marked by Aβ plaques and tau tangles, show only modest response to Aβ-targeting therapies, highlighting the need for new drug targets and therapeutic strategies[1].
- Tau pathology disrupts septin-regulated store-operated Ca^{2+} channels (SOCE), leading to excessive cytosolic Ca^{2+} accumulation that drives synaptic dysfunction, neuronal network disintegration, and accelerates molecular pathology (Figure 1).[2]
- REM127 is a novel small molecule that restores septin filament integrity and reduces Ca^{2+} influx by selectively targeting SOCE without affecting synaptic- or receptor-mediated Ca^{2+} signaling in physiological conditions[2].
- Electroencephalography (EEG) in AD subjects shows reduced posterior dominant alpha rhythm and early excitation/inhibition imbalance, favoring excitation (via glutamate reuptake inhibition) compared to healthy elderly individuals[1].
- This phase 2a clinical trial in mild-to-moderate AD subjects evaluated EEG spectral features as pharmacodynamic biomarkers of REM127 treatment response.

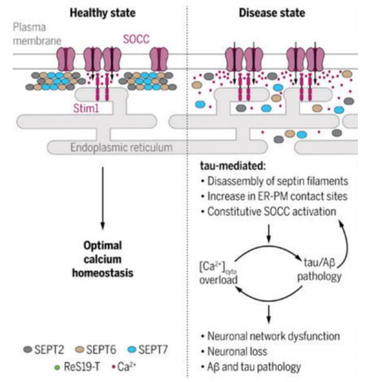

Figure 1. Ca^{2+} signaling hypothesis in AD.[2]

METHODS

1. Study design

- Phase 2a multicenter, randomized, double-blind, placebo-controlled trial in mild-to-moderate AD subjects, terminated early due to off-target, drug-induced liver injury.
- Each subject received either placebo or one of three oral doses of REM127 (b.i.d.) for 28 days.

Parameter	Placebo (n=4)	88 mg/day (n=5)	350 mg/day (n=3)	1400 mg/day (n=2)
Age (years)	69 ± 12	74 ± 5.3	76 ± 5.6	72 ± 19
Gender (m/f)	2/2	2/3	2/1	0/2
MMSE at screening	18 ± 1.7	19 ± 2.3	19 ± 1.2	12.5 ± 0.7
Aβ42 (pg/mL)	533 ± 227	479 ± 113	689 ± 253	567 ± 46
P-tau181 (pg/mL)	28 ± 15	41 ± 21	30 ± 4	62 ± 36

Table 1. Demographic and clinical characteristics of the study participants.

2. EEG analysis

- Eyes-closed vigilant-controlled (ECV) EEG was recorded with a Sienna Ultimate Amplifier at baseline (BL), day 15 (D15), and day 29 (D29).
- Preprocessing included line noise removal (ZapLine[3]), 0.5-40 Hz bandpass filtering, average referencing, and automated ocular/muscle artifact removal using independent component analysis.
- Power spectral density (PSD) was computed using Welch's method and decomposed into periodic (power of oscillations) and aperiodic (exponent, offset) components[4].
- Longitudinal changes in periodic and aperiodic features were compared between treatment and placebo groups and correlated with cognition, CSF biomarkers, and neurotransmitter concentration.

RESULTS

1. Power of posterior dominant rhythm increased within 15 days in REM127-treated subjects.

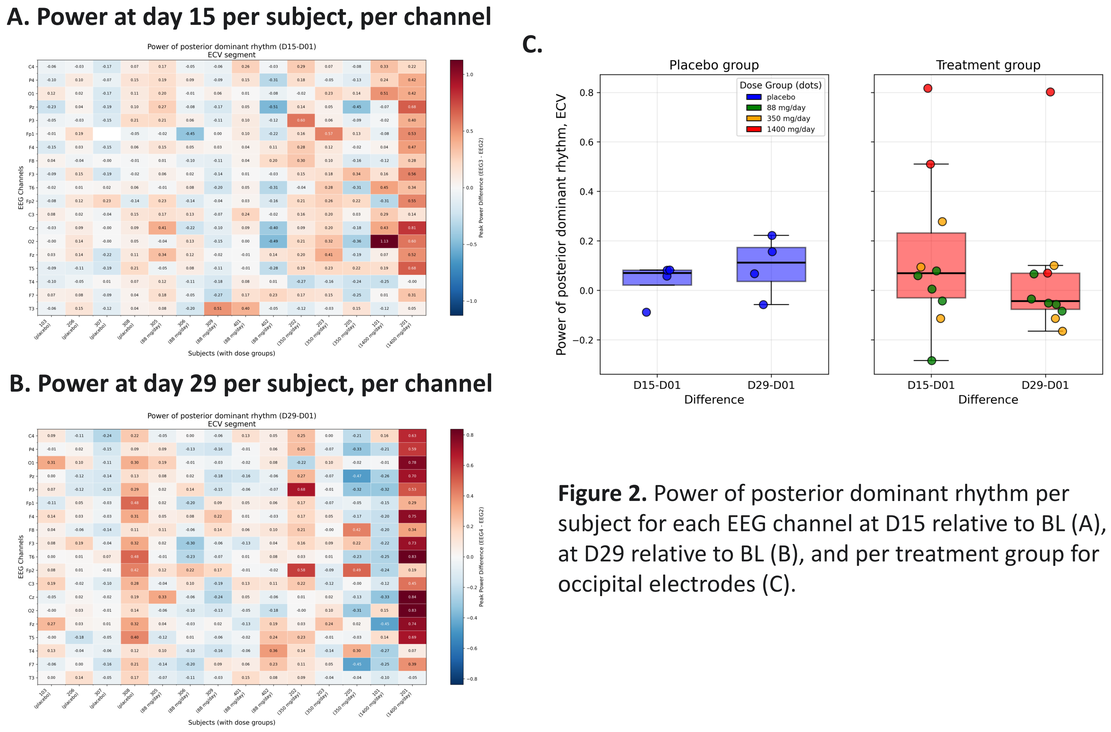

Figure 2. Power of posterior dominant rhythm per subject for each EEG channel at D15 relative to BL (A), at D29 relative to BL (B), and per treatment group for occipital electrodes (C).

- Subjects on **REM127 showed increased posterior dominant rhythm power on D15 relative to BL** compared to placebo, mostly driven by the two subjects receiving the 1400 mg dose (Figure 2).
- By D29, this oscillatory power declined in the treatment group relative to D15, whereas the placebo group showed an increase on D29 relative to BL, mainly driven by a single subject (Figure 2).

2. Longitudinal decreases in aperiodic features in REM127-treated subjects.

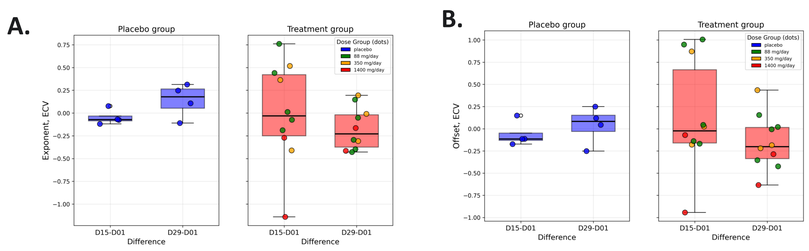

Figure 3. Aperiodic exponent (A) and offset (B) at D15 and D29 relative to BL per treatment group for occipital electrodes.

- The **aperiodic exponent decreased in the treatment group on D15 and D29 relative to BL**, but increased in the placebo group on D29 relative to BL (Figure 3A).
- The **aperiodic offset decreased in the treatment group on D15 and D29 relative to BL**, while it increased in the placebo group on D15 and D29 (Figure 3B).

3. Correlation matrix of EEG features and clinical and biological measures

- No significant correlations were observed between EEG features (posterior dominant rhythm power, aperiodic exponent, aperiodic offset) and CSF biomarkers (Aβ, tau), neurotransmitters (dopamine, GABA), and cognitive scores (MMSE, ADAS-Cog) (Figure 4).

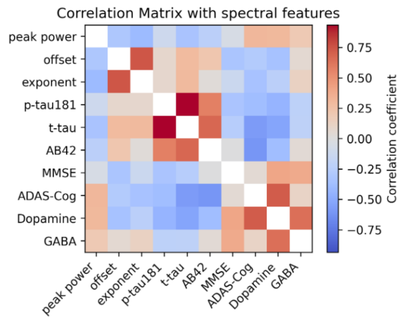

Figure 4. Correlation matrix between biomarker and EEG changes from BL to D29.

CONCLUSION

- REM127 increased the power of the posterior dominant rhythm within 15 days, indicating enhanced cortical activity and potential symptomatic benefits in AD.
- Longitudinal reduction of aperiodic offset and exponent indicate REM127 partially restored the excitation-inhibition imbalance seen in AD, potentially leading to healthier circuit function.
- Treatment effects on posterior dominant rhythm power were strongest on day 15, but likely masked by systemic toxicity by day 29, while aperiodic features continued to show longitudinal treatment effects.
- Periodic and aperiodic EEG features enable evaluation of rhythmic peaks without relying on canonical frequency bands and provide sensitive, non-invasive biomarkers of early pharmacodynamic effects in AD.

REFERENCES

[1]*Maestu, F., et al., Neuronal excitation/inhibition imbalance: core element of a translational perspective on Alzheimer pathophysiology. Ageing Res Rev, 2021. 69: p. 101372.*
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[3]*de Cheveigne, A., ZapLine: A simple and effective method to remove power line artifacts. Neuroimage, 2020. 207: p. 116356.*
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