Translational pharmacology of PRAX-944, a novel T-type calcium channel blocker for the treatment of essential tremor

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Essential Tremor: the most common movement disorder

Essential tremor: a high prevalence, high burden movement disorder

- Essential Tremor (ET) is the most common movement disorder; with 7x the prevalence of Parkinson's Disease
- ET affects ~7 million people in the US alone
- Burden of disease in ET extends beyond the tremor
- To date, there have been no medications developed specifically for people with ET
- Discontinuation rates for available treatments are high due to limited efficacy and poor tolerability

See also virtual poster "The Hidden Disease Burden and Treatment Experience of Patients with Essential Tremor: A Retrospective US Claims Analysis " [Abstract #1555]

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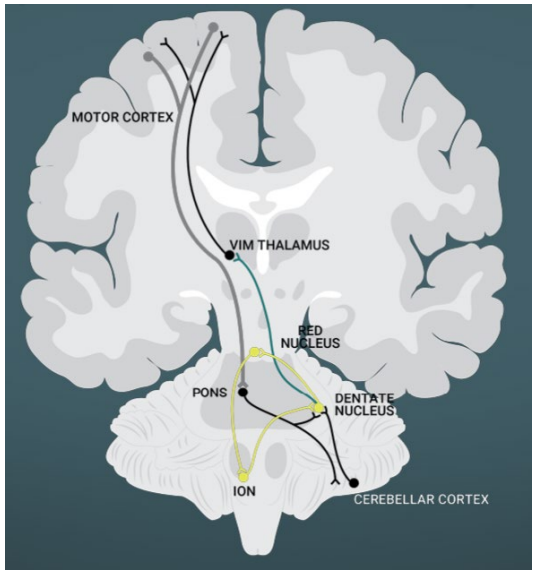
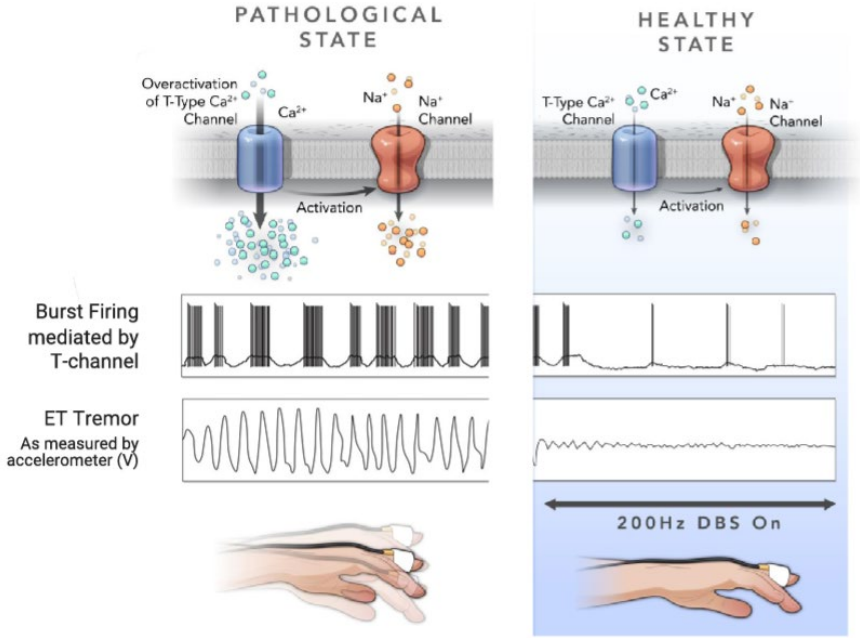
T-type calcium channels modulate neuronal firing patterns within the cerebello-thalamo-cortical circuit

T-Type calcium channels blockade represents a potential therapeutic target in ET

- Mutations in T-type Ca^{2+} channels are genetically linked to familial ET
- T-type Ca^{2+} channels drive burst firing in the CTC circuit; aberrant CTC bursting correlates with tremor in ET
- Deep brain stimulation reduces burst firing and tremor



Cerebello-thalamo-cortical circuit



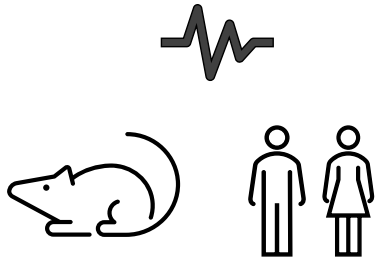
Right: Based on figure from Milosevic et al. 2018. Actual patient intraoperative real-time single-unit recordings of action potentials of individual neurons

Hypotheses and Objectives

PRAX-944 is a potent and selective small molecule T-type Ca^{2+} channel blocker currently in clinical development for the treatment of ET

- Due to the role of T-type Ca^{2+} channels in the CTC circuit, T-type Ca^{2+} channel blockade and subsequent reduction of CTC burst firing may provide effective treatment in ET
  - We first determined PRAX-944 effects in a rodent assay of ET, as well as general locomotor activity

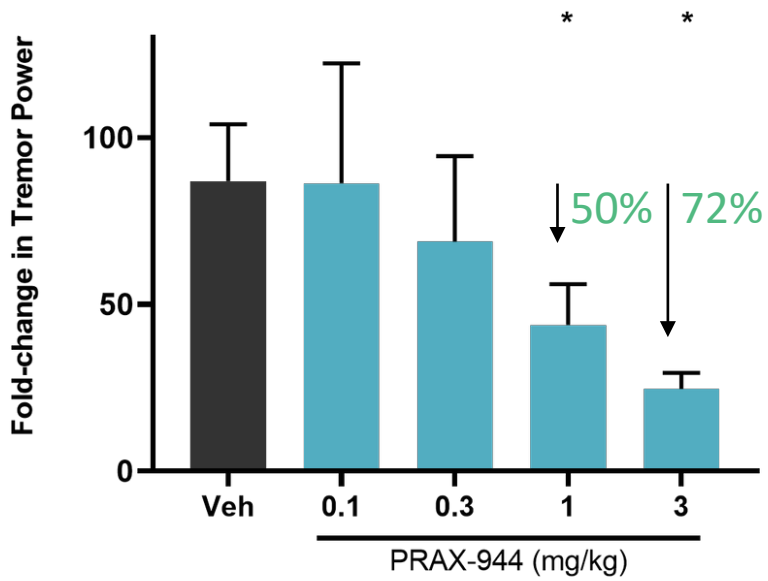
- T-type Ca^{2+} channels also play important roles in regulating cortical EEG power in the sigma frequency band (σ-power, 12-16 Hz) during NREM sleep
  - We therefore used NREM σ-power as a translational CNS biomarker of T-type Ca^{2+} blockade in rodent and human studies to determine whether pharmacodynamically active doses of PRAX-944 are well-tolerated



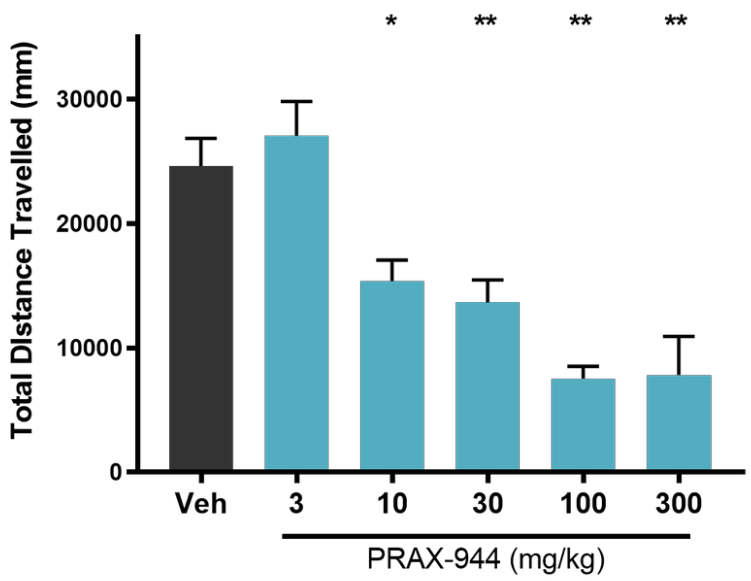
Collectively, our preclinical and clinical data were intended to inform the selection of potentially efficacious doses for subsequent trials in patients with ET

PRAX-944 dose-dependently reduced rat harmaline-induced tremor at doses that did not reduce locomotor activity

A Rat harmaline-induced tremor



B Rat spontaneous locomotor activity



PRAX-944 reduces harmaline-induced tremor with no evidence of locomotor side-effects

A. Fold-change in harmaline-induced tremor power = Average power post-harmaline / average baseline power (pre-harmaline).
B. Total distance travelled in the 30-minute sLMA test.

Mean ± SEM displayed. *$P < 0.05$, **$P < 0.01$ vs. Vehicle (Veh)

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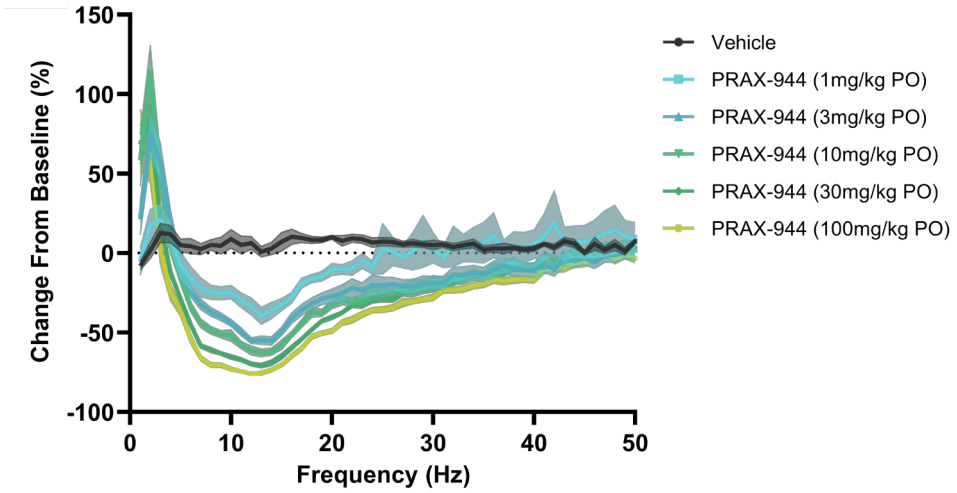
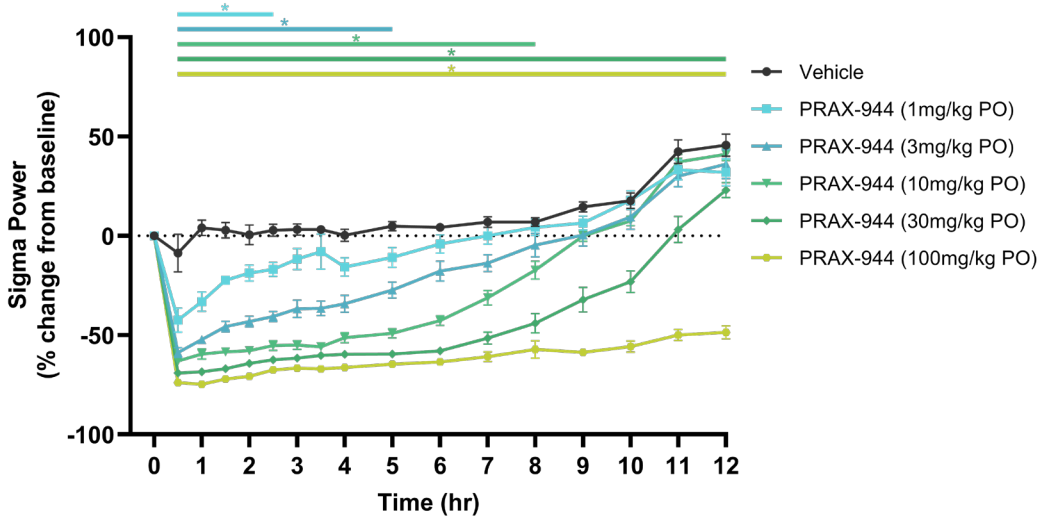
PRAX-944 dose-dependently reduced NREM sigma power in rats

A

Rat NREM: 30-60 min post-dose



B



PRAX-944 reduces NREM σ-power in rats, with evidence of an exposure-dependent relationship between PRAX-944 and NREM σ-power

A. Change in NREM spectral power relative to baseline, by treatment group (30-60 min after treatment).
B. Time course of NREM σ-power change by treatment group (over 12 hours). Treatment administered at Time = 0 hr.

33%-52% reduction in NREM σ-power at doses that reduced harmaline-induced tremor without locomotor side effects.

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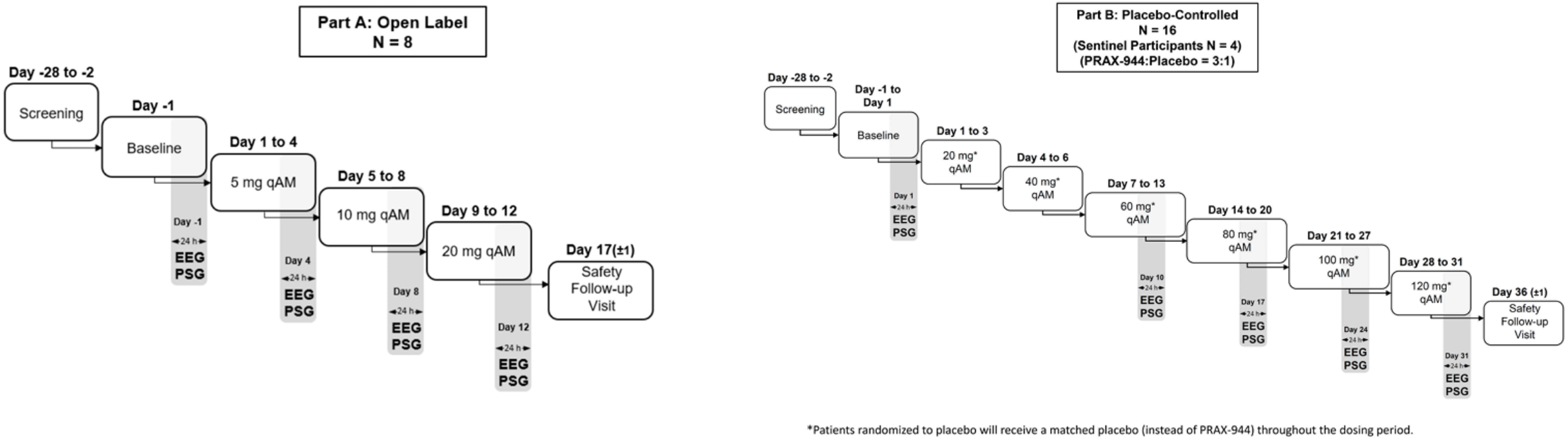
Mean ± SEM displayed. *$P < 0.05$ vs. Vehicle.

PRAX-944-105: a multiple ascending dose trial in healthy adult participants

- Within-participant design in healthy adult participants examining pharmacokinetics, safety, tolerability and pharmacodynamics of PRAX-944 over a wide dose range



*Patients randomized to placebo will receive a matched placebo (instead of PRAX-944) throughout the dosing period.

PRAX-944 was well-tolerated from 5 mg up to 120 mg daily with no serious or severe adverse events

- In both Parts A and B, most adverse events were mild and resolved without any intervention

PRAX-944-105 trial registration ACTRN12620000675921 (www.anzctr.org.au)

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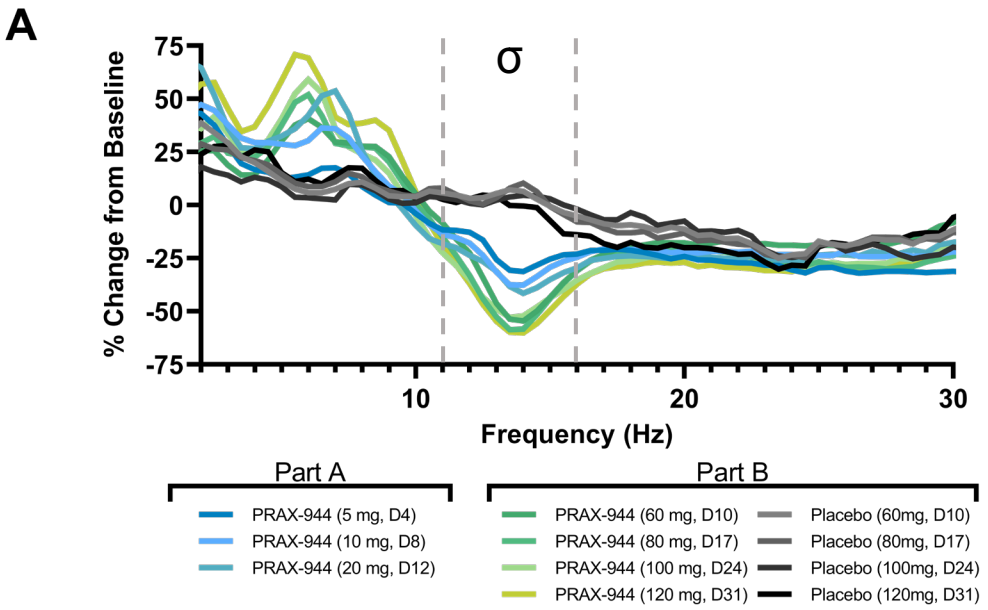
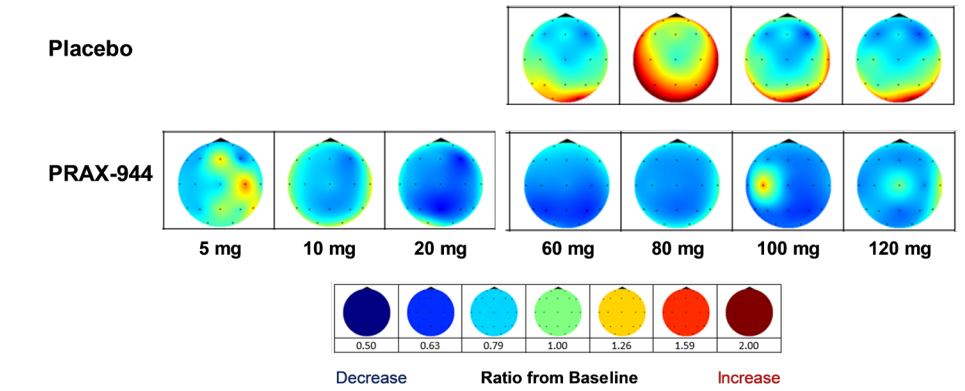
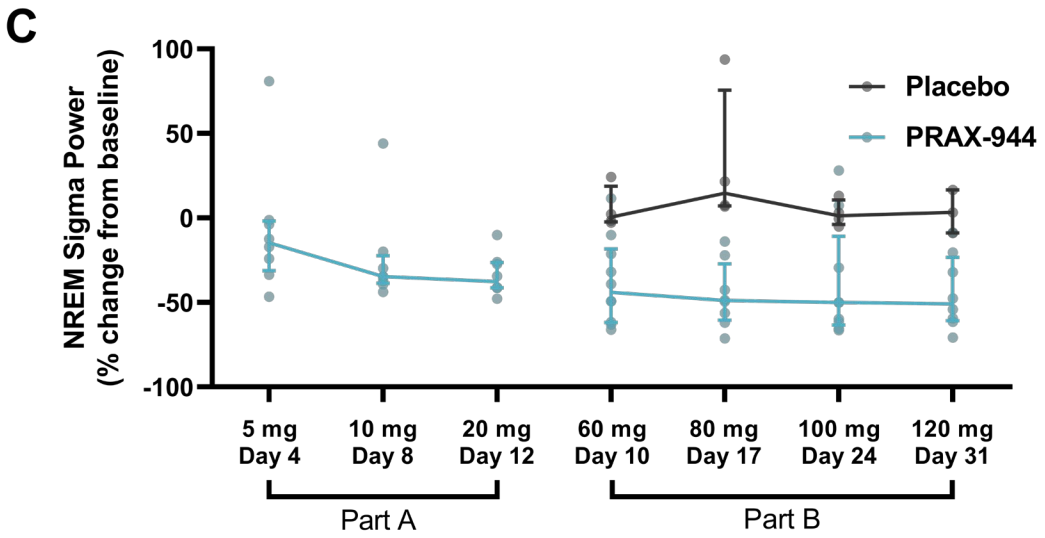
PRAX-944 reduced NREM sigma power in healthy participants at doses that were well tolerated (PRAX-944-105)







PRAX-944 reduced NREM σ-power in healthy participants at wide range of well-tolerated doses

A. Percentage change in absolute NREM spectral power relative to baseline, by treatment group.

B. EEG flat maps depicting absolute NREM σ-power change from baseline across each electrode.

C. Absolute NREM σ-power change from baseline. Data presented as % change from baseline based on the average of the 9 central electrodes. Circles denote values from individual participants; lines represent median +/- interquartile range.

34%–50% reduction in NREM σ-power at doses from 10-120 mg

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Summary and Conclusions

- Administration of PRAX-944 in rats and humans produced strong and consistent effects on NREM σ-power, representing a potentially clinically important translational CNS biomarker of T-type Ca^{2+} channel blockade
- In rats, reduced NREM σ-power was observed at PRAX-944 doses, and corresponding brain and plasma concentrations, that reduced harmaline-induced tremor, without evidence of locomotor side-effects
- In humans, the comparable reduction in NREM σ-power observed suggests that similar T-type Ca^{2+} channel blockade was achieved at a wide range of well-tolerated doses

Our combined clinical and preclinical findings suggest that the doses of PRAX-944 tested in healthy participants may hold promise for reducing tremor in patients with ET

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PRAX-944 Clinical Development

Ongoing Phase 2 studies of PRAX-944 in patients with ET will provide valuable further insights into the therapeutic potential of T-type Ca^{2+} channel blockers for ET, and the utility of NREM σ-power as a pharmacodynamic CNS biomarker of T-type Ca^{2+} channel blockade

- Phase 2a topline results are expected in May 2022; with initial results indicating tremor reduction in patients at well-tolerated doses
  - See virtual poster “PRAX-944-221: A Phase 2 Clinical Trial Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of PRAX-944 in Adults with Essential Tremor” [Abstract #1557]
- Phase 2b Essential1 study is currently ongoing and enrolling patients, with topline results expected in the second half of 2022 (https://essential1trial.com/)
  - See virtual poster “PRAX-944-222: A Phase 2 Randomized, Double-blind, Placebo-controlled Trial of PRAX-944 for the Treatment of Essential Tremor” [Abstract #1558]

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Questions?

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