A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial of PRAX-944 for the Treatment of Essential Tremor

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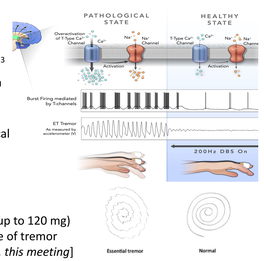
Background

- Essential tremor (ET) is the most common movement disorder, with high unmet patient needs.[1]
- ET is characterized by involuntary progressive tremor especially in the hands and upper limbs, contributing to patient disability.[2,3]
- Existing treatment options are limited, with high discontinuation rates due to poor tolerability and modest efficacy.[4]
- Mounting evidence indicates tremor is caused by increased neuronal burst firing and oscillations in cerebello-thalamo-cortical circuitry, which are thought to be dependent on T-type Ca^{2+} channel activity.[5-7]
- PRAX-944 is a novel, selective T-type Ca^{2+} channel blocker in clinical development for ET treatment.[8,9]
- Tolerability of pharmacodynamically-active doses of PRAX-944 (up to 120 mg) has been previously demonstrated,[8] as well as previous evidence of tremor reduction in adults with ET.[9] [*see also Olhaye et al second poster, this meeting*]
- The current Phase 2b trial further explores the safety and efficacy of 60 and 100 mg once-daily (QD) PRAX-944 compared to placebo in adult participants with moderate to severe ET.*

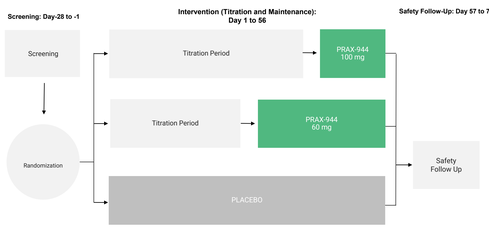


Methods

PRAX-944-222 (Essential1) Study Design*

- This multi-center, randomized, double-blinded, placebo-controlled, dose-range-finding clinical trial, with an optional Extension, will assess the efficacy, safety, and tolerability of PRAX-944 in participants aged 18 years or older who have a diagnosis of ET and have had symptoms for at least 3 years (**Table 1**).
- Approximately 131 adults with moderate-to-severe ET will be recruited.
- Severity of ET in this trial will be defined by eligibility criteria on The Essential Tremor Rating Assessment Scale Activities of Daily Living (TETRAS-ADL), Clinical Global Impression-Severity (CGI-S), and the sum of items 6 and 7 on the TETRAS-Performance Subscale (TETRAS-PS).
- Eligible participants must be off ET medications or stable on their medication for 1 month prior to screening.
- Participants will be randomized 1:1:1 to receive 56 days of titration to 1 of 2 PRAX-944 fixed-dose regimens (60 mg or 100 mg) or placebo, administered orally every morning (***Fig. 1***).
- The optional Extension will provide continuation of treatment to those previously randomized to active study drug and new treatment to those previously randomized to placebo.
- The Essential1 trial will involve safety and efficacy assessments captured across 3 study periods (***Fig. 1***, **Table 2**):
  - Screening/Baseline (up to 28 days); Intervention (56 days); Safety Follow-up (14 days).

*Figure 1. Essential1 Trial Schema**



*The Essential1 protocol was amended in June 2022. As such, there are differences between the submitted abstract and this poster. Key changes from the earlier protocol[9] include removal of the 20 mg treatment arm and amending the primary endpoint following Part B findings from the PRAX-944-221 trial; adjusting the enrollment goal and sample size to appropriately power the primary endpoint; streamlining study eligibility criteria to emphasize functional impairment; and minimizing assessment burden via reduced study visits and removal of Biostamp sub-study.

Trial registration: clinicaltrials.gov/ct2/show/NCT05021991

Participant Eligibility

Table 1. Essential1 Study Eligibility

Key Inclusion Criteria
Adult aged 18 years or older
Clinical diagnosis of ET, for at least 3 years, including tremor syndrome of bilateral upper limb action tremor
Moderate-to-severe functional impairment from tremor, defined as TETRAS-ADL subscale ≥20, the sum of items 6 and 7 on TETRAS-PS >4, and a CGI-S of at least "moderate"
Key Exclusion Criteria
Sporadically using a benzodiazepine, sleep medication, or anxiolytic that would confound tremor assessment
History or clinical evidence of other medical, neurological, or psychiatric condition that may explain or cause tremor, or medication, food, or supplement induced movement disorders
Prior magnetic resonance-guided focused ultrasound or surgical intervention for ET such as deep brain stimulation or thalamotomy
History of any suicide attempt, and/or suicidal ideation with intent within the past 2 years prior to Screening

Safety and Efficacy Assessments

Table 2. Essential1 Safety and Efficacy Assessments

Trial Period	Screening	Titration				Maintenance						Safety Follow-up
Day	**-28 to -1**	**1 (BL)**	**7 (±1)**	**14 (±1)**	**21 (±1)**	**28 (±1)**	**35 (±1)**	**42 (±1)**	**43 (±1**	**44 (±1)**	**54 (±1)**	**55 (±1)**	**56/EOT (±1)**	**70/EOS (±1)**
Safety Assessments														
Vital Signs	X	X		X		X		X					X	X
Physical Examination	X	X											X	X
Clinical Laboratory Evaluations	X	X						X					X	X
12-lead ECG	X	X						X					X	X
C-SSRS (Baseline/Screening)	X													
C-SSRS (Since Last Visit)		X		X		X		X					X	X
Phone Call/Check-in			X		X		X				X			
AE Monitoring	<----------							X					---------->	
Concomitant Meds/ Procedures	<----------							X					---------->	
Efficacy Assessments														
TETRAS ADL	X	X		X		X		X					X	X
TETRAS PS and Video Recording	X	X						X					X	
TETRAS CUL				X		X								
CGI-S	X	X		X		X		X					X	X
CGI-I				X		X		X					X	X
PGI-C				X		X		X					X	X

ADL=Activities of Daily Living; AE=adverse event; BL=baseline; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment (including early termination); ET=Essential Tremor; Meds=Medications; PGI-C=Patient Global Impression of Change; PS=Performance subscale; TETRAS=The Essential Tremor Rating Assessment Scale; TETRAS ADL= The Essential Tremor Rating Assessment Scale Activities of Daily Living; TETRAS CUL=The Essential Tremor Rating Assessment Scale Combined Upper Limb; TETRAS PS=The Essential Tremor Rating Assessment Scale Performance Subscale.

Target Enrollment and Power Calculation

- Approximately 131 participants are planned to be randomized to achieve approximately 99 evaluable participants (ie, 33 per treatment group/regimen).
  - Based on a non-evaluability rate of ~20%, and assuming 5 additional participants were randomized to the 20 mg regimen prior to protocol amendment.
- Assuming a 2-sided test at an alpha level of 0.05, a sample size of 33 evaluable participants per treatment group/regimen with Day 56 modified ADL data would provide ~80% power to detect an effect size of 0.6 between the pooled PRAX-944 (maximum dose level 60 mg and 100 mg regimens) and placebo groups for the primary endpoint of change from baseline in modified ADL.
- An effect size of 0.6 corresponds to a placebo adjusted difference of 3.6 points in the change from baseline modified ADL at Day 56 with an assumed standard deviation of 6 points.
- Enrollment for the Essential1 trial began in October 2021.

Objectives and Endpoints

*Table 3. Essential1 Study Objectives and Associated Endpoints**

Objective	Endpoint
Primary – Efficacy	
• To evaluate the efficacy of PRAX-944 compared to placebo in participants with ET	• Change from baseline to Day 56 on the modified ADL
Secondary – Efficacy	
• To further evaluate the efficacy of PRAX-944 compared to placebo in participants with ET	• Change from baseline to Day 56 on the CGI-S • CGI-I score at Day 56 • Change from baseline to Day 56 on the following: o TETRAS-ADL score o TETRAS-PS total score o TETRAS-UL score (TETRAS-PS item 4) o TETRAS-CUL score (TETRAS-PS sum of items 4, 6, 7, and 8) • PGI-C score at Day 56 • Change from baseline to Days 14, 28, and 42 on the following: o Modified ADL o CGI-S o TETRAS-ADL total score o TETRAS-UL score o TETRAS-CUL score • CGI-I and PGI-C scores at Days 14, 28, and 42 • Change from baseline to Day 42 on the TETRAS-PS total score
Exploratory – Efficacy	
• To evaluate the efficacy of PRAX-944 in participants with ET in the Extension part of the trial	• Change from baseline to Days 70, 84, 99, 129, 159, and 189 in the following: o Modified ADL o CGI-S o TETRAS-ADL total score o TETRAS-PS total score o TETRAS-UL score o TETRAS-CUL score • CGI-I and PGI-C scores at Days 70, 84, 99, 129, 159, and 189
Safety	
• To evaluate the safety and tolerability of PRAX-944 compared to placebo in participants with ET	• Incidence and severity of AEs, including discontinuation of study drug due to AEs • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in ECG parameters • Incidence of C-SSRS measured suicidal ideation or behavior

ADL=Activities of Daily Living; AE=adverse event; BAI=Beck Anxiety Inventory; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=Essential Tremor; PGI-C=Patient Global Impression of Change; PGI-C=Patient Global Impression of Change; PS=Performance subscale; TETRAS=The Essential Tremor Rating Assessment Scale; TETRAS ADL= The Essential Tremor Rating Assessment Scale Activities of Daily Living; TETRAS CUL=The Essential Tremor Rating Assessment Scale Combined Upper Limb.; TETRAS PS=The Essential Tremor Rating Assessment Scale Performance Subscale; TETRAS UL=The Essential Tremor Rating Assessment Scale Upper Limb.

Conclusions

- **The Essential1 trial will evaluate the safety and efficacy of titration to PRAX-944 60 mg, or 100 mg compared to placebo in participants with ET.**
- **The primary objective of this trial is to evaluate the efficacy of PRAX-944 compared to placebo in participants with ET.**
- **A secondary objective is to establish the dose-response profile of PRAX-944 with respect to efficacy.**
- **Expanding on preliminary findings, the Essential1 trial will further examine the safety and efficacy of PRAX-944 in adults with ET, and will determine optimal doses and endpoints for evaluation in later phase studies.**
- **Importantly, the unique design seeks to address the sub-optimal benefit-risk profile of current therapies and associated unmet needs in ET.**

References

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