A Phase 2 Clinical Trial Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of PRAX-944 in Adults with Essential Tremor

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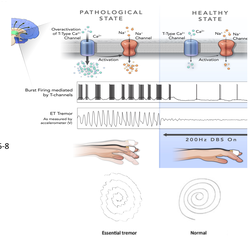
Background

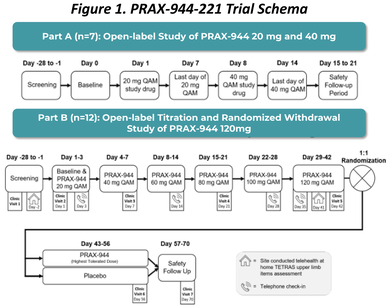
- Essential tremor (ET) is the most common movement disorder, with high unmet patient needs.[1]
- ET is characterized by involuntary progressive tremor especially in the hands and upper limb, contributing to patient disability.[2,3]
- Existing treatment options are limited, with high discontinuation rates due to poor tolerability and modest efficacy.[4]
- Mounting evidence points to increased neuronal burst firing and oscillations in cerebello-thalamo-cortical (CTC) circuitry as main drivers of tremor, with modulation of CTC neuronal burst firing patterns thought to be dependent on T-type Ca^{2+} channel activity.[5-8]
- PRAX-944 is a novel, selective T-type Ca^{2+} channel blocker in clinical development for ET treatment.[9,10]
- We present results from PRAX-944-221, a Phase 2 clinical trial evaluating efficacy, safety, tolerability, and pharmacokinetics of PRAX-944 in adults with ET.



Methods

- PRAX-944-221 was a 2-part trial focused on adult patients (≥18 years) with ET.
- Trial registration: clinicaltrials.gov (NCT05021978)
- **Part A: Open label**
  - PRAX-944 20 mg administered orally every morning for 7 days followed by 40 mg every morning for 7 days
  - Eligible participants were receiving either no medications or 1 stable dose tremor medication, excluding primidone.
  - Primary outcome: change from baseline in upper limb tremor assessed by The Essential Tremor Rating Assessment Scale (TETRAS-UL).
  - Secondary outcomes included change from baseline in measures of tremor severity assessed by The Essential Tremor Rating Performance Scale (TETRAS-PS), as well as safety and tolerability measures.
  - Mean change from baseline in TETRAS scores were transformed using Weber-Fechner equations to calculate percent changes in tremor amplitude.[11]
- **Part B: Open-label titration followed by randomized, double-blind, placebo-controlled withdrawal**
  - Daily dose levels were titrated from 20 mg up to 120 mg during the open-label phase with at least 14 days of dosing at the highest tolerated dose for each participant.
  - In the randomized, double-blind, placebo-controlled withdrawal phase, participants were either maintained on their final open-label dose or switched to placebo for 14 days.
  - Primary outcome: safety and tolerability; secondary outcomes included TETRAS-UL and other measures of disease impact including accelerometry, TETRAS-PS and TETRAS activities of daily living (TETRAS-ADL).
  - Presented here are accelerometry-based TETRAS-UL findings and exploratory efficacy analyses involving modified ADLs, derived based on selected clinician measured TETRAS-ADL and TETRAS-PS item scores.

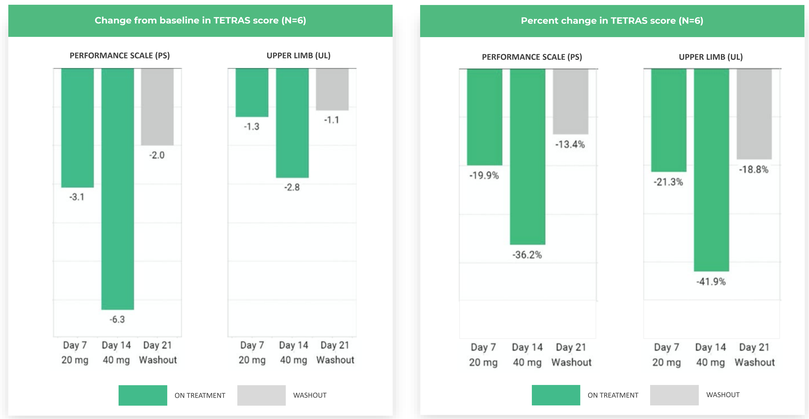
Figure 1. PRAX-944-221 Trial Schema



Part A: PRAX-944 Shows Dose-Dependent Reduction in TETRAS Scores

- Seven participants received PRAX-944 in Part A with 6 participants completing all study visits. Five (83%) participants included in efficacy analyses were taking concomitant propranolol during the intervention period.
- Mean baseline TETRAS-UL score was 12.4 (range 10-15; corresponding to moderate ET).
- PRAX-944 was associated with dose-dependent reductions in tremor amplitude indicated by mean reduction in:
  - TETRAS-PS decrease of 6.3 points from baseline on Day 14 (***Fig. 2**, left*), corresponding to a 36% reduction in tremor severity (***Fig. 2,** right*).
  - TETRAS-UL decrease of 2.8 points from baseline on Day 14 (***Fig. 2**, left)*, corresponding to a 42% reduction in upper limb tremor amplitude (***Fig. 2***, *right*).

Figure 2. PRAX-944-221 Part A data demonstrates dose-dependent reduction TETRAS scores



PRAX-944 Safety and Tolerability

- PRAX-944 is designed to enable once-daily dosing; titration and fit for purpose formulation are key to tolerability profile
- Previous work has demonstrated PRAX-944 tolerability in healthy participants up to 120 mg, with no maximum tolerated dose identified[8]
- Part A and B findings from the PRAX-944-221 trial showed a consistent safety profile with no new safety findings.
- Eight of 11 participants completed open-label titration phase of Part B at highest dose of 120 mg; three of 14 evaluable participants discontinued, due to treatment emergent adverse events (TEAE), with 1 discontinuation unrelated to study drug in Part B.
- TEAEs were all mild to moderate, with the exception of one severe AE of essential tremor that occurred in a placebo arm patient following withdrawal of PRAX-944.
- All TEAEs leading to down-titration or discontinuation were mild to moderate.

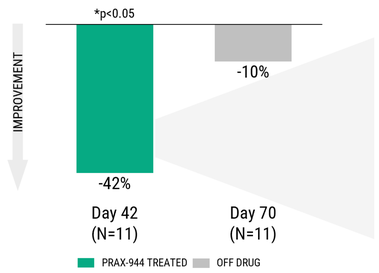
Conclusions

- **Our findings from PRAX-944-221 provide preliminary evidence that PRAX-944 can reduce tremor symptoms at well-tolerated doses in patients with ET.**
- **Part B demonstrated marked functional benefits, with withdrawal of PRAX-944 resulting in regression to baseline severity.**
- **TEAEs leading to down-titration or discontinuation were mild to moderate, with no new safety findings identified.**
- **Continuing investigations, including an 8-week, randomized, placebo-controlled, dose-range finding Phase 2b trial [PRAX-944-222 (Essential1); NCT05021991], will determine optimal doses for evaluation in registrational studies in ET.**

Part B: Functional Benefits Observed on Treatment

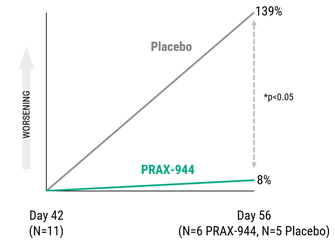
- Eleven of 14 evaluable patients completed both open-label and randomized withdrawal (6 PRAX-944, 5 placebo) phases.
- Marked functional benefit was observed on treatment with PRAX-944, with withdrawal resulting in regression to baseline severity (***Fig. 3 and 4***).
- The observed functional benefit from PRAX-944 was supported by tremor analyses (***Fig. 5 and 6***).
- Spiral task drawings demonstrating the impact of PRAX-944 on ability to draw during the open-label and withdrawal phases are shown in ***Fig. 7.***

Figure 3. Modified ADLs in open label: mean % change from baseline



*Nominal p-value based on ANCOVA

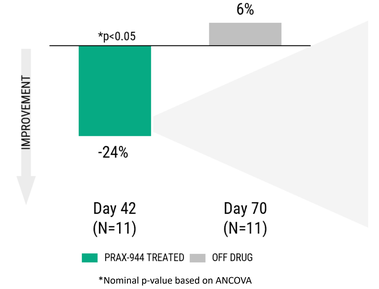
Figure 4. Modified ADLs in randomized withdrawal: mean % change from Day 42



*Nominal p-value based on ANCOVA

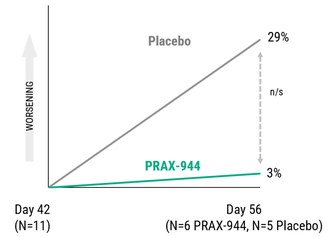
The modified ADL is a composite sum of items 1 to 11 of the TETRAS-ADL subscale and items 6 and 7 on the TETRAS-PS

Figure 5. Kinesia One in open label: mean % change from baseline



*Nominal p-value based on ANCOVA

Figure 6. Kinesia One in randomized withdrawal: mean % change from Day 42



Kinesia One assessments are based on TETRAS-UL tasks performed by participants while wearing a Kinesia One accelerometer

Figure 7. Example of spiral task (item 6 of TETRAS-PS) from Part B patient

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