Essential1: Results from a Phase 2 Trial Evaluating the Tolerability, Safety, and Efficacy of Ulixacaltamide in Adults with Essential Tremor

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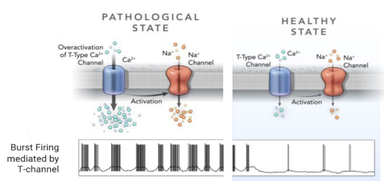
Background

- Essential tremor (ET) is the most common movement disorder, with high unmet patient need.[1,2]
- ET is characterized by involuntary progressive tremor especially in the hands and upper limbs, contributing to patient disability.[3,4]
- Existing treatment options are limited, with high discontinuation rates due to poor tolerability and modest efficacy.[5]
- Mounting evidence indicates tremor is caused by disrupted neuronal burst firing in underlying circuitry; thought to be dependent on T-type Ca^{2+} channel activity.[6-8]
- Ulixacaltamide (PRAX-944) is a novel, selective T-type Ca^{2+} channel blocker currently in clinical development for ET treatment.[9,10]
- Tolerability of pharmacodynamically-active doses (up to 120 mg) has been previously demonstrated,[9] as well as previous evidence of tremor reduction in adults with ET.[10]



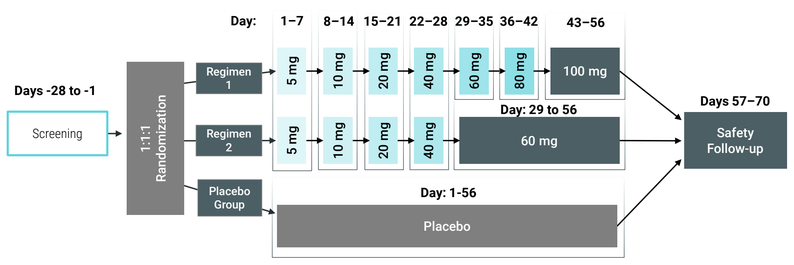
➢ ***Here, we report results from the Essential1 Phase 2b trial which explored the efficacy and safety of 60 and 100 mg once-daily (QD) ulixacaltamide compared to placebo in adults with moderate to severe ET.***

Methods

Essential1 Study Design

- Multi-center, randomized, double-blinded, placebo-controlled, dose-range-finding trial, with optional Extension
- Participants were randomized 1:1:1 to receive 56 days of titration to 1 of 2 ulixacaltamide fixed-dose regimens (60 mg or 100 mg) or placebo, administered orally every morning.
- Safety and efficacy assessments were captured across 3 study periods: Screening/Baseline (up to 28 days); Intervention (56 days); Safety Follow-up (14 days).
- The primary efficacy endpoint was The Essential Tremor Rating Assessment Scale (TETRAS) modified Activities of Daily Living (mADL) total score; derived based on selected clinician measured TETRAS-ADL and TETRAS-Performance Subscale (TETRAS-PS) item scores.

Figure 1. Essential1 Design



PRIMARY ENDPOINT
- Change from baseline to Day 56 on the TETRAS modified Activities of Daily Living (mADL, ***Fig. 2–4***)

SECONDARY ENDPOINTS
- Clinical Global Impression-Severity (CGI-S, ***Fig. 5 & 6***)
- Patient Global Impression-Change (PGI-C, ***Fig. 5 & 6***)
- TETRAS-ADL total score, TETRAS-UL score, TETRAS-CUL score, TETRAS-PS score ***(Fig. 2)***

POST-HOC ANALYSES
- mADL excluding TETRAS-PS items ***(Fig. 2 (middle) & 6)***

CUL = Combined Upper Limb; UL = Upper Limb

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

Key Participant Inclusion and Exclusion Criteria

- CLINICAL DIAGNOSIS OF ET OF ≥3 YEARS
- MODERATE TO SEVERE FUNCTIONAL IMPAIRMENT DETERMINED USING TETRAS AND CGI-S
- COULD CONTINUE PROPRANOLOL AT A STABLE DOSE
- NO PRIOR SURGICAL INTERVENTION OR FOCUSED ULTRASOUND FOR TREATMENT OF ET

TETRAS = TRG Essential Tremor Rating Assessment Scale; CGI-S = Clinical Global impression – Severity

Modified TETRAS ADL measures observed

1. Speaking
2. Feeding with a spoon
3. Drinking from a glass
4. Hygiene
5. Dressing
6. Pouring
7. Carrying food trays, plates, or similar items
8. Using keys
9. Writing
10. Working
11. Overall disability with most affected task

PS6. Spirals (left, right)
PS7. Handwriting

Each measure is individually scored from 0-3

0 = Slightly abnormal. Tremor is present but does not interfere with __.
1 = Mildly abnormal. Spills a little.
2 = Moderately abnormal. Spills a lot or changes strategy to complete task
3 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup

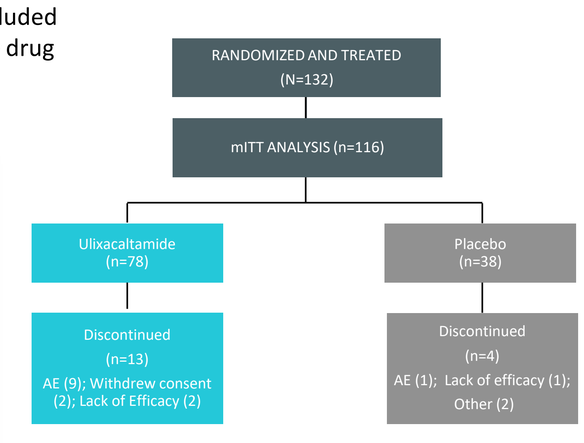
TOTAL SCORE OF UP TO 42

Participant Disposition and Baseline Characteristics

- 132 adults were randomized and treated; 116 were included in mITT analysis; all of whom received ≥1 dose of study drug

Table 1. Demographics and Baseline Characteristics (mITT)

	ULIXACALTAMIDE (n = 78)	PLACEBO (n = 38)
Age, mean (min, max)	70.4 (32, 86)	67.7 (29, 88)
Gender (Male / Female, %)	59% / 41 %	58% / 42%
Family history of ET	59 (76%)	23 (61%)
Propranolol use	27 (35%)	9 (24%)
Duration of ET, mean (years)	20.3	20.2
mADL score, mean (min, max)	20.6 (12, 32)	20.8 (12, 34)
ADL score, mean (min, max)	29.0 (20, 38)	28.6 (19, 39)
mADL excluding PS , mean (min, max)	16.4 (9, 25)	16.4 (8, 25)



mITT analysis: Defined as all patients enrolled under Version 4 of Protocol (or enrolled in prior version and eligible for V4), who were randomized to treatment, and received at least 1 dose of study drug [n=116].
Excluded from mITT analysis are 16 patients enrolled under the earlier protocol version and did not meet Version 4 inclusion/exclusion criteria and dose levels.
Safety analysis population (N=132).

Ulixacaltamide Was Generally Well-tolerated

*Table 2. Essential1 Tolerability Summary**

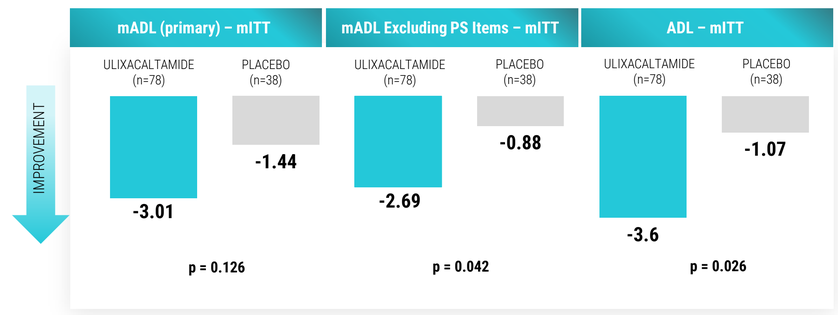
	ULIXACALTAMIDE (n=91)	PLACEBO (n=41)
SUBJECTS-ANY TEAE	*70 (76.9%)*	*21 (51.2%)*
TEAEs >5%		
Dizziness	13 (14.3%)	2 (4.9%)
Constipation	9 (9.9%)	0
Headache	8 (8.8%)	1 (2.4%)
Fatigue	8 (8.8%)	1 (2.4%)
Anxiety	6 (6.6%)	0
Feeling abnormal	6 (6.6%)	0
Paraesthesia	6 (6.6%)	0

*3 SAEs in 2 subjects, all deemed unrelated to treatment (exacerbation of COPD in 1 patient; esophageal obstruction & gastric adenocarcinoma in 1 patient).

Table 3. Essential1 Discontinuations Summary – mITT

	ULIXACALTAMIDE (n=78)	PLACEBO (n=38)
Discontinuation	13 (17%)	4 (11%)
Discontinuation due to AEs	9 (12%) (1) Hallucination (1) Restless Legs (1) Anxiety (2) Dizziness (1) Feeling Abnormal (1) Confusion (1) Constipation (1) Mental Impairment	1 (3%) (1) Adenocarcinoma, gastric
Days to AE (min, max)	(3, 39)	(28, 28)

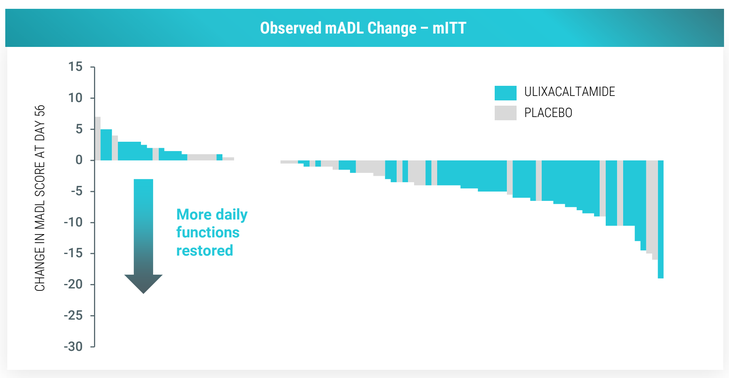
Essential1 Efficacy Results

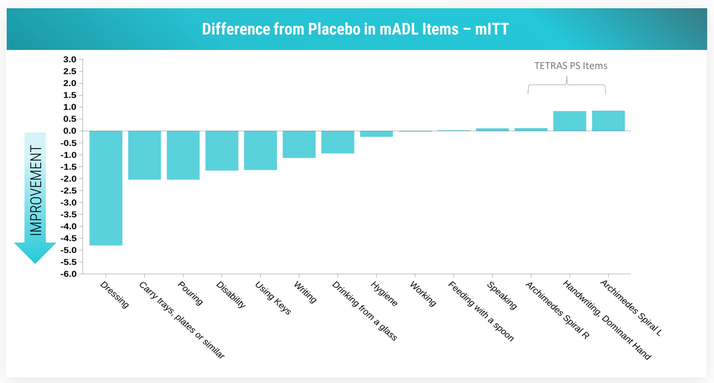


Mixed Model Repeated Measures (MMRM), Adjusted by baseline value, propranolol use, and familial history of ET. All p values are nominal.

Figure 2. Least Squares Mean Change in mADL and ADL Score at Day 56 by Treatment Group
Ulixacaltamide Demonstrated Improvement Over Placebo in the mADL, mADL Excluding TETRAS-PS items, and TETRAS-ADL Score.

Figure 3. Observed Change in mADL Score at Day 56 in Individual Patients
More Patients Taking Ulixacaltamide Showed Greater Improvements in mADL Scores Compared to Patients on Placebo

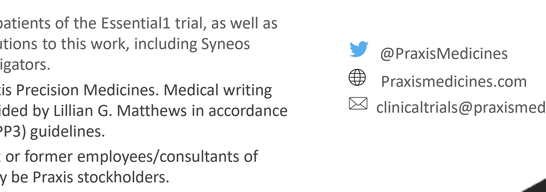




MMRM, Adjusted by baseline value, propranolol use, and familial history of ET.

Figure 4. Fold-Change Difference Between Placebo and Ulixacaltamide at Day 56 for mADL Individual Item Scores Adjusted by Placebo
Ulixacaltamide Demonstrated Consistent Effect Relative to Placebo Across ADL Scored Items in Essential1 Study

Figure 6. Post-hoc Responder Analysis at Day 56
Patients Taking Ulixacaltamide Had Greater Response Rates Compared to Patients on Placebo for the mADL and mADL Excluding PS Items



*Chi-sq comparisons in Day 56 response rates between ulixacaltamide and placebo;
Response rates reflect % of patients achieving a Minimally Clinical Important Difference (MCID) based on distribution method and a 0.5 and 1.0 SD threshold.[11]
One standard deviation equals 4.92 for mADL, 4.67 for ADL, and 4.07 for mADL excluding PS.

Figure 5. Patient and Clinician-Reported Change in Status
Patients and Investigators Reported Higher Overall Improvement in Status with Ulixacaltamide vs Placebo

All p-values are nominal; *RANK ANALYSIS; **RANK ANCOVA

Conclusions

- **Ulixacaltamide demonstrated improvement in the mADL primary efficacy endpoint relative to placebo that did not reach statistical significance, and achieved nominal statistical significance in the TETRAS-ADL secondary endpoint.**
- **Nominal statistically significant improvements were observed in CGI-S and PGI-C.**
- **Ulixacaltamide was well tolerated, with no new safety findings.**
- **Based on the observed efficacy and safety profile, we will engage with the FDA in an end of Phase 2 meeting in June 2023 and intend to initiate the ulixacaltamide Phase 3 program for the treatment of ET in 2H23.**

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