Patient-Focused, Clinically Meaningful Endpoints as Evidence of Improved Outcomes and Durability of Effect Following Ulixacaltamide Treatment in Adults with Essential Tremor: Findings from Essential1

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Background

- Despite being the most common movement disorder, Essential Tremor (ET) remains underrecognized and poorly treated with almost half of patients who seek pharmacological therapy discontinuing medications due to limited efficacy and poor tolerability.[1-5]
- Thus, there is an urgent need for novel therapies with improved efficacy and minimal side effects.
- Ulixacaltamide (PRAX-944) is a differentiated, selective T-type Ca^{2+} channel blocker in clinical development for movement disorders.
- Phase 2b (Essential1, NCT05021991) results in adult ET showed improvement on multiple endpoints including the TETRAS Activities of Daily Living (ADL) and Patient Global Impression of Change (PGI-C) vs placebo at Day 56, alongside a well-tolerated safety profile.[6,7]
- Notably, TETRAS ADL, but not the Performance Subscale, correlated with patient-focused clinical outcome assessments (COA).[6,7]
- Recent FDA guidance highlights the importance of patient-focused COA related to treatment effect;[8] central to this, is the definition of clinical trial endpoints representing functionally relevant, patient-focused clinically meaningful change.
- While the concept of clinically meaningful change has been extensively studied in other movement disorders and other neurological conditions[9,10], to date, this has not been reported in ET.

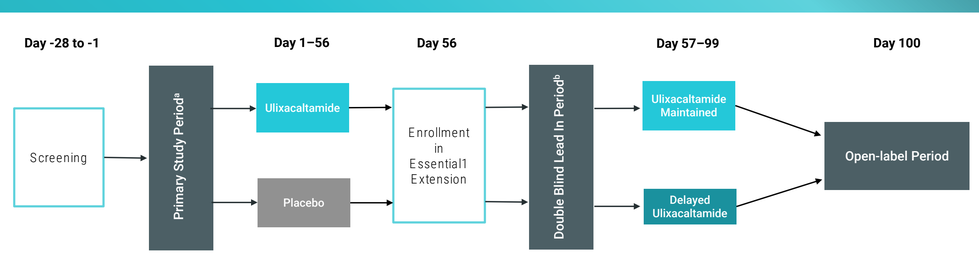
➢ ***Here we explore ADL as a reliable, patient-centered measure of ulixacaltamide efficacy and durability of effect.***

Methods

Essential1 Study Design

- 132 adults with moderate to severe ET were enrolled in Essential1, an 8-week double-blinded, placebo-controlled study with optional Extension.
- Participants were randomized to ulixacaltamide QAM or placebo (Day 1-56), followed by blinded lead-in (DBLI; Day 56-99) during which all participants were titrated to ulixacaltamide before transitioning to an unblinded open-label period (***Fig. 1***).
- Safety and efficacy measures were assessed including TETRAS-ADL (and derivate scales including mADL11 – comprising TETRAS-ADL items, excluding social impact, individually scored from 0-3) and PGI-C.
- Meaningful Score Differences (MSD) capturing clinically meaningful within-patient change in ADL measures were explored using distribution and anchor-based methods with PGI-C as anchor, and corresponding responder analyses conducted.

Figure 1. Essential1 Schema



Trial registration and full trial details: clinicaltrials.gov/ct2/show/NCT05021991

[a] In the primary study period, participants were randomized to receive 56 days of titration to 1 of 2 ulixacaltamide fixed-dose regimens (60 mg or 100 mg QAM) or placebo. No differences were observed between dose groups.
[b] The Essential1 Extension provided continuation of treatment to those previously randomized to active study drug and new treatment to those previously randomized to placebo. Continuing participants participated in a 43-day DBLI Period during which all participants were titrated to the 100 mg dose in a blinded fashion before transitioning to an unblinded open label period.

Participant Disposition and Baseline Characteristics

- 132 adults were originally randomized and treated; 116 were included in mITT analysis of Essential1, all of whom received at least 1 dose of study drug.
- Of those eligible, 75 continued through the DBLI part of the study; 65 were included in completer analysis.

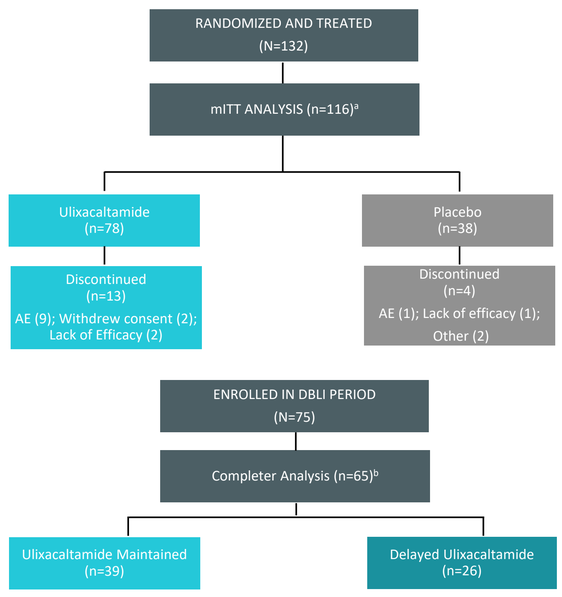


Table 1. Demographics and Baseline Characteristics (mITT), Primary Study Period

	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
ADL score, mean (min, max)	29.0 (20, 38)	28.6 (19, 39)
mADL11, 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 ≥1 dose of study drug.
[a]Excluded from mITT analysis are 16 patients enrolled under the earlier protocol versions and did not meet Version 4 inclusion/exclusion criteria and dose levels.
[b]Excluded from Completer analysis are 10 patients who were enrolled but discontinued during the course of the DBLI period (4 due to AEs, 3 withdrew consent, 3 other).
Safety analysis population (N=132).

Ulixacaltamide is Generally Well-tolerated

*Table 2. Essential1 D56 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

Ulixacaltamide Continues to Be Well-tolerated with No New Safety Signals through Day 99

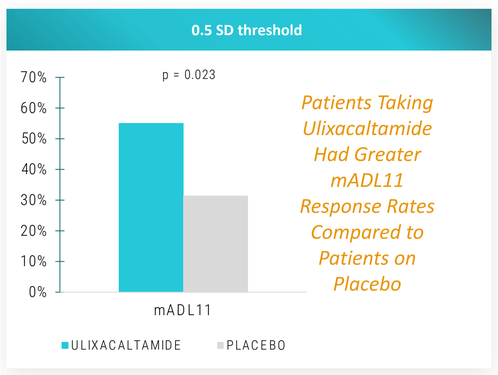
*3 SAEs in 2 subjects, all deemed unrelated to treatment (exacerbation of COPD in 1 patient; esophageal obstruction & gastric adenocarcinoma in 1 patient).

mADL11 as a Measure of Ulixacaltamide Efficacy and Durability

mADL11 is a Reliable, Clinically Meaningful, Patient-focused COA

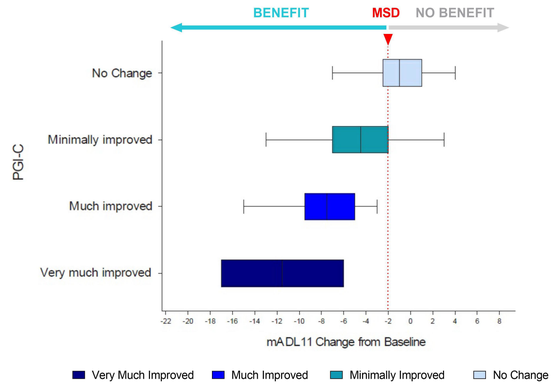
- When examining the magnitude of change in ADL-related scales meaningful to patients, specifically mADL11, distribution and anchor-based methods yielded similar results. An MSD was consistently defined as ≥2 points (***Fig. 2*** and ***Fig. 3***), representing a field-first definition of meaningful within-patient change in adult ET.

Figure 2. Responder Analysis Distribution Method (Day 56, mITT)



Results based on Chi-sq comparisons in Day 56 response rates between ulixacaltamide and placebo; Response rates reflect % of patients achieving an MSD based on the Minimally Clinical Important Difference (MCID) distribution method [11] and a 0.5 SD threshold (equivalent to 2.035 point improvement in mADL11).

Figure 3. Improvement Summary Anchor Based Method (Day 56, mITT)

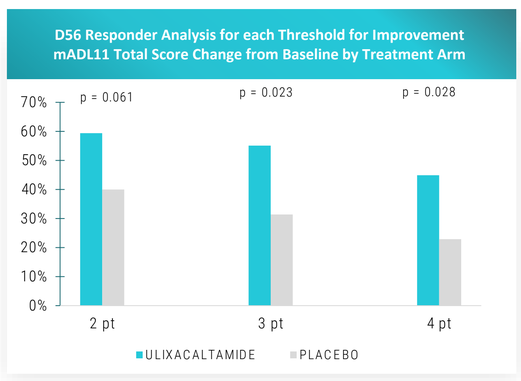


Results based on anchor-based method (PGI-C anchor).[12] mADL11 score change from baseline to Day 56 was evaluated relative to PGI-C change to identify the within-patient meaningful change (ie. MSD). Dashed red line represents the minimum threshold for improvement in mADL11 identified as an MSD of ≥2 points.

Ulixacaltamide Treatment Leads to Changes > MSD

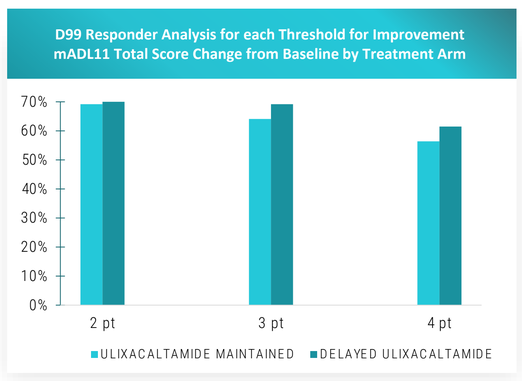
- For mADL11, the MSD of ≥2 points was exceeded by 41 (60%) ulixacaltamide vs 14 (40%) placebo-treated participants, with significantly greater proportions of responders observed in treatment relative to placebo arms at higher cutoffs (***Fig. 4***).
- Sustained responder rates were observed during the DBLI period for ulixacaltamide-continuing participants and increased for those transitioning from placebo to ulixacaltamide (***Fig. 5***).

Figure 4. Responder Analysis (Day 56, mITT)



Results based on Chi-sq comparisons in Day 56 response rates between ulixacaltamide and placebo; Response rates reflect % of patients achieving meaningful change from Day 1 to Day 56 based on anchor-based method and an MSD of ≥2 points. Responder rates at higher cutoffs of 3 and 4 points are also shown.

Figure 5. Responder Analysis (Day 99, Completer Analysis)

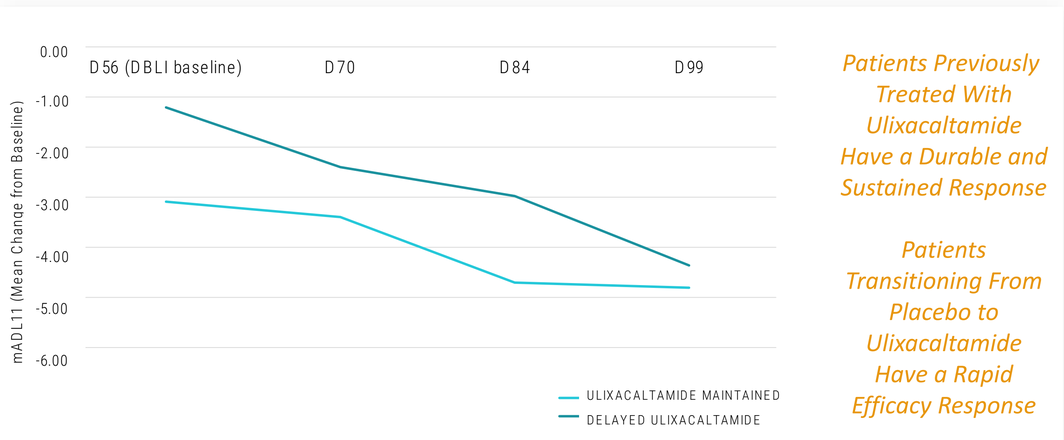


Results based on Chi-sq comparisons in Day 99 response rates between ulixacaltamide and placebo; Response rates reflect % of patients achieving meaningful change from Day 1 to Day 99 based on anchor-based method and an MSD of ≥2 points. Responder rates at higher cutoffs of 3 and 4 points are also shown.

Ulixacaltamide Demonstrates Sustained mADL11 Improvement

- Sustained improvements in mADL11 were observed after 8 weeks for ulixacaltamide-continuing participants and increased for those transitioning from placebo to ulixacaltamide (***Fig. 6***).

Figure 6. Ulixacaltamide Durability of Effect Based on mADL11 (Day 56 to Day 99, Completer Analysis)



Least squares mean change from baseline in mADL11 based on mixed model repeated measures model, adjusted by propranolol use and familial history of ET.

Conclusions

- **This is the first time an MSD is defined in ET using a large patient dataset and a focus on measures determined to be most meaningful to patients.**
- **We highlight mADL11 as a reliable, patient-focused COA related to ulixacaltamide efficacy and durability of effect, with important decision-making implications for ET therapies.**
- **Following a successful End-of-Phase 2 meeting with the FDA in June 2023, we are initiating Essential3, the ulixacaltamide Phase 3 study for the treatment of ET, in Q4 23.**

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Acknowledgments We thank the patients of the Essential1 trial, as well as our collaborators for their contributions to this work, including Syneos Health, the clinical sites and investigators.

Funding All work is funded by Praxis Precision Medicines. Medical writing and editorial assistance were provided by Lillian G. Matthews in accordance with Good Publication Practice (GPP3) guidelines.

Disclosures All authors are current or former employees/consultants of Praxis Precision Medicines and may be Praxis stockholders.

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Presented at:
International Congress of Parkinson's Disease and Movement Disorders
27 - 31 August 2023
Copenhagen, Denmark