

Efficacy and Safety of Ulixacaltamide in Essential Tremor: Topline Phase 3 Results from ESSENTIAL3 Study 1 (Parallel-Design Study)

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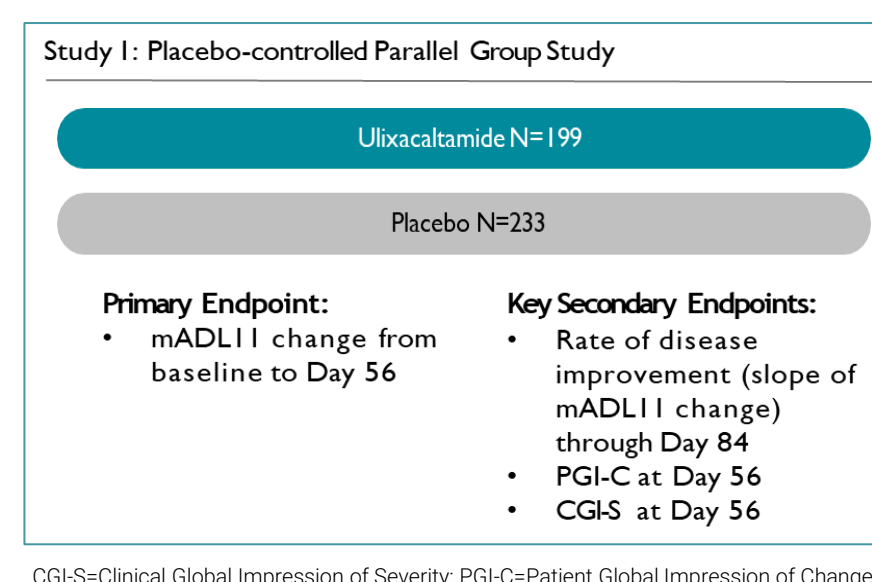
BACKGROUND

- ~7 million people in the US live with essential tremor (ET), one of the most common movement disorders.
- A progressive neurologic disorder, ET is characterized by involuntary tremor causing significant functional disability and presenting profound disruption to daily activities and quality-of-life.
- Existing treatment options are limited, with high discontinuation rates due to poor tolerability and limited efficacy.
- Ulixacaltamide HCl is a selective T-type calcium channel (TTCC) modulator in development for ET, representing the first mechanism-based approach to ET treatment.
- The ESSENTIAL3 Phase 3 Program comprised two simultaneous 12-week pivotal studies with blinded assignment: Study 1 (parallel-group design, PD) and Study 2 (randomized withdrawal, RW, [Plenary PLS5-001](#)), conducted under a unified protocol using a decentralized model, with optional long-term safety extension.
- Here we report results from Study 1 demonstrating the efficacy, safety, and tolerability of ulixacaltamide vs. placebo in adults with ET, representing the first positive Phase 3 findings in ET.

METHODS

ESSENTIAL3 Study 1 Design

- Randomized, double-blind, placebo-controlled trial enrolling participants aged 18–85 years with ET (symptoms ≥3 years; if on ET medication(s), stable dose for ≥28 days prior to screening).
- Integrated, innovative, decentralized design:
 - Unified, single screening and eligibility review process, with study allocation blinded to investigators, participants, and study staff
 - ET diagnosis confirmed by standardized neuro exam adjudicated by Movement Disorder specialists on Eligibility Review Committee
 - Site staff blinded to protocol criteria for threshold of disability and mADL11 stability
 - Contemporaneous data entry with no visibility to endpoint transformation
- Participants randomized 1:1 to ulixacaltamide 60 mg QD (after 2-week titration) or placebo for 12 weeks.
- All primary and key secondary efficacy analyses use the modified intent-to-treat (mITT) population defined as all randomized participants who received ≥1 dose of study drug and had ≥1 post-baseline efficacy assessment.



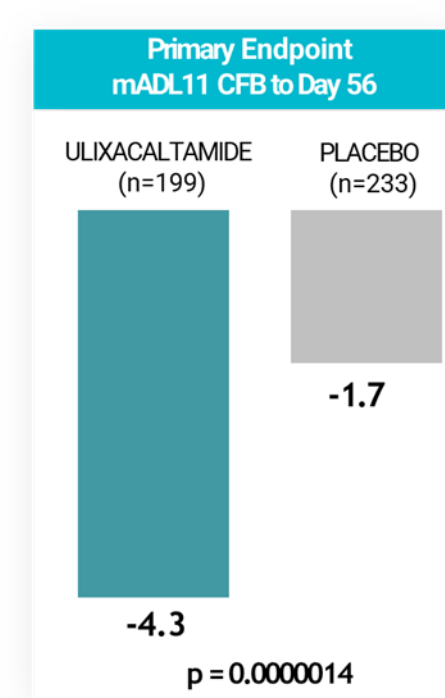
| POPULATIONS | ULIXACALTAMIDE | PLACEBO |
|--------------|----------------|-------------|
| Enrolled/ITT | 236 (100%) | 237 (100%) |
| Safety | 233 (98.7%) | 234 (98.7%) |
| mITT | 199 (84.3%) | 233 (98.3%) |

ESSENTIAL3 Study 1 Demographics and Baseline Characteristics (mITT)

| | ULIXACALTAMIDE (N=199) | PLACEBO (N=233) |
|---|------------------------|----------------------|
| Age, Mean (SD) | 67.9 (9.1) | 68.9 (8.1) |
| Gender, Male/Female % | 57.3% / 42.7% | 56.7% / 43.3% |
| Race, White/Other % | 98.5% / 1.5% | 95.7% / 4.3% |
| Years since ET Onset, Mean (Median) | 29.8 (26.0) | 31.1 (27.0) |
| ET symptoms worsened over past 3 years, Yes % | 188 (94.5%) | 216 (92.7%) |
| Currently on ET Medication, Yes % | 44.2% | 48.1% |
| Currently on Propranolol, Yes % | 35.7% | 36.5% |
| Family History of ET, Yes/No/Unknown % | 71.9% / 20.6% / 7.5% | 72.1% / 19.7% / 8.2% |
| Presence of Intention Tremor, Yes % | 65.3% | 66.1% |
| mADL11, Mean (SD) | 18.5 (2.4) | 18.4 (2.4) |
| Patient Global Impression – Severity, Mean (SD) | 3.0 (0.7) | 2.9 (0.7) |
| Clinician Global Impression – Severity, Mean (SD) | 4.0 (0.6) | 4.0 (0.6) |

PRIMARY ENDPOINT – SIGNIFICANT CLINICAL BENEFIT AT DAY 56

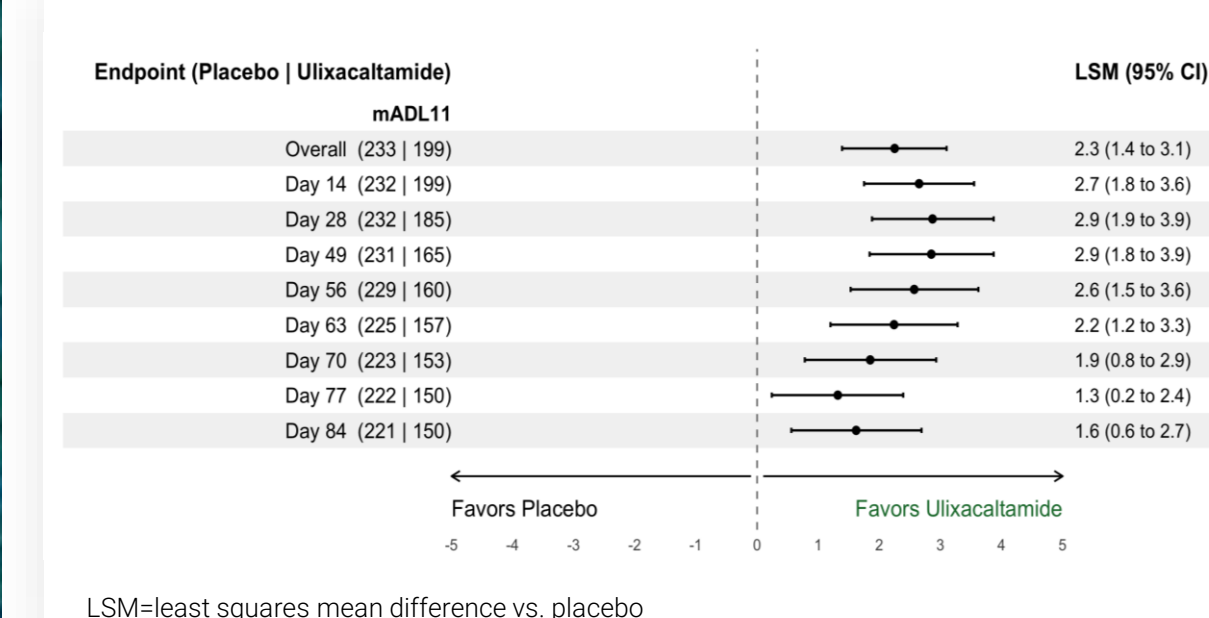
- Ulixacaltamide demonstrated a statistically significant clinical improvement of -2.57 points in the primary endpoint, mADL11 change at Day 56 vs. placebo (95% CI, -3.62 to -1.53; p=0.0000014).
- Sensitivity analyses included assessment of the change in mADL11 across the 12 weeks of treatment (to Day 84).
- Treatment separation emerged early by Day 14 and was sustained through Day 84.



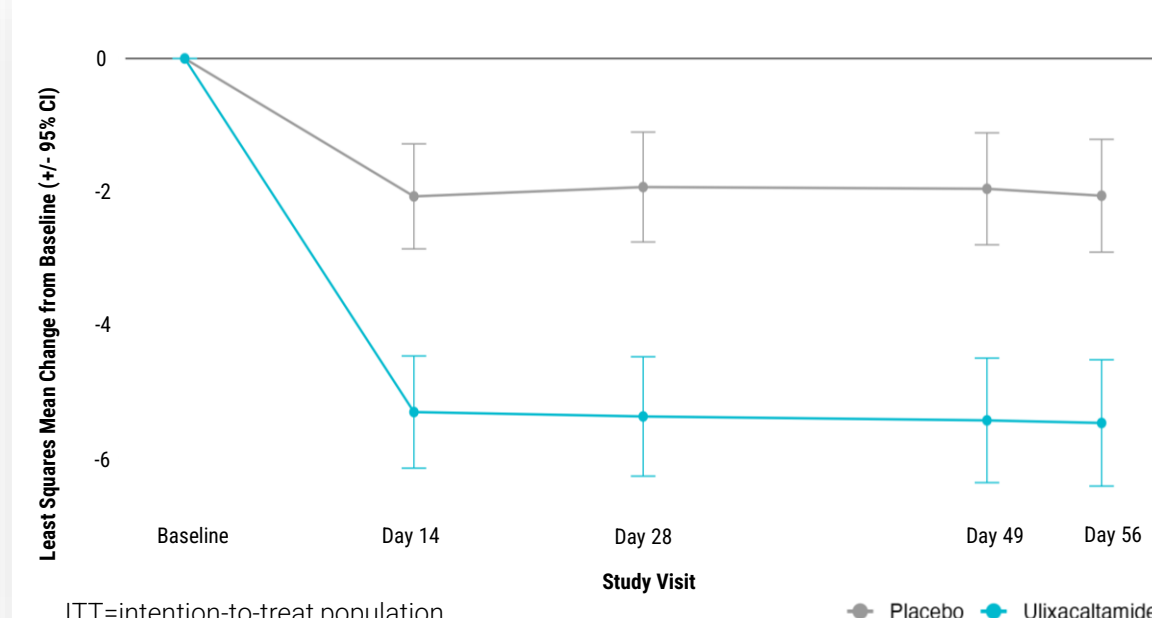
Exploratory Sensitivity Analysis

- Pre-specified tipping point sensitivity analysis evaluating resilience of primary analysis up to a penalty of 2.5 points resulted into benefit in favor of ulixacaltamide of -1.63 (-2.70, -0.57), p=0.0026.

Robust mADL11 Change from Baseline Over 12 Weeks (mITT)



Rapid Onset and Durable Clinically Meaningful Effect Similarly Observed in TETRAS-ADL (ITT)



ULIXACALTAMIDE IS GENERALLY WELL TOLERATED

- Once-daily ulixacaltamide was generally well tolerated, with no drug-related SAEs.
- Most common TEAEs (≥10% of participants) were constipation, dizziness, euphoric mood, and brain fog.
- Most TEAEs occurred during titration, were mild to moderate and resolved.
- CNS AEs tended to start early and resolve during the titration phase.
- Discontinuations were primarily due to AEs, with most common due to dizziness and brain fog.

ESSENTIAL3 Study 1 Tolerability Summary

| | ULIXACALTAMIDE (N=233) | PLACEBO (N=234) |
|---|------------------------|-----------------|
| Participants with any TEAE | 221 (94.9%) | 177 (75.6%) |
| Participants with: | | |
| Mild TEAEs | 98 (42.0%) | 89 (38.0%) |
| Moderate TEAEs | 109 (46.8%) | 78 (33.3%) |
| Severe TEAEs | 14 (6.0%) | 10 (4.3%) |
| Participants with any SAE* | 2 (0.9%) | 8 (3.4%) |
| Participants with drug-related TEAEs leading to discontinuation | 63 (27.0%) | 4 (1.7%) |
| Discontinued from the study | 83 (35.6%) | 13 (5.6%) |

*None related to study drug

CONSISTENT, CLINICALLY MEANINGFUL AND STATISTICALLY SIGNIFICANT RESPONSE ACROSS KEY SECONDARY ENDPOINTS AND SUBGROUP ANALYSIS

- Secondary endpoint hierarchical fixed-sequence testing revealed clinically meaningful and statistically significant benefit vs. placebo in rate of disease improvement (slope of mADL change) through Day 84, and both PGI-C and CGI-S at Day 56.

| Key Secondary Endpoint (mITT) | Least Squares Mean Difference vs Placebo (95% CI) | P-value |
|-------------------------------|---|---------|
| Rate of Disease Improvement | -2.27 (-3.11, -1.42) | <0.0001 |
| PGI-C at Day 56 | -0.60 (-0.81, -0.39) | <0.0001 |
| CGI-S Change at Day 56 | -0.29 (-0.46, -0.12) | 0.0007 |

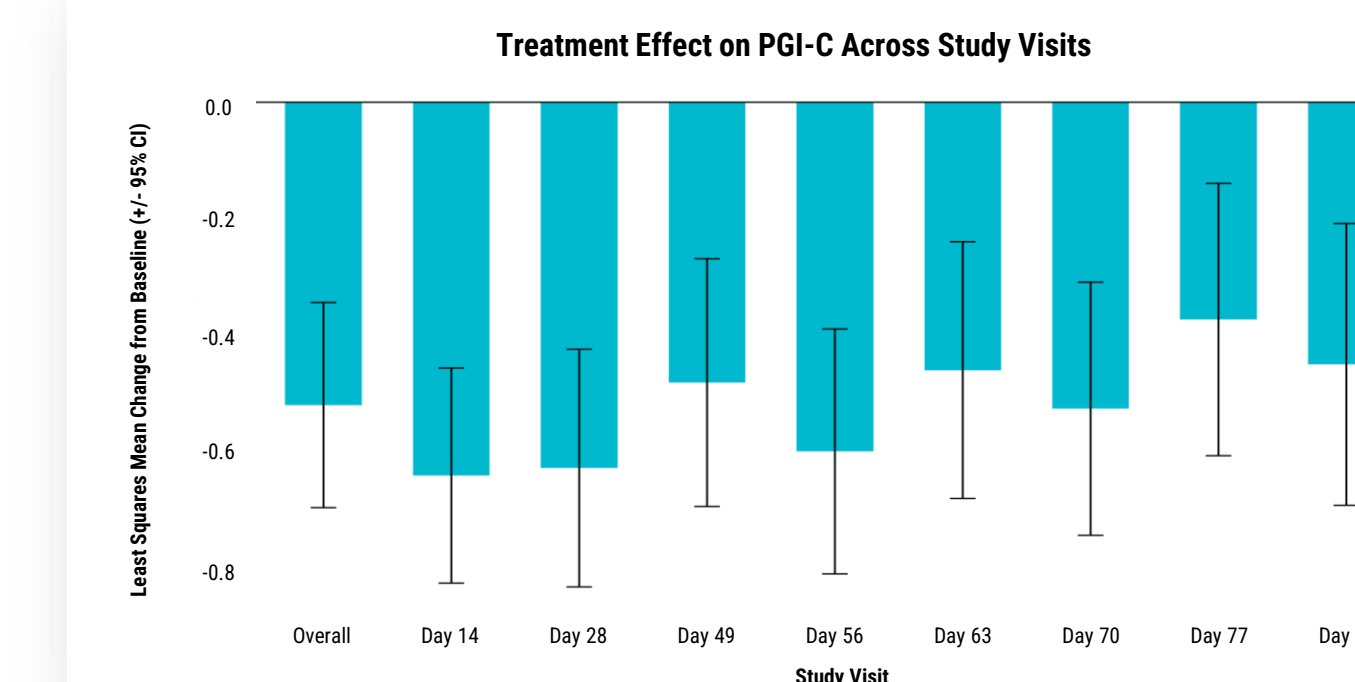
CGI-S=Clinical Global Impression of Severity; PGI-C=Patient Global Impression of Change

Patient Global Impression of Change Clinically and Statistically Significant Across Study Visits (mITT)

Directly Linked to Minimum Clinically Important Difference (MCID) Anchor Definition of ~1.25 Points in mADL11*

Concordance Between Anchor and Distribution Methods for MCID

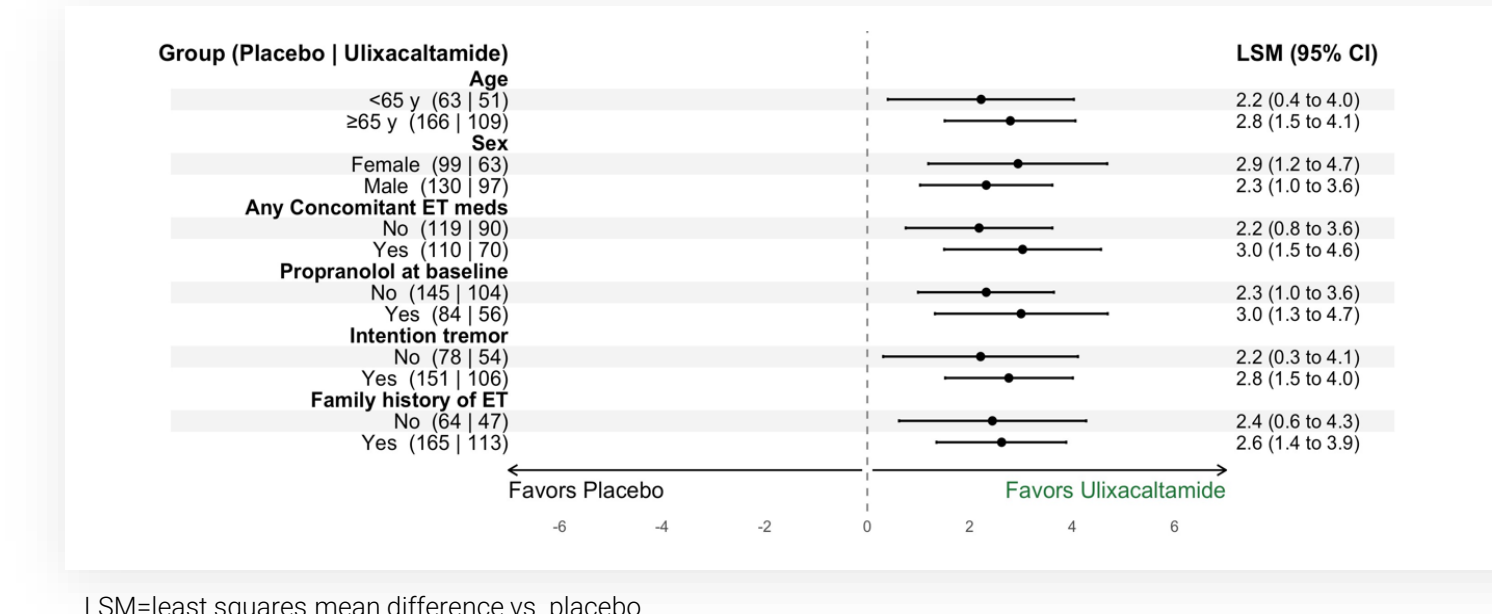
*MCID (-1.25) derived using ROC analysis (Youden J statistic) anchored to clinical improvement at Day 56



Exploratory Subgroup Analysis

- Pre-specified subgroup analyses demonstrated generally consistent treatment effects with mADL11 improvement comparable across prespecified populations defined by age, sex, concomitant ET meds, concomitant propranolol use, intention tremor status, and family history.

Consistent Response Across Subgroups at Day 56 (mITT)



CONCLUSIONS

- ESSENTIAL3 is the first positive Phase 3 program in ET. Study 1 represents the first evidence that pharmacologic TTCC modulation with ulixacaltamide leads to well tolerated, clinically meaningful benefit.
- Supportive results from pre-specified parallel-group combined analyses integrating Study 1 PD and Study 2 RW data are presented in [Poster 17-003](#).
- ESSENTIAL3 results position ulixacaltamide as a first-in-class therapy with potential to redefine the ET treatment landscape.

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