Ulixacaltamide Demonstrates Superiority Over Placebo as Monotherapy and as Add-on to Propranolol in Essential Tremor: Phase 3 ESSENTIAL3 Study 1

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BACKGROUND

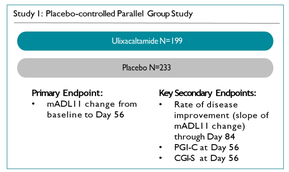
- ~7 million people in the US live with essential tremor (ET), one of the most common movement disorders, which is characterized by involuntary tremor that causes significant functional disability and profound disruption to daily activities and quality of life.
- Propranolol remains the only FDA-approved oral ET treatment, yet it is either contraindicated or provides inadequate control to the majority of patients.
- Ulixacaltamide HCl targets T-type calcium channels (TTCCs) in the cerebello-thalamo-cortical circuit, a key tremor network, through a mechanism distinct from β-adrenergic antagonism, supporting the potential for efficacy independent of propranolol use.

➢ ***Here we report results from ESSENTIAL3 Phase 3 Study 1 (NCT06087276) demonstrating the efficacy, safety, and tolerability of ulixacaltamide vs. placebo in adults with ET, including prespecified subgroup analysis demonstrating consistent superiority over placebo, including with and without background propranolol use.***

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.



CGI-S=Clinical Global Impression of Severity; mADL11=TETRAS-ADL items 1-11, modified score; PGI-C=Patient Global Impression of Change

ESSENTIAL3 STUDY 1 DISPOSITION

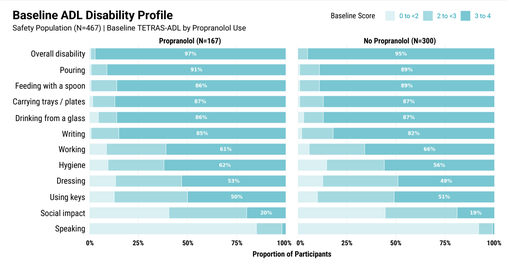
POPULATIONS	ULIXACALTAMIDE	PLACEBO
Enrolled/ITT	236 (100%)	237 (100%)
Safety	233 (98.7%)	234 (98.7%)
mITT	199 (84.3%)	233 (98.3%)

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 % **Currently on Propranolol,** Yes %	44.2% 35.7%	48.1% 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%
TETRAS-ADL, Mean (SD)	30.7 (3.0)	30.6 (3.0)
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)

BROAD BASELINE DISABILITY REGARDLESS OF BACKGROUND PROPRANOLOL

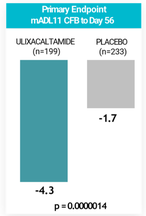
- The **E**ssential **T**remor **R**ating **A**ssessment **S**cale – **A**ctivities of **D**aily **L**iving (TETRAS-ADL) subscale is a 12-item clinician-administered assessment of daily activities impacted by tremor, with impact to each function rated on a 5-point Likert scale from 0 to 4; higher scores indicate greater disability.
- Participants demonstrated broad baseline disability across ADLs, with >95% overall disability, irrespective of background propranolol use.



ULIXACALTAMIDE DEMONSTRATES RAPID, SIGNIFICANT CLINICAL BENEFIT

Primary Endpoint – Significant Clinical Benefit at Day 56

- Ulixacaltamide demonstrated a statistically significant clinical improvement of −2.57 points in 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.



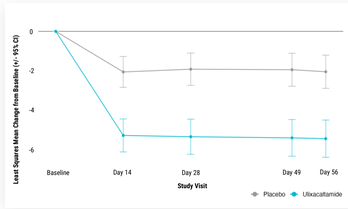
Key Secondary Endpoints – Consistent, Clinically Meaningful and Statistically Significant Response

- Secondary endpoint hierarchical fixed-sequence testing revealed clinically meaningful and statistically significant benefit vs. placebo in rate of disease improvement (slope of mADL11 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

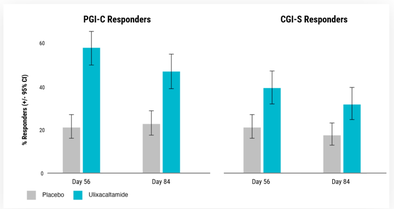
CGI-S=Clinical Global Impression of Severity; PGI-C=Patient Global Impression of Change

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



ITT=intention-to-treat population

Benefit Maintained Across Patient-Reported and Clinician-Assessed Outcomes (ITT)



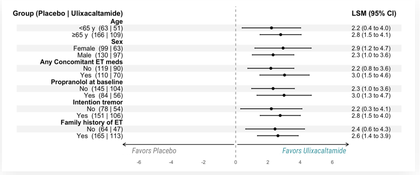
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SIGNIFICANT BENEFIT WITH AND WITHOUT BACKGROUND PROPRANOLOL USE

Subgroup Analysis

- Pre-specified subgroup analyses demonstrated generally consistent treatment effects, with mADL11 improvement over placebo observed across pre-specified populations.
- Results were statistically significant with or without propranolol use, with an mADL11 treatment difference of −3.00 points (p=0.0005) among propranolol users, representing effect size d ≥ 0.6.
- Ulixacaltamide demonstrated consistent superiority over placebo with no treatment-by-subgroup interaction.

Consistent Response Across Pre-specified Subgroups at Day 56 (mITT)



LSM=least squares mean difference vs. placebo

Responder Analysis

- Broad, significant improvement observed across multiple affected activities and outcome measures in participants on propranolol.

Improvement in Participants on Background Propranolol Across Functional and Global Outcome Measures

Day 56 Responder Analysis | Functional and Global Improvement
Background Propranolol | Selected Response Thresholds | Exploratory Observed-Case Analysis

Response Criterion	Ulixacaltamide % (n/N)	Placebo % (n/N)	Placebo-adjusted Benefit (95% CI)	Nominal P-value
Share of initially affected activities improved				
≥50% of initially affected activities	42.9% (24/56)	16.7% (14/84)	+26.2% (10.9, 40.7)	< 0.05
≥75% of initially affected activities	23.2% (13/56)	2.4% (2/84)	+20.8% (10.0, 33.5)	< 0.05
Global outcomes (standalone): clinician- and patient-rated				
CGI-S improved ≥1 category	35.3% (18/51)	18.2% (14/77)	+17.1% (1.7, 32.5)	< 0.05
PGI-S improved ≥1 category	44.2% (23/52)	25.7% (19/74)	+18.6% (1.8, 34.5)	< 0.05
PGI-C at least minimally improved	56.4% (31/55)	22.1% (17/77)	+34.3% (17.5, 48.8)	< 0.05
PGI-C much or very much improved	30.9% (17/55)	2.6% (2/77)	+28.3% (15.9, 41.6)	< 0.05
Composite Outcomes: ≥4 initially affected activities improved PLUS global criterion below				
+ CGI-S improved ≥1 category	30.0% (15/50)	10.4% (8/77)	+19.6% (5.6, 34.3)	< 0.05
+ PGI-S improved ≥1 category	28.6% (14/49)	6.8% (5/74)	+21.8% (8.4, 36.2)	< 0.05
+ PGI-C at least minimally improved	36.5% (19/52)	10.4% (8/77)	+26.1% (11.5, 40.6)	< 0.05
+ PGI-C much or very much improved	28.8% (15/52)	0.0% (0/77)	+28.8% (17.3, 42.3)	< 0.05
+ CGI-S improved ≥1 category + PGI-C at least minimally improved	28.6% (14/49)	4.2% (3/71)	+24.3% (11.3, 38.5)	< 0.05

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

ULIXACALTAMIDE IS GENERALLY WELL TOLERATED

- Once-daily ulixacaltamide was generally well tolerated, with no drug-related serious adverse events.
- 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 adverse events tended to start early and resolve during the titration phase.
- Discontinuations were primarily due to adverse events, with most common due to dizziness and brain fog.

CONCLUSIONS

- **ESSENTIAL3 is the first positive Phase 3 program in ET, with ulixacaltamide demonstrating consistent superiority over placebo, across all subgroups, including among propranolol users.**
- **Sensitivity analyses in the propranolol subgroup confirm robustness of findings across increasing response thresholds and functional and global endpoints, supporting the potential for mechanistic complementarity between TTCC modulation and β-adrenergic antagonism.**
- **These data position ulixacaltamide as a first-in-class, clinically meaningful therapy for the currently treated or treatment-seeking ET population.**

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