

Combined Efficacy and Safety of Ulixacaltamide in Essential Tremor: Topline Results from the Phase 3 ESSENTIAL3 Program

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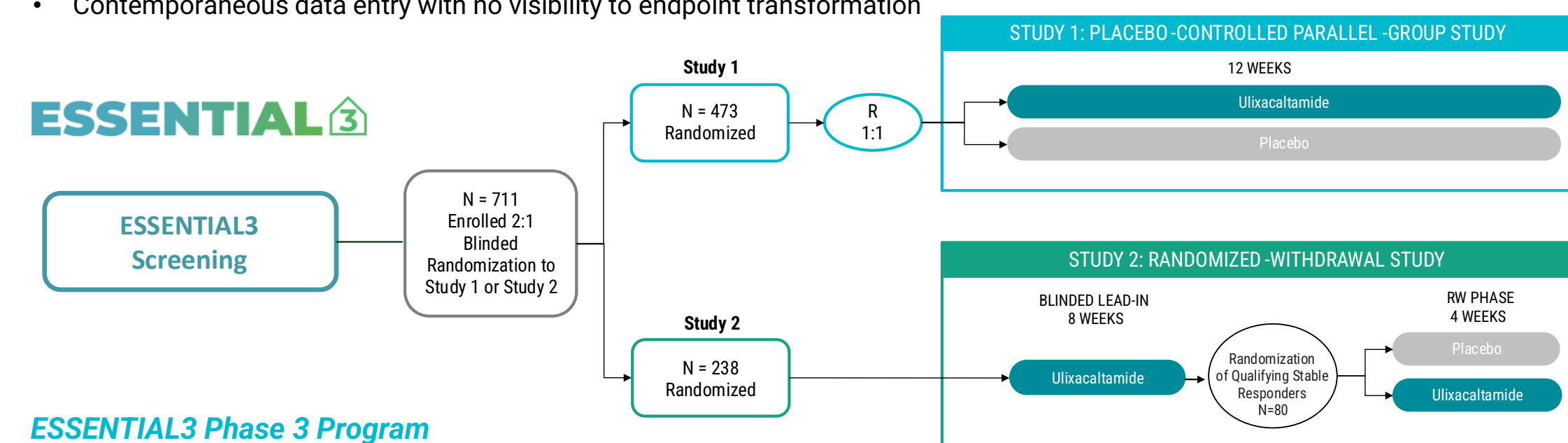
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BACKGROUND

- Essential tremor (ET) is one of the most common movement disorders, affecting millions worldwide, characterized by significant functional disability and profound impact on daily activities.
- Despite its prevalence, there have been no new treatments for ET since propranolol's approval ~40 years ago, with most therapies discontinued because of tolerability or modest efficacy.
- Ulixacaltamide HCl is a selective T-type calcium channel (TTCC) modulator, representing the first mechanism-based approach to ET treatment.
- The ESSENTIAL3 Program was designed to provide a comprehensive evaluation of ulixacaltamide's efficacy and tolerability through two simultaneous 12-week pivotal studies, with blinded assignment: Study 1 (parallel-group design, PD, [Poster 17-002](#)) and Study 2 (randomized withdrawal, RW, [Plenary PL5-001](#)), conducted under a unified protocol using a decentralized model, with optional long-term safety extension.
- Here we report the efficacy and safety of ulixacaltamide in adults with ET across the pivotal Phase 3 ESSENTIAL3 Program, based on pre-specified parallel-group combined analyses integrating Study 1 PD and Study 2 RW data.

ESSENTIAL3: TWO POSITIVE PH 3 STUDIES UNDER A UNIFIED PROTOCOL

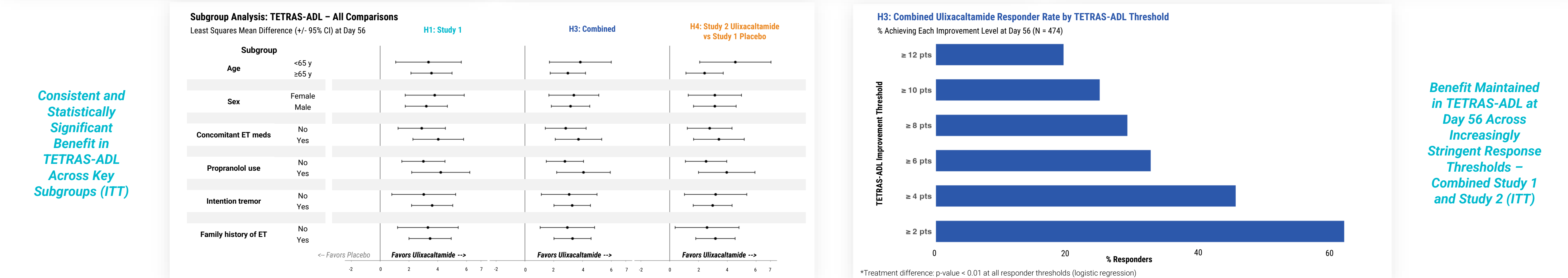
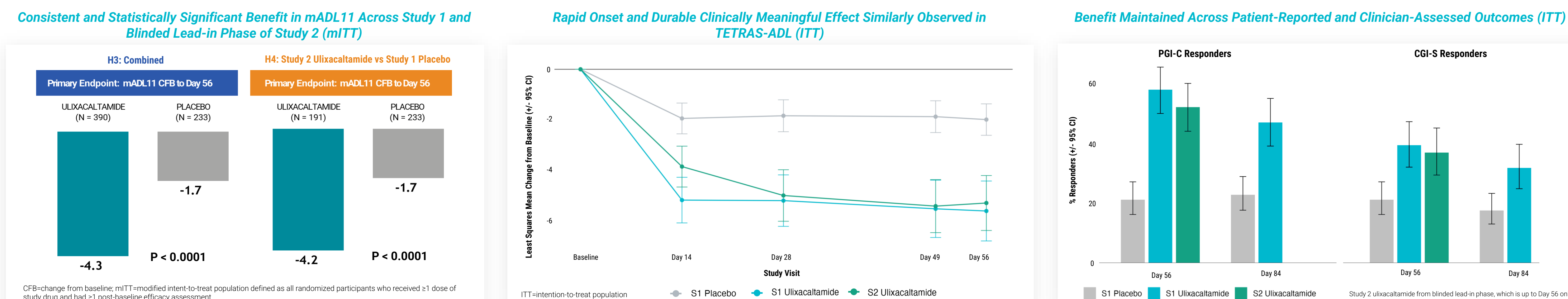
- Randomized, double-blind, placebo-controlled trial enrolling participants aged 18–85 years with ET (symptoms ≥3 years; if on ET medication(s), stable dose for ≥28 days prior to screening).
- Integrated, innovative, decentralized design with a unified, single screening and eligibility review process with blinded assignment allowed data to be combined across the two ESSENTIAL3 pivotal studies, Study 1 PD and Study 2 RW.
 - ET diagnosis confirmed by standardized neuro exam adjudicated by Movement Disorder specialists on Eligibility Review Committee
 - Site staff blinded to protocol eligibility criteria for threshold of disability and mADL11 stability, and threshold to qualify as responder in Study 2 RW
 - Contemporaneous data entry with no visibility to endpoint transformation



Hypothesis 1 Study 1 Parallel group design (PD)	Hypothesis 2 Study 2 Blinded Stable responder, randomized-withdrawal design (RW)	Hypothesis 3 Studies 1+2 Ulixacaltamide / Study 1 Placebo	Hypothesis 4 Study 2 Ulixacaltamide / Study 1 Placebo
Poster 17-002	Plenary PL5-001		
How do patients compare between ulixacaltamide and placebo after 56 days of intervention in the PD study?	For patients exposed to ulixacaltamide in the RW study who improved by at least 3 points in the mADL11 scale, which proportion maintains response after randomization staying on ulixacaltamide compared to placebo?	How does the combined group of patients receiving ulixacaltamide in both studies (PD and RW) compare to placebo patients from the PD study after 56 days of intervention?	How do patients receiving ulixacaltamide in the RW study compare to placebo patients from the PD study after 56 days of intervention?

- Pre-specified hypotheses evaluated overall treatment effect across studies while exploratory analyses assessed consistency across demographic and clinical factors.
- For hypotheses 1, 3 & 4, the primary endpoint was change from baseline to Day 56 in mADL11 (TETRAS-ADL items 1–11, modified score).

PRIMARY ENDPOINT MET, WITH CONSISTENT CLINICALLY MEANINGFUL BENEFIT ACROSS PARALLEL-GROUP COMBINED ANALYSES – STUDY 1 PD AND STUDY 2 RW



ESSENTIAL3 SAFETY SUMMARY – STUDY 1 PD AND STUDY 2 RW

ESSENTIAL3 Program Tolerability Summary

	STUDY 1		STUDY 2
	ULIXACALTAMIDE (N=233)	PLACEBO (N=234)	ULIXACALTAMIDE (N=231)
Participants with any TEAE	221 (94.9%)	177 (75.6%)	209 (90.5%)
Participants with:			
Mild TEAEs	98 (42.0%)	89 (38.0%)	87 (37.7%)
Moderate TEAEs	109 (46.8%)	78 (33.3%)	105 (45.5%)
Severe TEAEs	14 (6.0%)	10 (4.3%)	17 (7.4%)
Participants with any SAE*	2 (0.9%)	8 (3.4%)	4 (1.7%)
Participants with drug-related TEAEs leading to discontinuation	63 (27.0%)	4 (1.7%)	65 (28.1%)

*None related to study drug

- Once-daily ulixacaltamide was generally well tolerated across studies, with no drug-related SAEs.
- No significant drug-drug interactions.
- Most TEAEs occurred during titration, were mild to moderate and resolved.
- Most common TEAEs (≥10%) were constipation, dizziness, euphoric mood, brain fog, headache, paraesthesia and insomnia.
- Discontinuations were primarily due to AEs, with most common due to dizziness and brain fog.

CONCLUSIONS

- Primary evidence of efficacy across the ulixacaltamide development program is based on mADL11, a functional assessment directly related to daily activities with significant quality-of-life impact for patients with ET.
- Combined ESSENTIAL3 analyses demonstrate consistent, well-tolerated efficacy with rapid onset and durable benefit. Treatment effects were consistent across subgroups, with concordant improvements in patient- and clinician-reported outcomes supporting significant and clinically meaningful benefit.
- ESSENTIAL3 findings position ulixacaltamide as a first-in-class therapy addressing a longstanding unmet need in ET.

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