2026 AAN – Abstract of Distinction – Movement Disorders

Maintenance of Response and Durability of Effect with Ulixacaltamide in Essential Tremor: Topline Phase 3 Results from ESSENTIAL3 Study 2 (Randomized Withdrawal Study)

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Disclosure: Dr. Farmer is a speaker and consultant for the following companies – Abbvie, Acadia, Amneal, Neurocrine, Supernus and Teva

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Essential Tremor: High burden, characterized by significant functional disability, loss of independence and social isolation

7M

Americans affected

One of the most common movement disorders

>85%

Report functional disability

impacting daily activities like writing, eating, dressing, and social engagement

41%

Receive any treatment

Vast majority untreated or undertreated

<20%

Stay on therapy 2+ years

High discontinuation due to poor tolerability

- Propranolol, FDA-approved in 1986, remains the only approved therapy
- Limited efficacy, multiple contraindications in the elderly, and high discontinuation rates

Louis ED, Ottman R. *Tremor Other Hyperkinet Mov (N Y)*. 2014;4:259; Louis ED, et al. *Movement Disorders*. 2001;16(5):914-20; Elble RJ. *Curr Neurol Neurosci Rep*. 2013 Jun;13(6):353; Putzke JD, et al. *J Neurol Neurosurg Psychiatry*. 2006 Nov;77(11):1235-7; Vetterick C, et al. *Adv Ther*. 2022;39(12):5546-5567; Praxis Data on File

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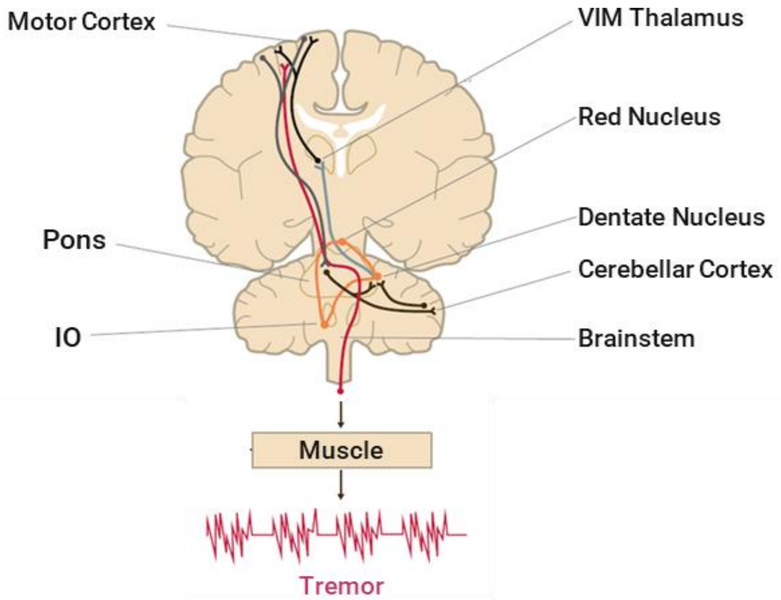
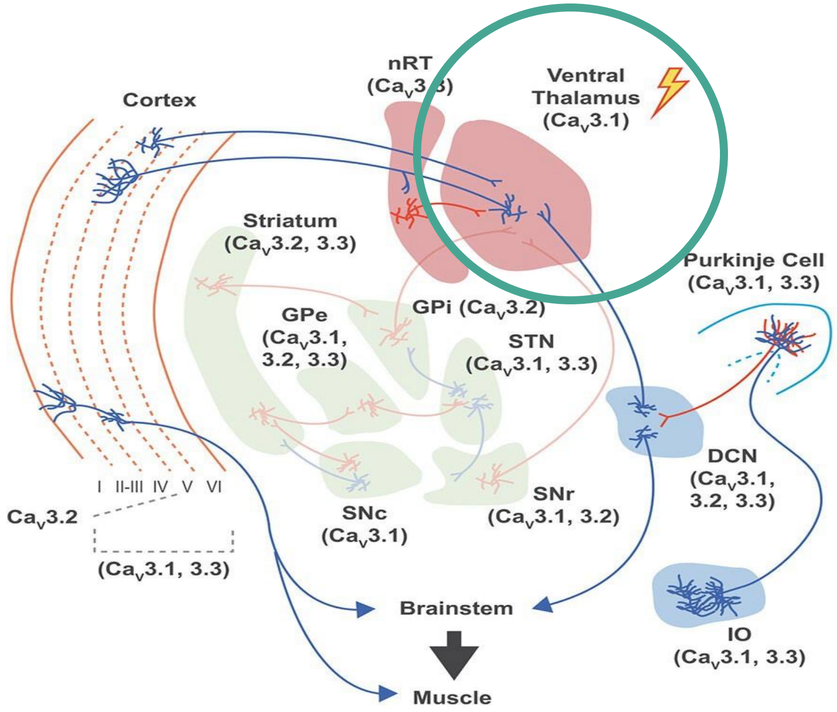
Ulixacaltamide HCl: The first mechanism-based approach to treating ET at its neurophysiological source

Aberrant T-type calcium channel activity in the cerebello-thalamo-cortical circuit drives essential tremor

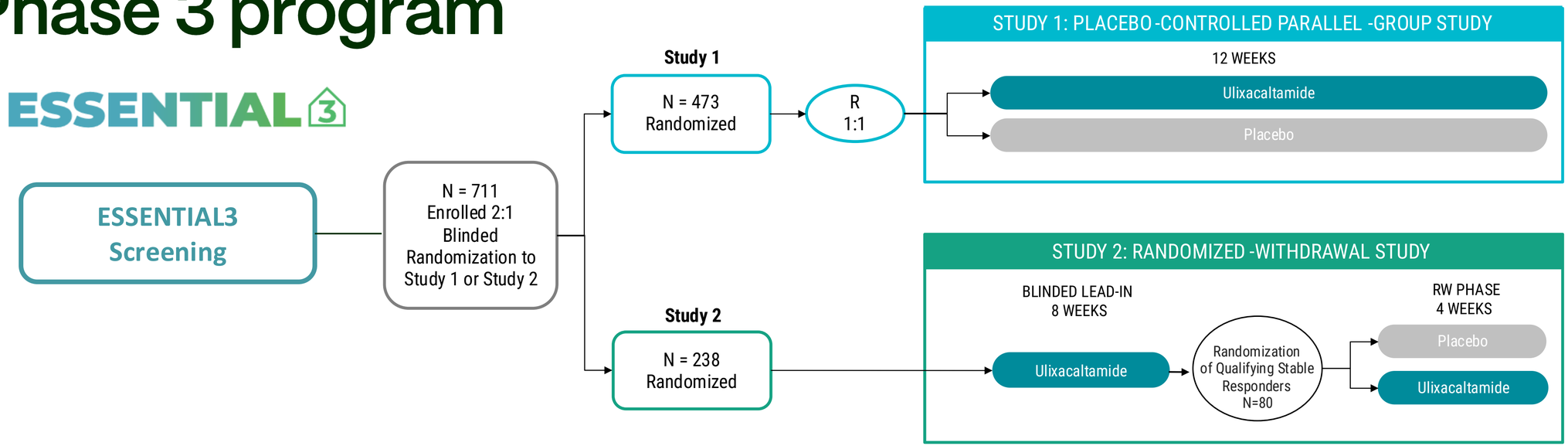


Targeting T-type calcium channels offers circuit-level normalization



Images from Matthews LG et al. *Ann Clin Transl Neurol.* 2023 Apr;10(4):462–483.

ESSENTIAL3: An innovative, fully decentralized Phase 3 program



Unified Recruitment, Screening and Visit Procedures

- Patients had comprehensive secondary pre-screening calls and medical records reviewed by MDs with movement disorder experience prior to referral to Central Coordinating Site
- 3 fellowship-trained movement disorder specialist PIs and >40 sub-investigators coordinated execution under standardized procedures, reducing inter-site variability
- Assessments (TETRAS-ADL, C/PGI) were conducted with participants at home, minimizing potential bias from clinic-based assessment

Eligibility Confirmation

- Comprehensive intake and screening (ET/medical history, medical records) performed across 4 visits in screening period
- Standardized neuro exams recorded and adjudicated by MD Specialists on the Eligibility Review Committee to review ET history and confirm ET diagnosis

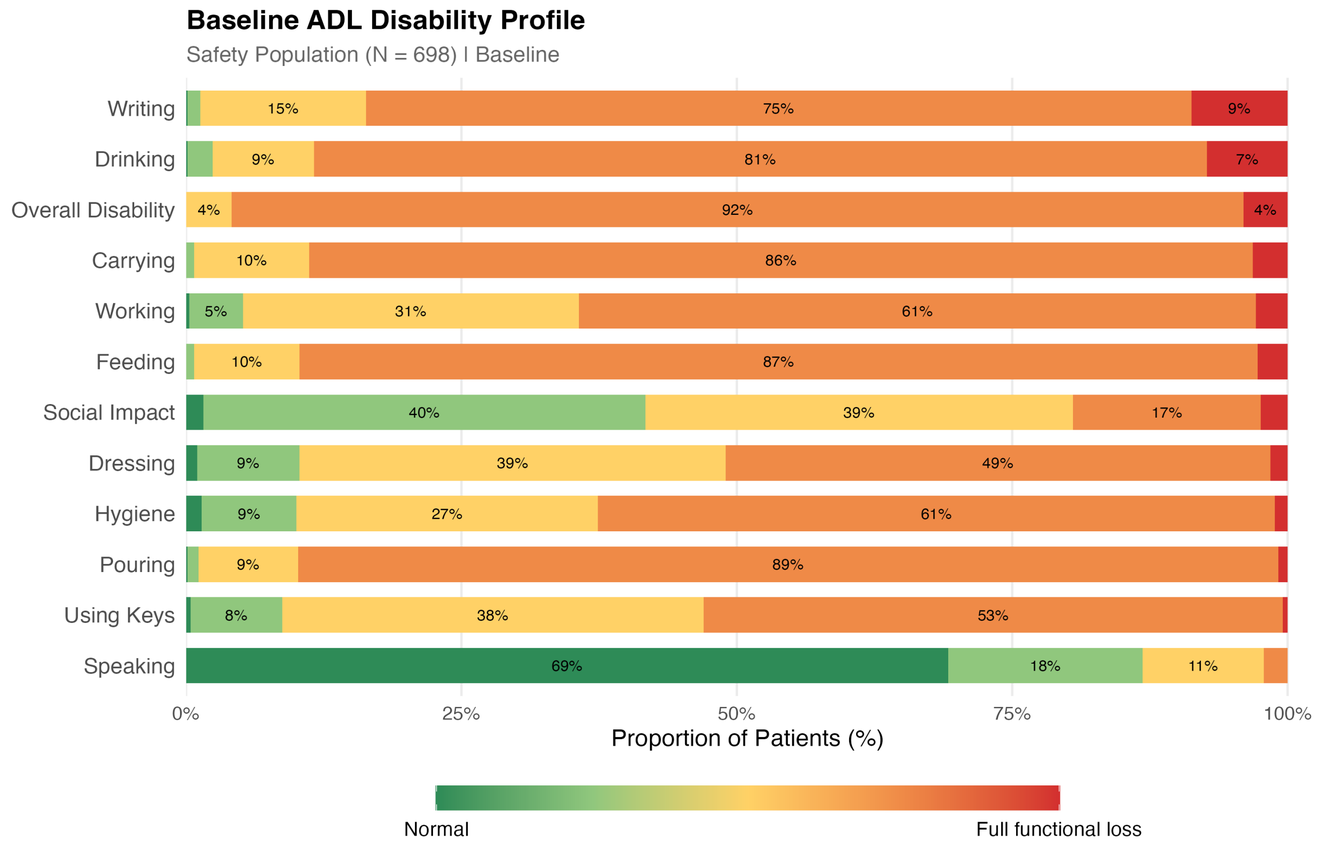
Blinding Protections

- Blinded study allocation and treatment arm allocation (in both studies)
- Investigators, site staff and participants were blinded to enrollment criteria for threshold of disability and mADL11 stability, and threshold to qualify as a responder for RW phase in Study 2
- Contemporaneous, centralized data entry at all visits, with blinded transformation from TETRAS-ADL to mADL11 Total Score

C/PGI=clinical and patient global impression; ET=essential tremor; mADL11=modified ADL 11-item score; TETRAS-ADL=The Essential Tremor Rating Assessment Scale – Activities of Daily Living subscale

ESSENTIAL3: Baseline demographics illustrate disease burden and functional disability with essential tremor

ESSENTIAL3 Safety Population Baseline (N = 698)	
Age, Mean (SD)	68 (8.5)
Years since ET onset, Mean (Median)	30 (17.6)
ET symptoms worsened over past 3 years, Yes %	94%
Currently on ET medications, Yes % **Never treated,** %	46% 20%
Family history of ET, Yes/No/Unknown %	72% / 21% / 7%
TETRAS-ADL, Mean (SD)	30.8 (3.0)
mADL11, Mean (SD)	18.6 (2.5)



ET=essential tremor; mADL11=modified ADL 11-item score ; SD=standard deviation; TETRAS-ADL=The Essential Tremor Rating Assessment Scale – Activities of Daily Living subscale

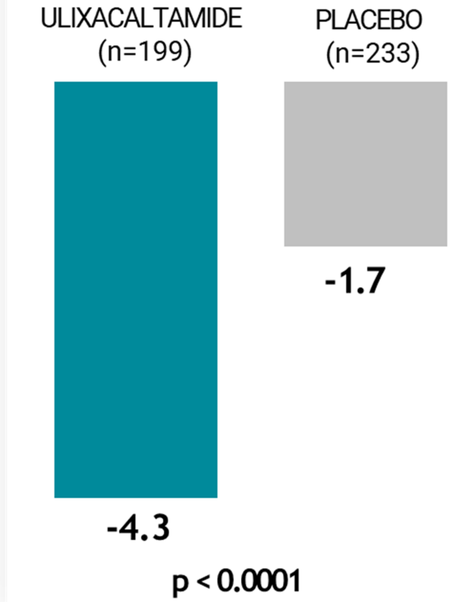
ESSENTIAL3 Study 1: Parallel-group design

Primary and all key secondary endpoints were clinically meaningful and statistically significant

STUDY 1
Parallel-group design

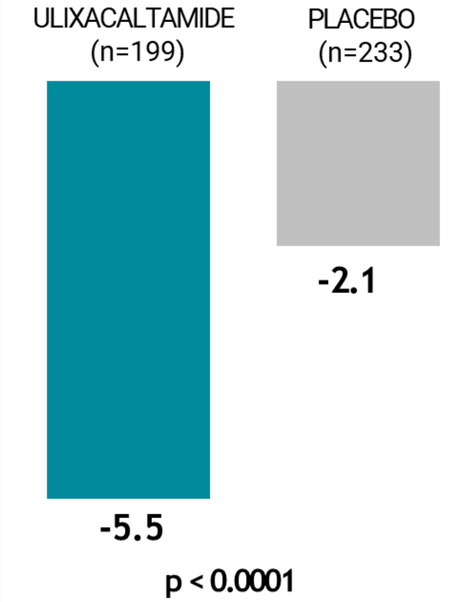
How do patients compare between ulixacaltamide and placebo after 56 days of intervention in the PD study?

Primary Endpoint
mADL11 CFB to Day 56



Key Secondary Endpoints	LS Mean Δ vs Placebo (95% CI)	P-value
Rate of Disease Improvement (slope)	−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

ADL CFB to Day 56

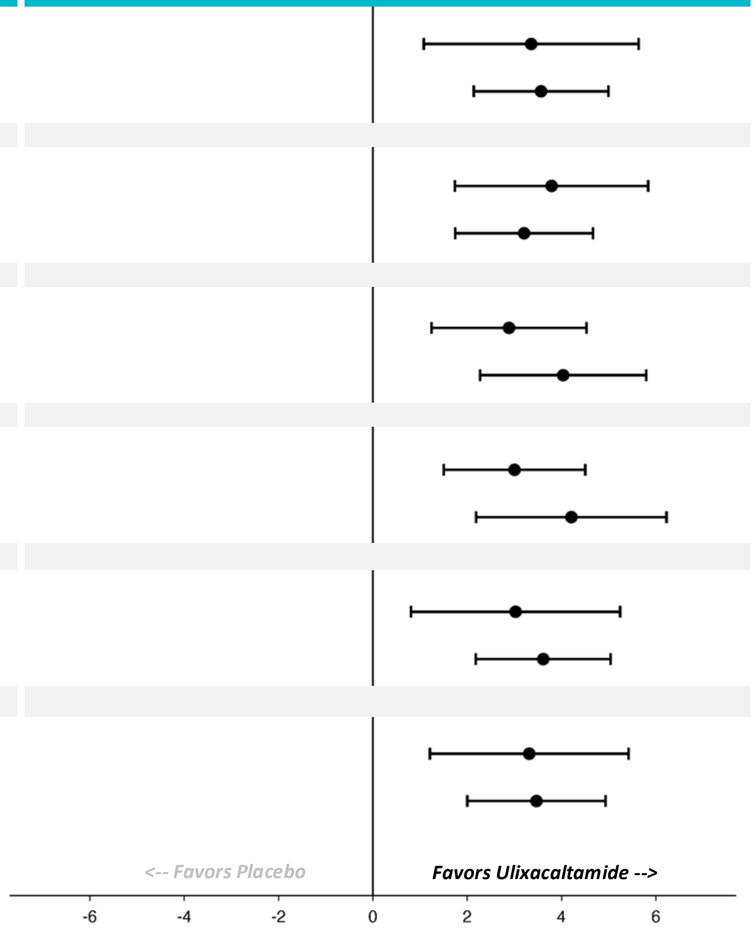


Primary and key secondary efficacy analyses use the modified intent-to-treat (mITT) population defined as all randomized participants who received ≥1 dose of study drug and had ≥1 post-baseline efficacy assessment
CFB=change from baseline; CGI-S=Clinical Global Impression of Severity; PGI-C=Patient Global Impression of Change; LS=least squares

Consistent improvement in ADL across key subgroups

Clinically meaningful and statistically significant effect irrespective of baseline demographics

Subgroup		LSM (95% CI)	P-value
Age	<65 y	3.36 (1.08, 5.63)	< 0.01
	≥65 y	3.57 (2.14, 4.99)	< 0.01
Sex	Female	3.79 (1.74, 5.84)	< 0.01
	Male	3.21 (1.74, 4.67)	< 0.01
Concomitant ET meds	No	2.89 (1.24, 4.53)	< 0.01
	Yes	4.03 (2.27, 5.79)	< 0.01
Propranolol use	No	3.00 (1.50, 4.50)	< 0.01
	Yes	4.21 (2.19, 6.23)	< 0.01
Intention tremor	No	3.03 (0.81, 5.24)	< 0.01
	Yes	3.61 (2.18, 5.04)	< 0.01
Family history of ET	No	3.32 (1.21, 5.42)	< 0.01
	Yes	3.47 (2.00, 4.94)	< 0.01



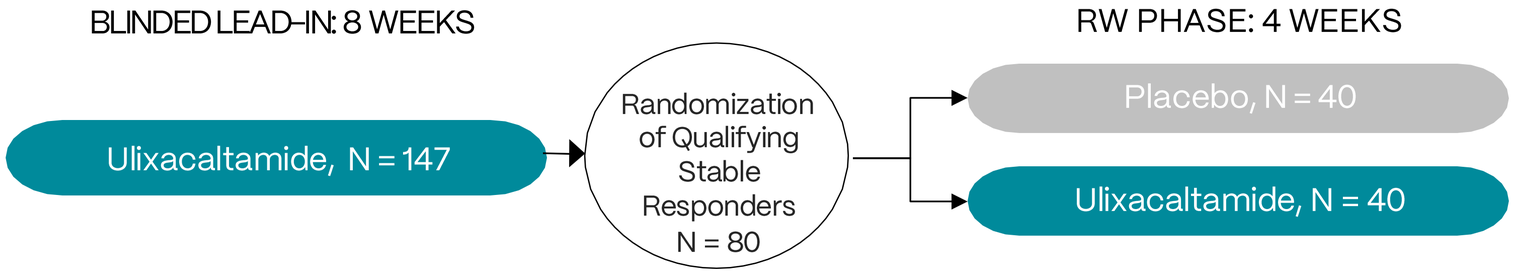
Intention-to-treat Population; LSM=least squares mean

ESSENTIAL3 Study 2 : Randomized Withdrawal design

STUDY 2

Blinded stable-responder, randomized withdrawal design

For patients exposed to ulixacaltamide in the RW study who improved by ≥3 points in the mADL11 scale, which proportion maintains response after randomization staying on ulixacaltamide compared to placebo?



Primary Endpoint:

- The proportion of participants that maintain response, as defined by change in mADL11 score, following randomized withdrawal

Key Secondary Endpoints:

- Rate of disease improvement (slope of mADL11 change) from Day 56 through Day 84
- PGI-C at Day 84
- Change in CGI-S from Day 56 to Day 84

Primary and key secondary efficacy analyses use the modified intent-to-treat (mITT) population defined as all randomized, qualified stable responders who met the prespecified 3-pt improvement , received at least one dose of study drug during the RW phase, had at least one post-RW baseline efficacy assessment

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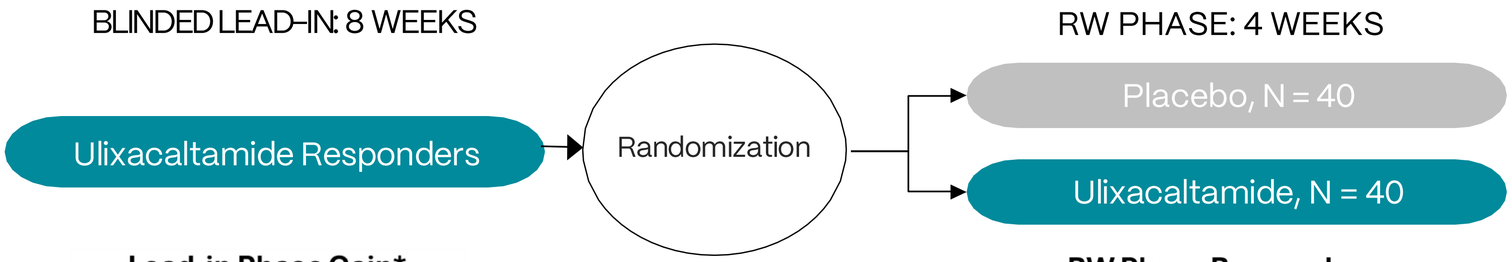
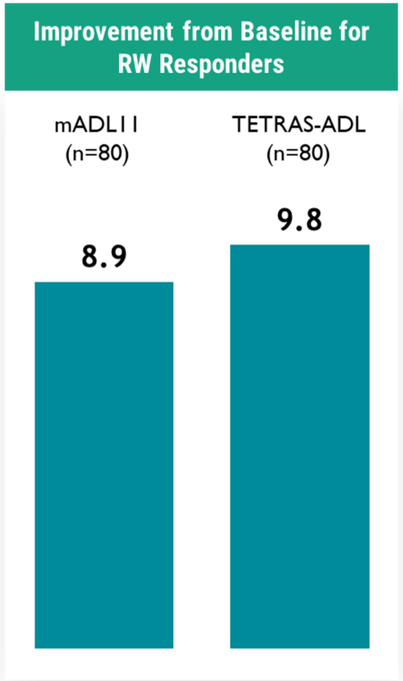
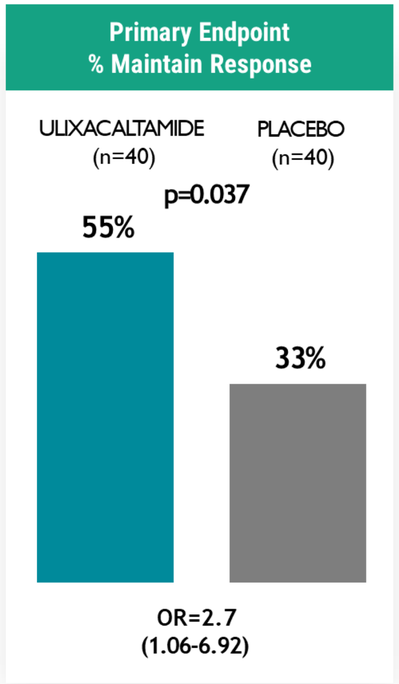
Study 2: Significant gains realized during the blinded lead-in, followed by superiority of maintenance during RW phase for ulixacaltamide treated patients



Lead-in Phase Gain*



RW Phase Responders

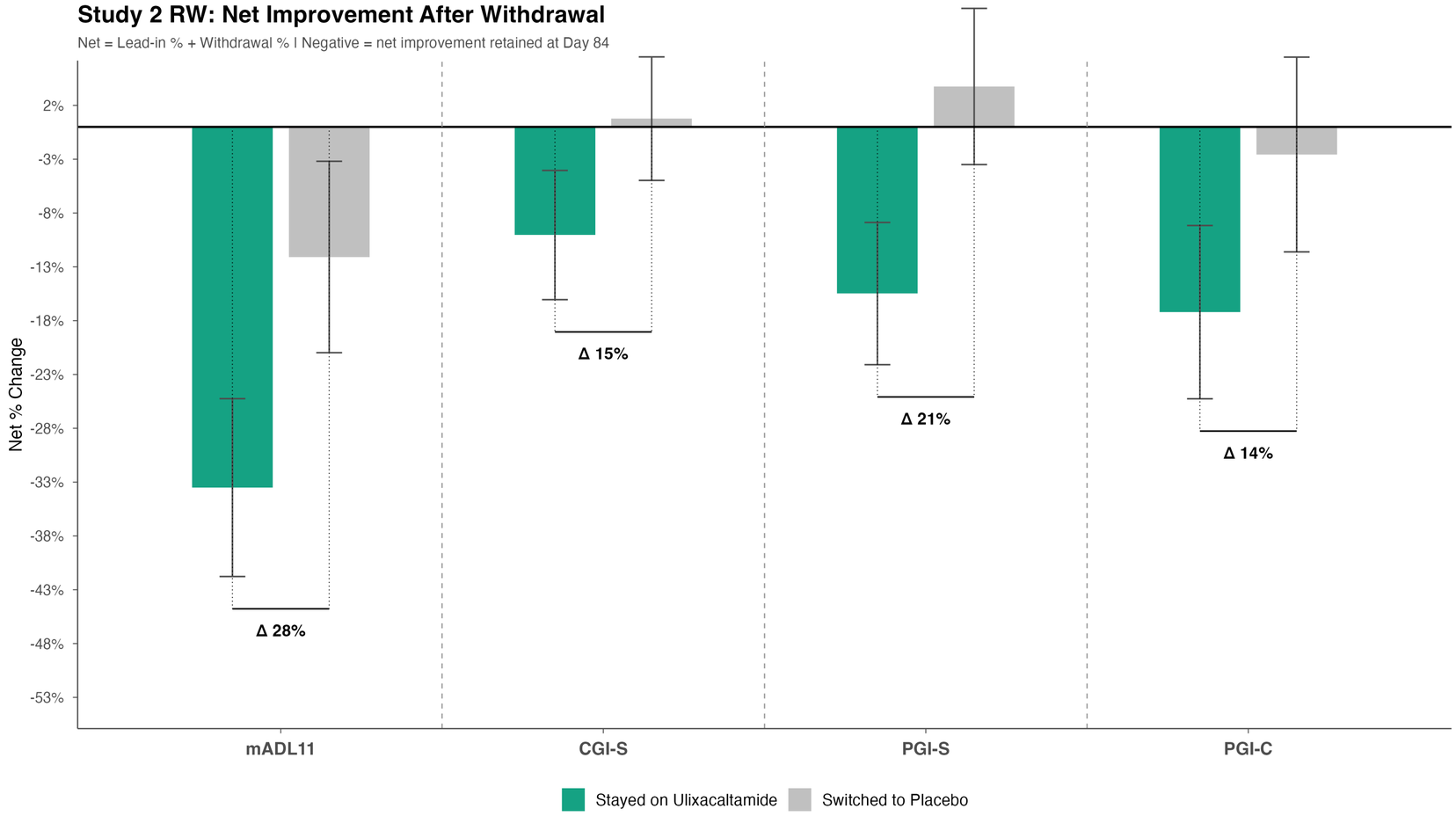


*Lead-in phase gain LS mean for patients who were randomized at Day 56 into the RW phase from baseline, p<0.001

Stable responder defined as 3 points reduction in the mADL11 from baseline to the average of Day 49 and 56, loss of response status defined as 2 consecutive visits in the RW phase with 3 points or more change from RW baseline

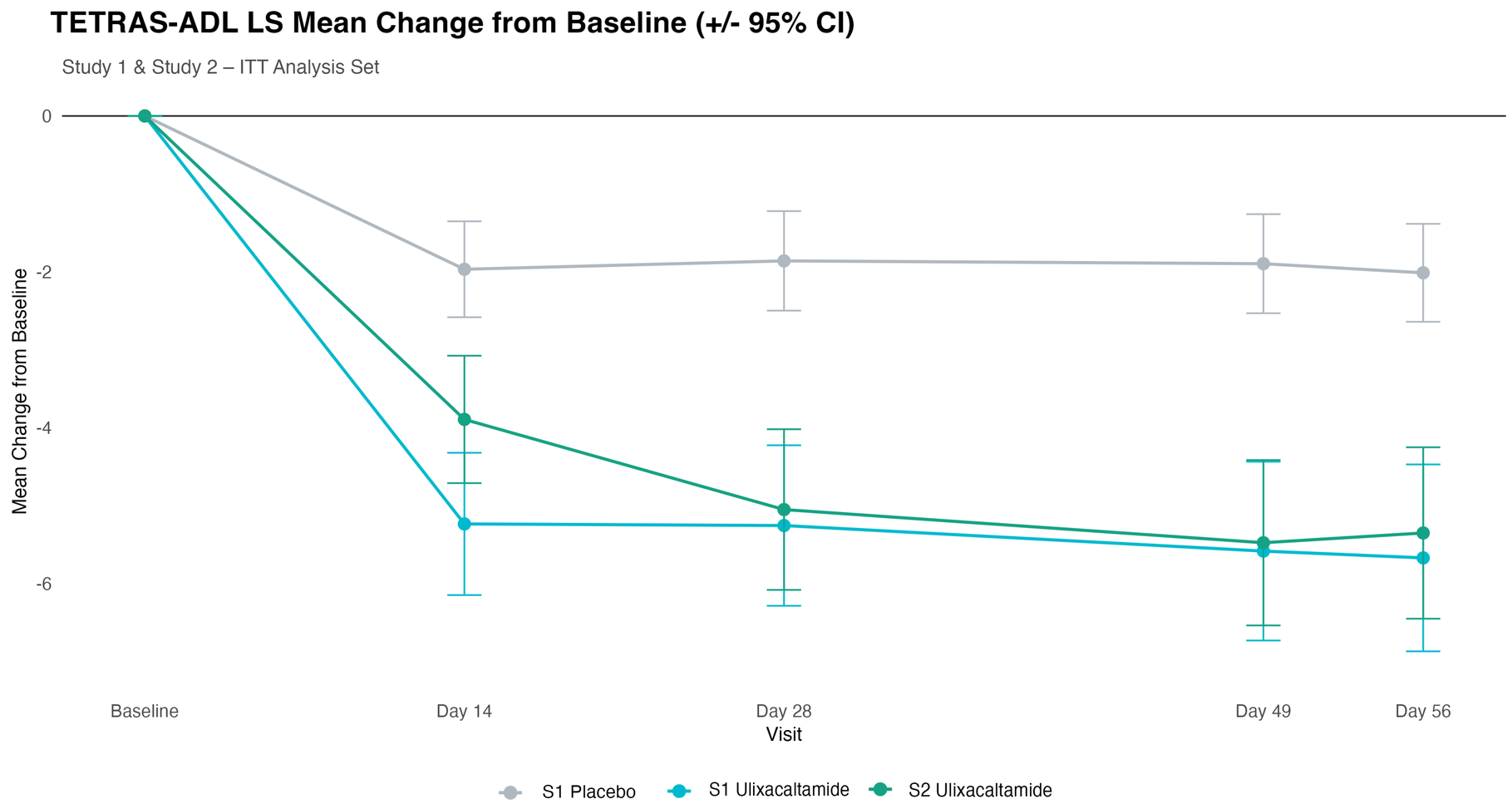
Substantial clinical improvement during blinded lead–in, followed by clear divergence between treatment groups in RW phase

Benefit maintained across endpoints while on ulixacaltamide versus placebo in the RW Phase



Rapid and consistent effect observed across Study 1 double–blind and Study 2 blinded lead–in

Clinically meaningful and statistically significant ADL benefit similarly observed in both studies

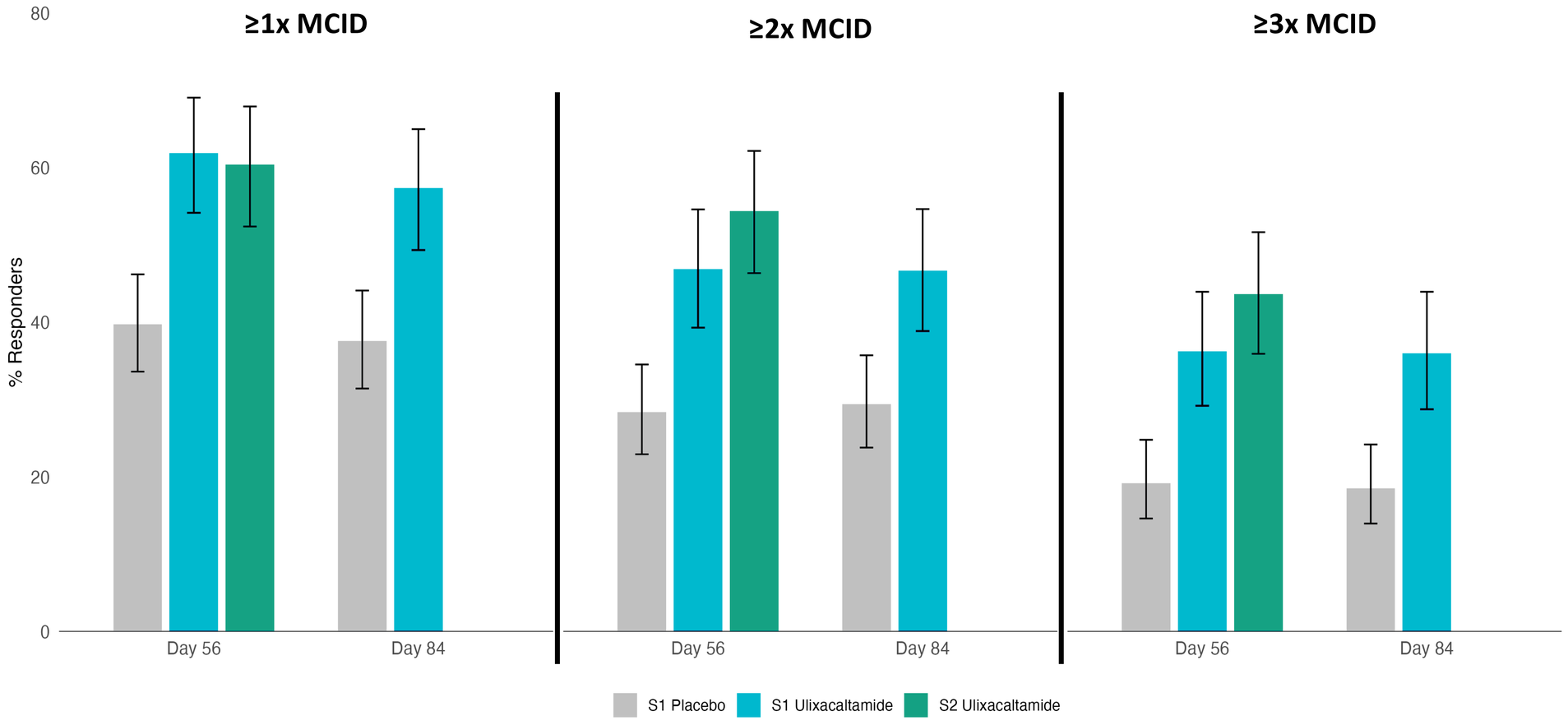


Large, consistent and durable response across studies

Benefit maintained in primary endpoint across increasingly stringent response thresholds

mADL11: Proportion Achieving MCID-Based Improvement Thresholds

MCID = -1.25 (ROC Youden J, D56) | ITT Analysis Set

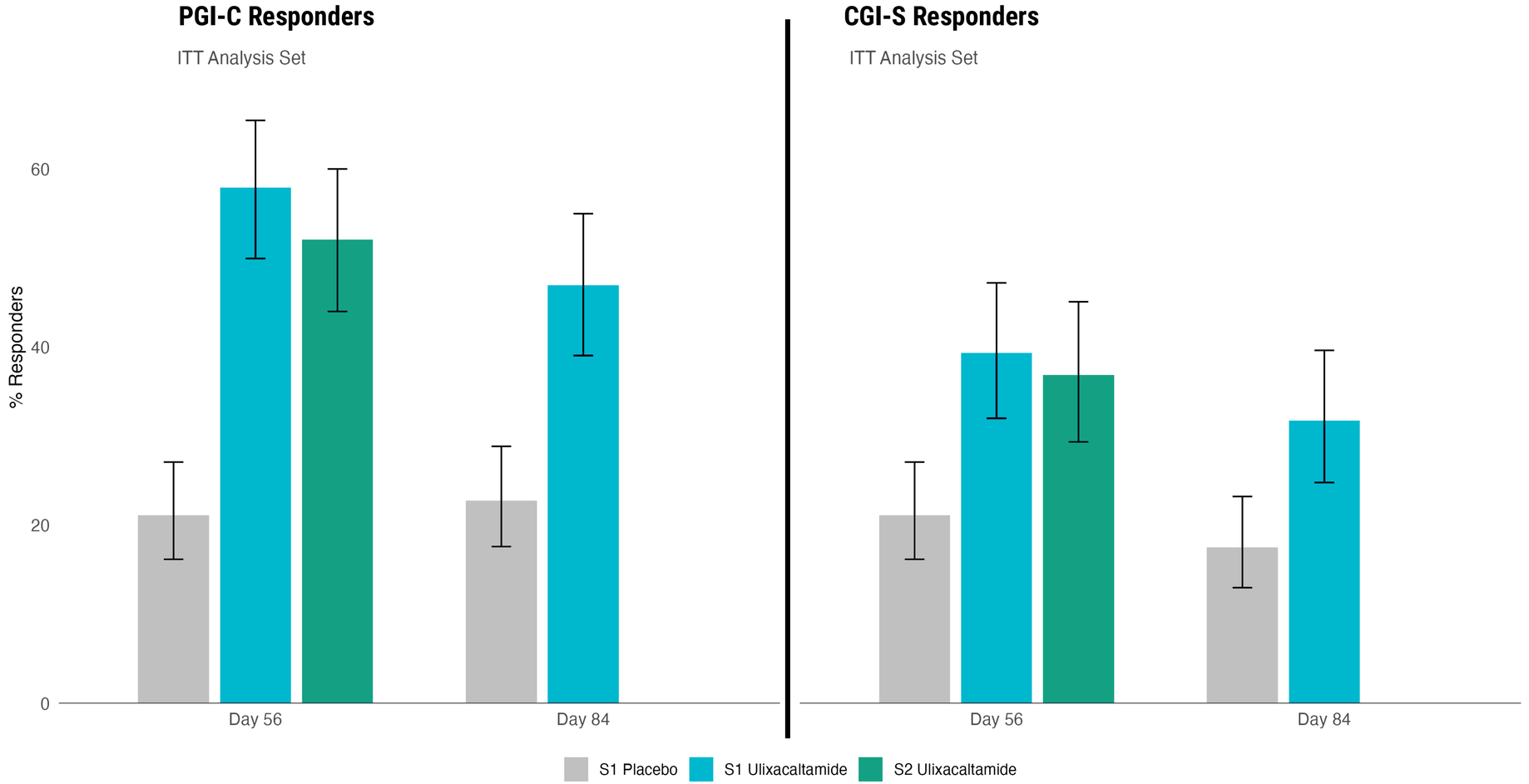


MCID=minimum clinically important difference

Study 2 ulixacaltamide from blinded lead-in phase, which is up to Day 56 only

Consistent response in the Global Impression Scales

Benefit maintained across patient-reported and clinician-assessed outcomes



Study 2 ulixacaltamide from blinded lead–in phase, which is up to Day 56 only

ESSENTIAL3 Safety Population: Overview of AEs

Once-daily ulixacaltamide was generally well tolerated across studies

OVERVIEW OF ADVERSE EVENTS

	STUDY 1		STUDY 2
	ULIXACALTAMIDE (N=233)	PLACEBO (N=234)	ULIXACALTAMIDE (N=231)
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%)
Discontinued from the study	83 (35.6%)	13 (5.6%)	88 (38.1%)

*none related to study drug

- No serious AEs related to ulixacaltamide
- No significant drug–drug interactions
- Most TEAEs occurred during titration, were mild to moderate and resolved
- CNS AEs occurred early in treatment and resolved quickly
- Most common TEAEs (≥10%) in participants treated with ulixacaltamide 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

AE=adverse event; SAE=serious adverse event; TEAE=treatment emergent adverse event

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ESSENTIAL3 Summary

First positive Phase 3 Program for a drug in essential tremor

Ulixacaltamide represents the first pharmacologically targeted therapy for ET

Results were clinically meaningful and statistically significant showing consistency across studies, endpoints and subpopulations

Generally well tolerated, with no drug-related SAEs, most AEs occur within titration period

Breakthrough Therapy Designation granted based on clinical results and superiority to propranolol
FDA approval expected in January 2027

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Acknowledgements

Jill Farmer[1]*, Salima Brillman[2]*, Alexander Shtilbans[3,4]*, Monique Giroux[5], Melanie Fridley[5], Kimberly Crimin[5], Minao Tang[5], Taylor Crush[5], Claudio Santos[5], Steve Petrou[5], Alyssa Wyant[5]*, Megan Sniecinski[5]*, Marcio Souza[5]*, on behalf of the ESSENTIAL3 Study Team

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