PRAXIS

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# Essential3 Program Topline Results

October 16, 2025

# Forward Looking Statements

This presentation may contain “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial conditions, including but not limited to express or implied statements regarding the current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, , including statements regarding the estimated market for our product candidates, if approved, our development plans, our preclinical and clinical results and other future conditions, including our cash runway, and the safety, efficacy, and regulatory and clinical design or progress, potential regulatory submissions, approvals and timing thereof of any of our product candidates. Any forward-looking statements in this presentation are based on management’s current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks relating to: (i) the success and timing of our ongoing clinical trials, (ii) the success and timing of our product development activities and initiating clinical trials, (iii) the success and timing of our collaboration partners’ product development activities, (iv) the timing of and our ability to obtain and maintain regulatory approval of any of our product candidates, (v) our plans to research, discover and develop additional product candidates, (vi) our ability to enter into collaborations for the development of new product candidates, (vii) our ability to establish manufacturing capabilities, and our collaboration partners’ abilities to manufacture our product candidates and scale production, (viii) our ability to meet any specific milestones set forth herein, and (ix) the potential addressable market sizes for product candidates. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

For further information regarding the risks, uncertainties and other factors that may cause differences between our expectations and actual results, you should review the “Risk Factors” section of our Annual Report on Form 10-K for the year ended December 31, 2024 filed with the Securities and Exchange Commission (“SEC”) and our other filings with the SEC.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

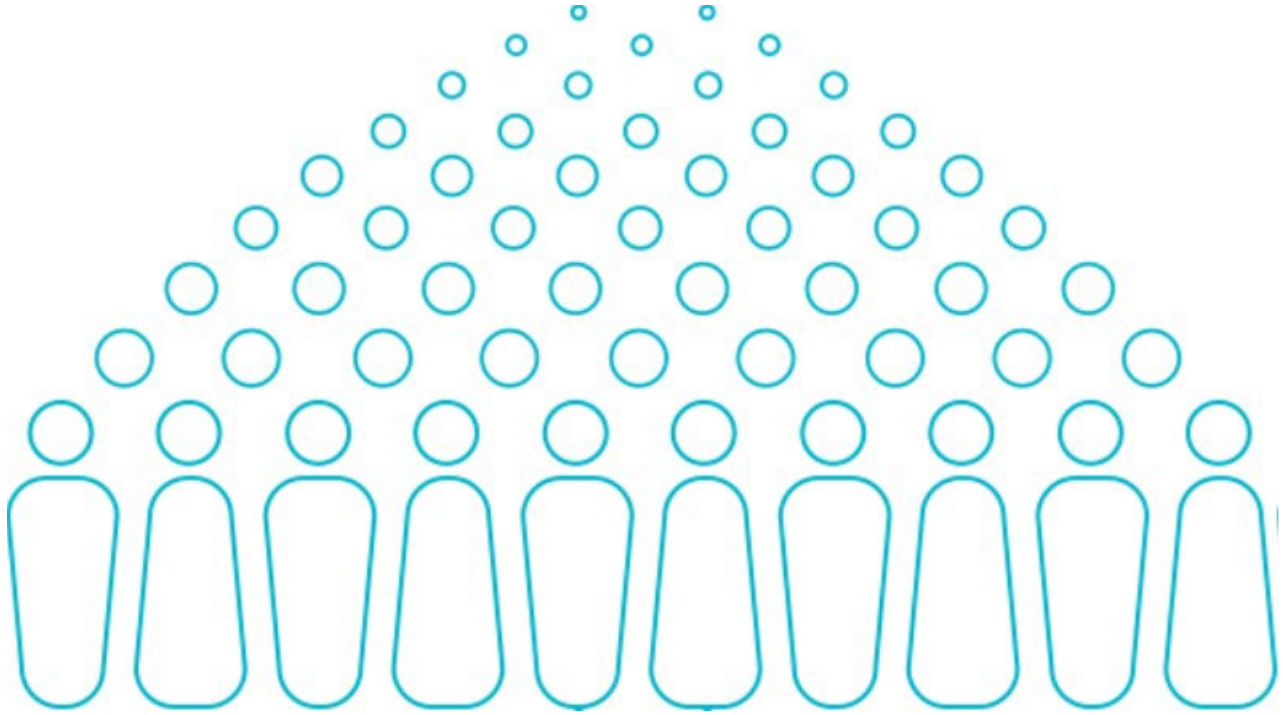
# Essential3 Program – Ulixacaltamide HCl

First positive Phase 3 program for a drug in Essential Tremor

Both studies in the Essential3 Program met their primary endpoints

Generally well tolerated, with no drug-related SAEs

Praxis has submitted a pre-NDA meeting request to the FDA



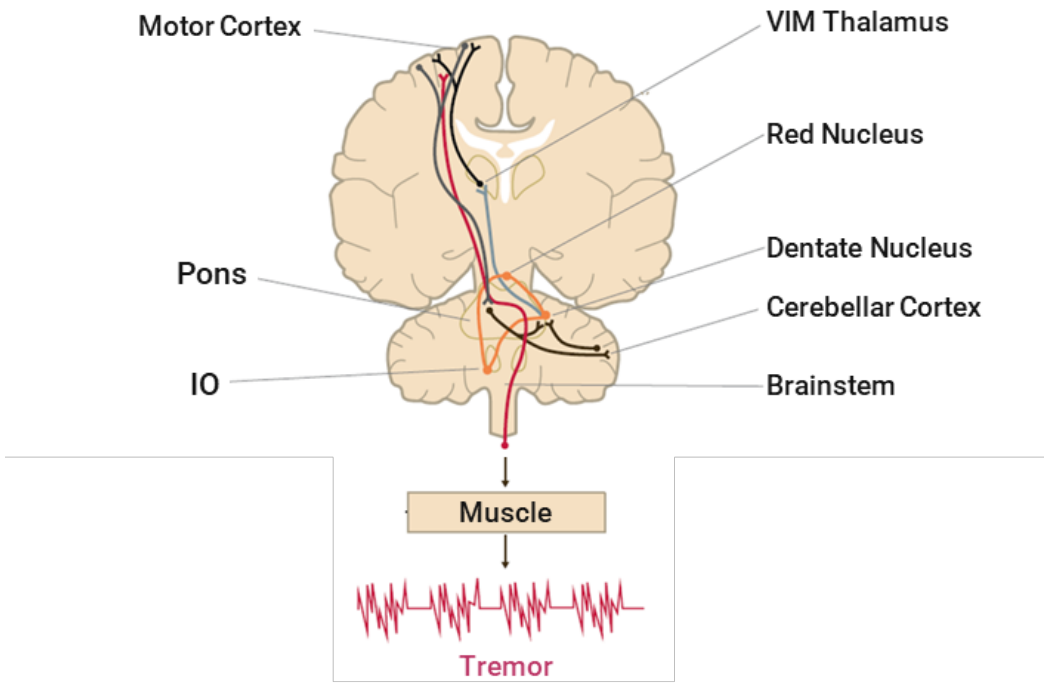
**No specific drugs developed for ET currently approved**

An estimated **7 million people** in the U.S. live with ET

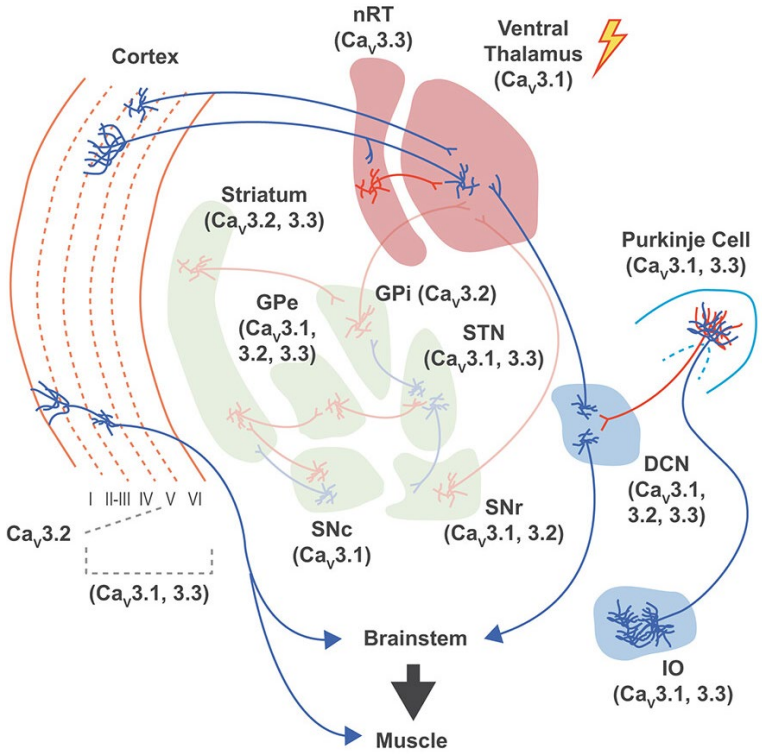
**With deep gratitude to the people living with ET who participated in our clinical studies, and to all the ET families and advocates who guide our work**

# Precision modulation of tremor circuits through T-type calcium channel modulation

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




Targeting T-type $Ca^{2+}$ channels offers circuit-level normalization




Images from Matthews et al. Ann Clin Transl Neurol. 2023

# Essential3 Program Topline Results

# Timeline of Essential3 Program

| Essential1 Readout March 2023 | End of Phase 2 FDA Meeting June – Sept 2023 | Essential3 Initiated November 2023 | Study 1 Interim Analysis February 2025 | Key Updates in SAP and Protocol September 2025 | Essential3 Topline Readout |
|---|---|---|---|---|---|
| *Established endpoint and dose for registrational study* | *Alignment on endpoint, dose and design of Phase 3 program* | *Rapid and sustained interest by patients and providers. Two simultaneous studies enrolling.* | *Futility recommendation by IDMC for Study 1*<br><br>*Praxis decided to continue Study 1 and Study 2* | *Change in primary endpoint of Study 1 from Day 84 to Day 56; simplified key secondary endpoints* | |

Unblinding

# Essential3 is the First Successful Program in Essential Tremor

*Several important clinical questions answered*

**Hypothesis 1**
**Study 1**
Parallel-group design (PD)

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

**Hypothesis 2**
**Study 2**
Blinded Stable-responder, randomized withdrawal design (RW)

*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?*

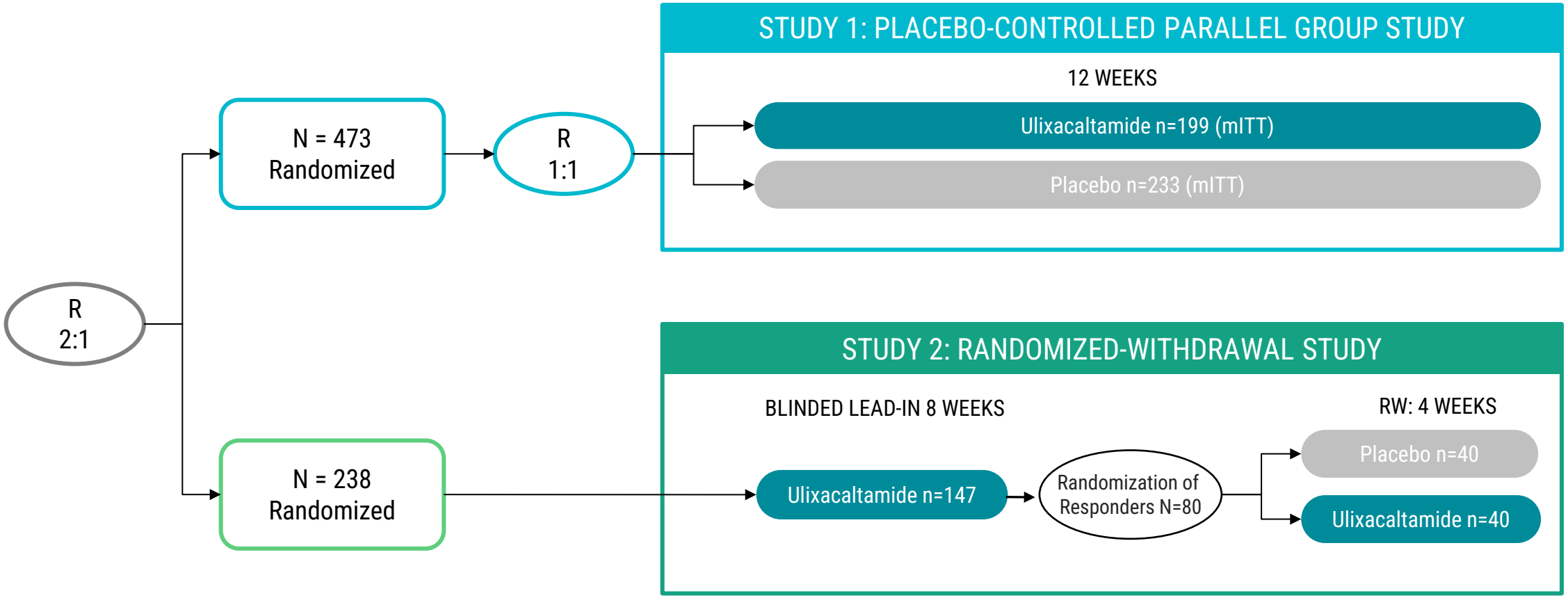
**Hypothesis 3**
**Studies 1+2 Ulixa / Study 1 PBO**

*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?*

**Hypothesis 4**
**Study 2 Ulixa / Study 1 PBO**

*How do patients receiving ulixacaltamide in the RW study compare to placebo patients from the PD study after 56 days of intervention?*

# Essential3: An ambitious and innovative Phase 3 program




Blinded randomization 2:1 (Study 1: Study 2) occurred following completion of screening

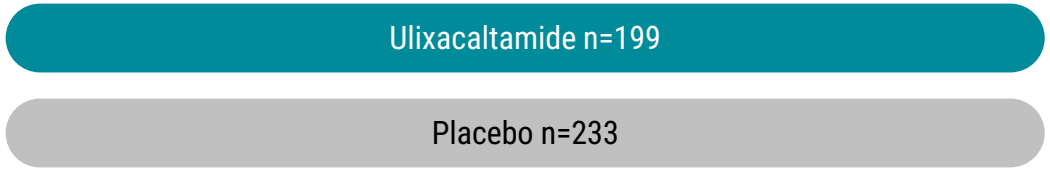
Blinded randomization 1:1 (Ulixacaltamide: Placebo) for treatment arm allocation in Study 1 and for treatment arm allocation of Responders into the randomized withdrawal phase in Study 2

# Essential3 Study 1 – Parallel design

**Hypothesis 1**
**Study 1**
Parallel-group design

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

Study 1: Placebo-controlled Parallel Group Study




**Primary Endpoint:**
- mADL11 change from baseline to Day 56

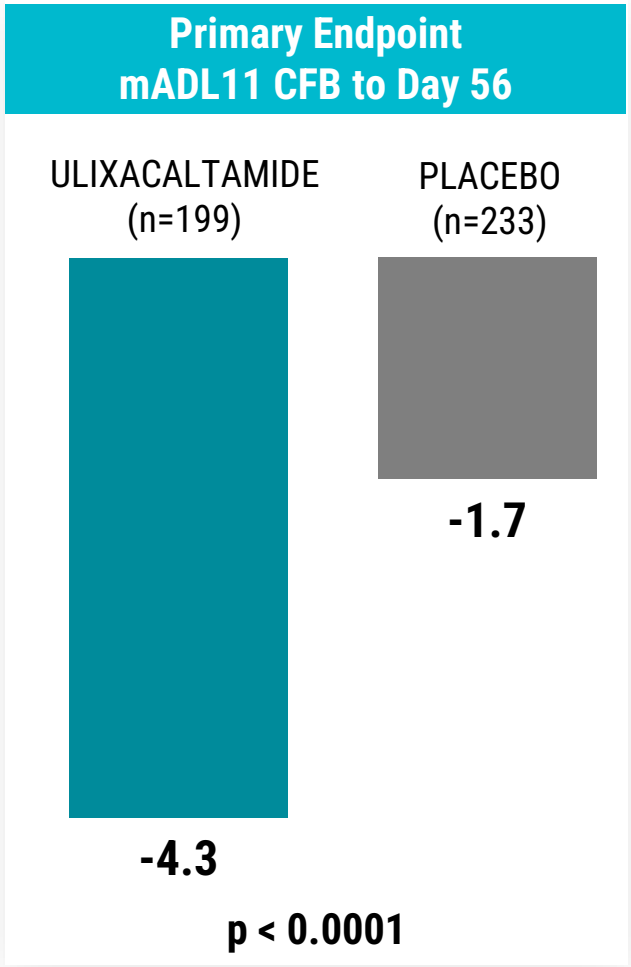
**Key Secondary Endpoints:**
- Rate of disease improvement (slope of mADL11 change) through Day 84
- PGI-C at Day 56
- CGI-S at Day 56

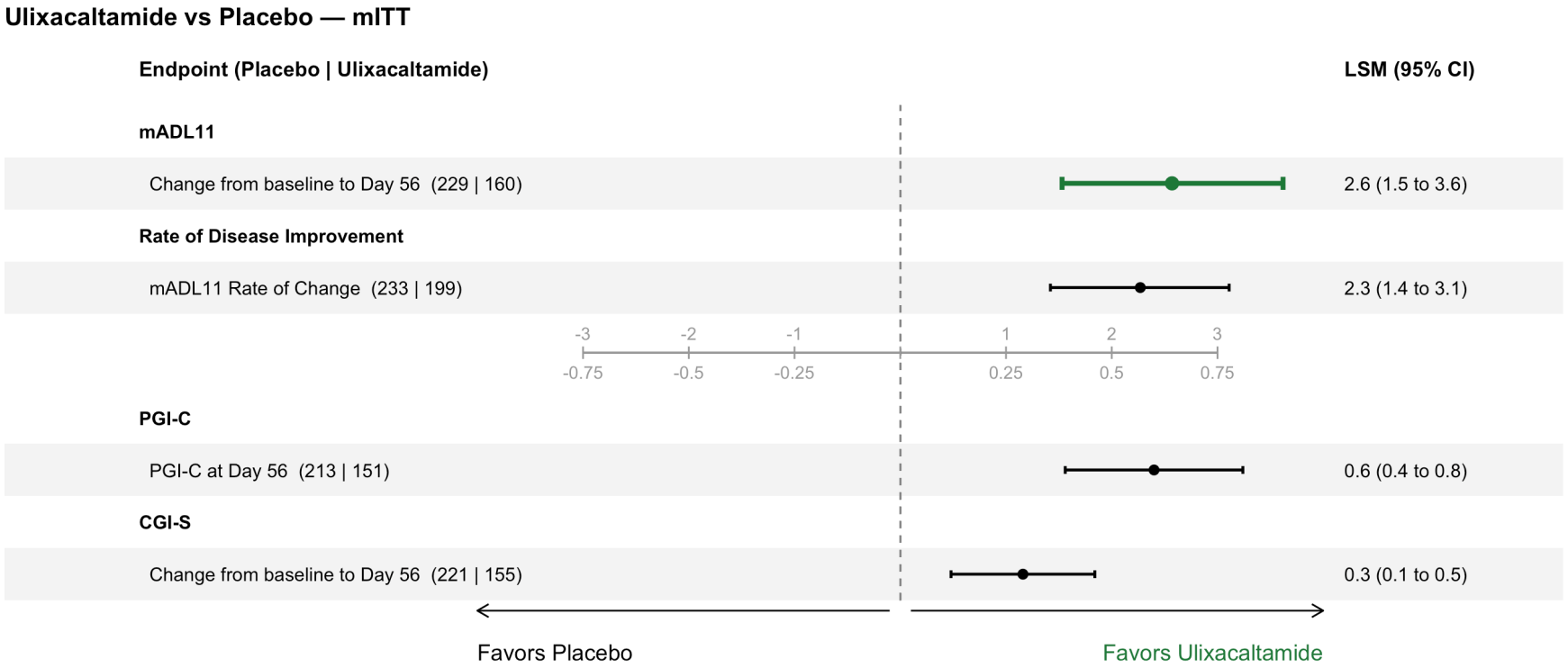
All efficacy analyses use the modified intent-to-treat (mITT) population defined as all randomized participants who received at least one dose of study drug and had at least one post-baseline efficacy assessment.

# Study 1 Baseline demographics - 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 %<br>**Currently on Propranolol,** Yes % | 44.2%<br>35.7% | 48.1%<br>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) |

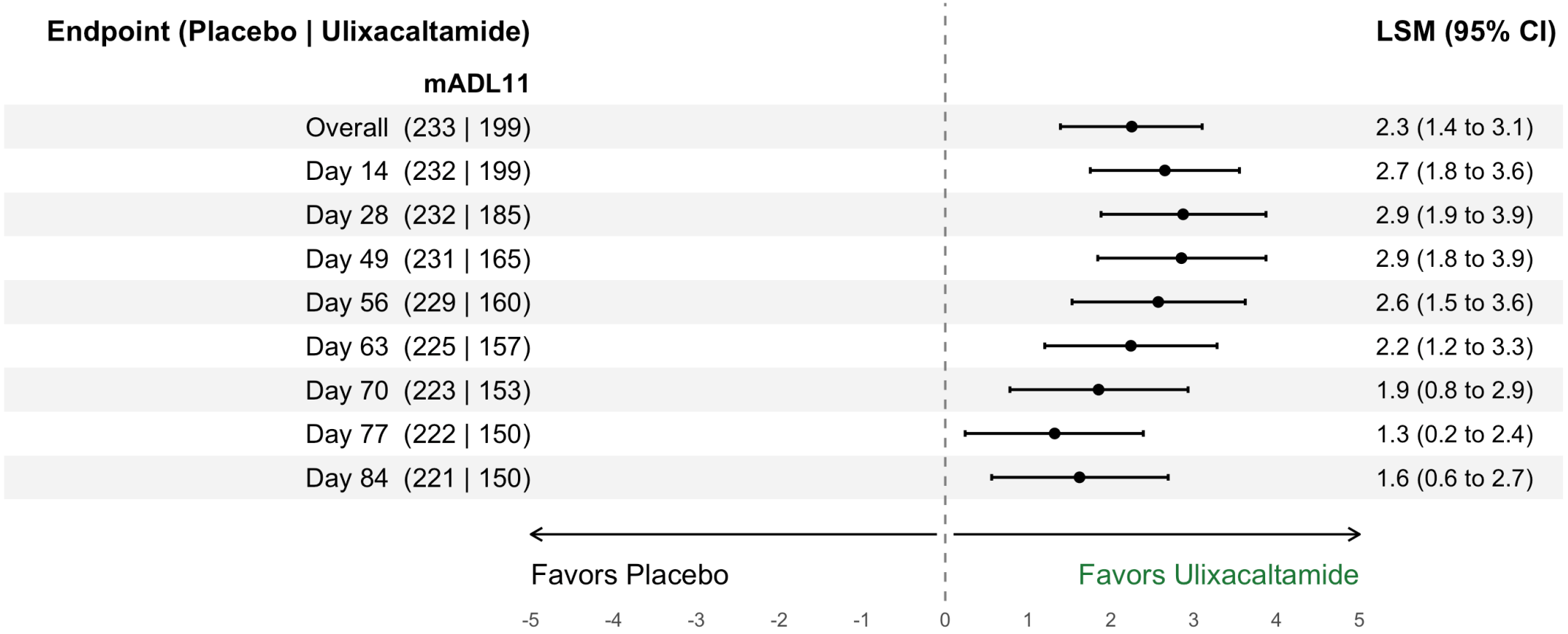
# Study 1 - Primary and all key secondary efficacy endpoints met



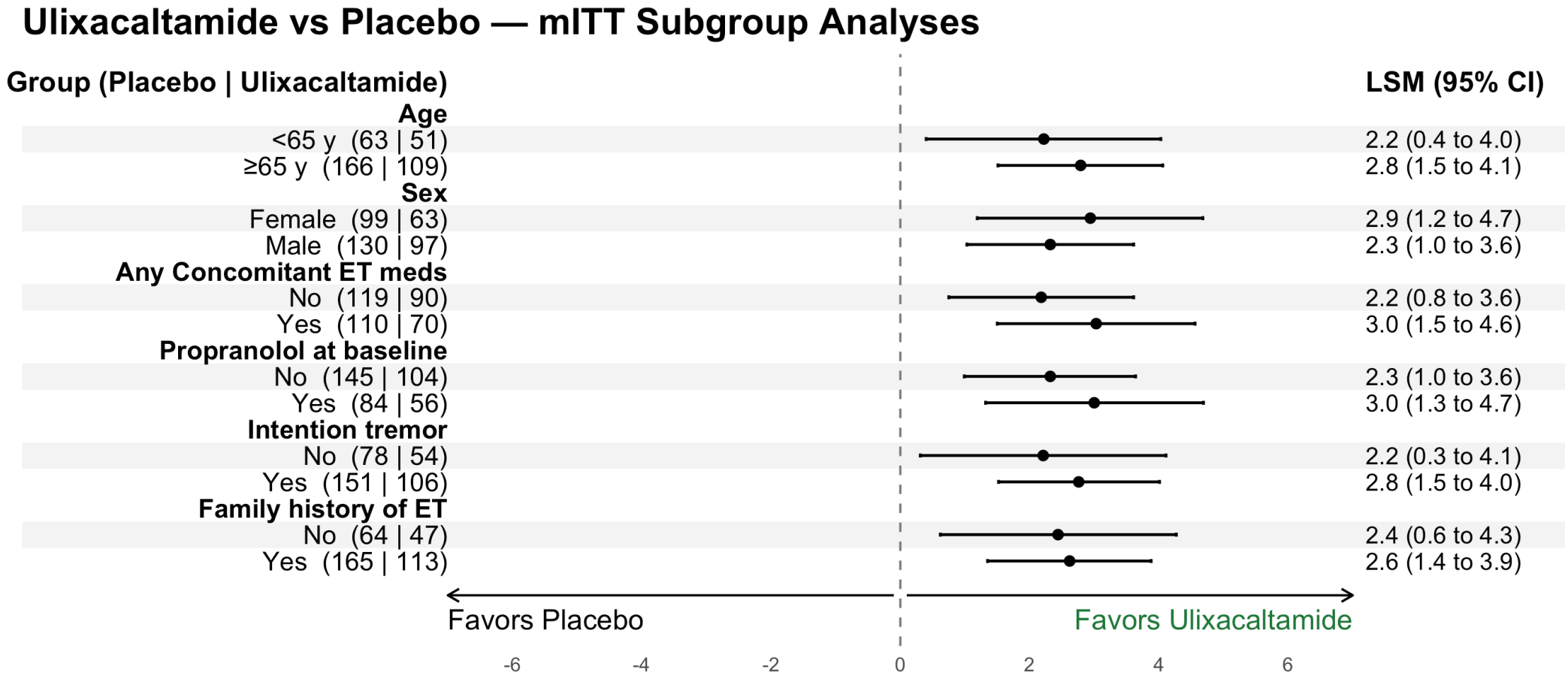




LS means for the mADL11 were estimated using a mixed model for repeated measures with treatment group, visit (categorical), treatment-by-visit interaction, randomization strata (IT status, propranolol use, family history of ET), and baseline mADL11 score as fixed effects; subject was a random effect with an unstructured covariance matrix. Sensitivity to missingness was done with a pre-specified delta-adjusted tipping-point analysis which remained statistically significant at the maximum pre-specified shift (Δ = 2.5; p = 0.0026), exceeding the ~½ SD robustness criterion of Ratitch et al. (2013) and confirming strong resilience of the primary endpoint to non-MAR assumptions.

# Study 1 - Rapid and consistent response over 12 weeks



# Study 1 efficacy – Robust response across subgroups

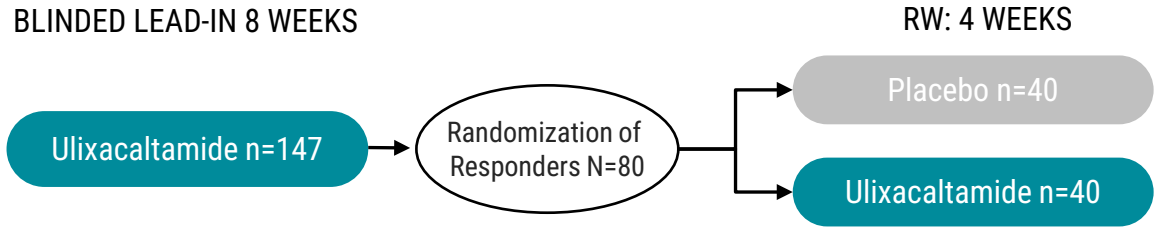


# Essential3 Study 2 – Randomized Withdrawal design

**Hypothesis 2**

Blinded stable-responder, randomized withdrawal design

*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?*




**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

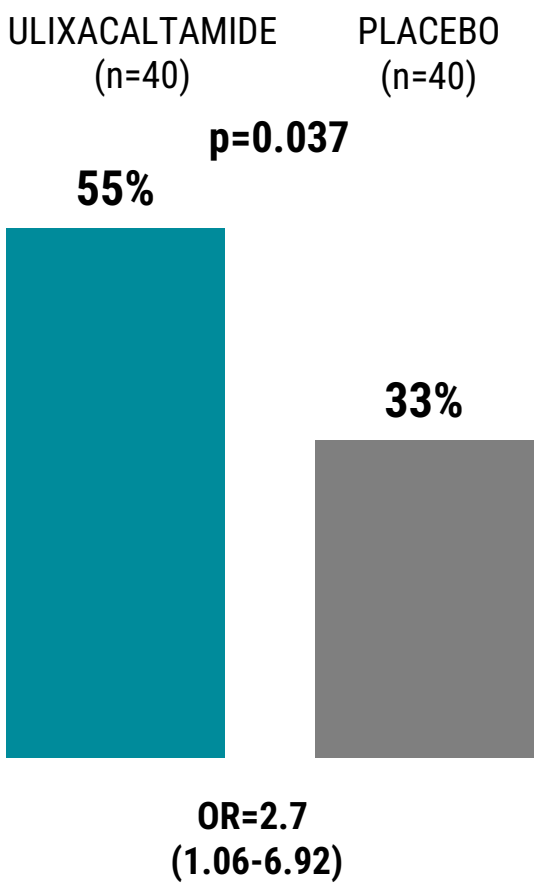
All efficacy analyses use the modified intent-to-treat (mITT) population defined as all randomized responders who received at least one dose of study drug during the randomized withdrawal phase and had at least one post-RW baseline efficacy assessment.

# Study 2 – RW baseline demographics – stable-responders

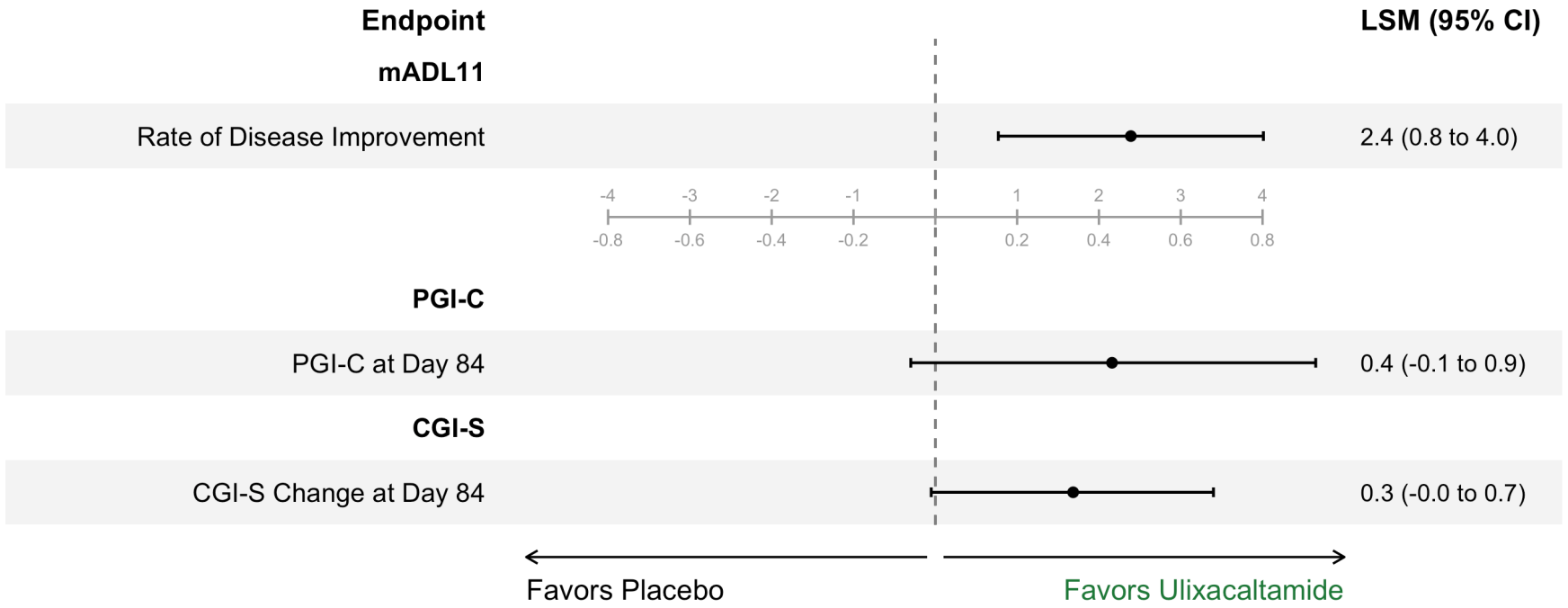
| | BLINDED LEAD-IN ULIXACALTAMIDE | ULIXACALTAMIDE STABLE RESPONDERS |
|---|---|---|
| **Age,** Mean (SD) | 67.9 ( 7.9) | 67.3 (8.4) |
| **Gender,** Male/Female % | 51.8% / 48.2% | 55.0% / 45.0% |
| **Race,** White/Other % | 96.3% / 3.7% | 95.0% / 5.0% |
| **Years since ET Onset,** Mean (Median) | 28.7 (25.0) | 28.5 (24.5) |
| **ET symptoms worsened over past 3 years,** Yes % | 95.8% | 93.8% |
| **Currently on ET Medications,** Yes %<br>**Currently on Propranolol,** Yes % | 42.4%<br>34.6% | 41.3%<br>38.8% |
| **Family History of ET,** Yes/No/Unknown % | 73.3% / 22.0% / 4.7% | 76.3% / 18.8% / 5.0% |
| **Presence of Intention Tremor,** Yes % | 63.9% | 53.75% |
| **mADL11,** Mean (SD) | 19.0 (2.5) | 10.6 (4.8) |
| **Patient Global Impression – Severity,** Mean (SD) | 3.0 (0.7) | 1.2 (0.6) |
| **Clinician Global Impression – Severity,** Mean (SD) | 4.0 (0.7) | 3.1 (0.9) |

# Study 2 efficacy - Primary and first secondary endpoint met

**Primary Endpoint**
**% Maintain Response**




**Ulixacaltamide vs Placebo — Key Secondary Endpoints**

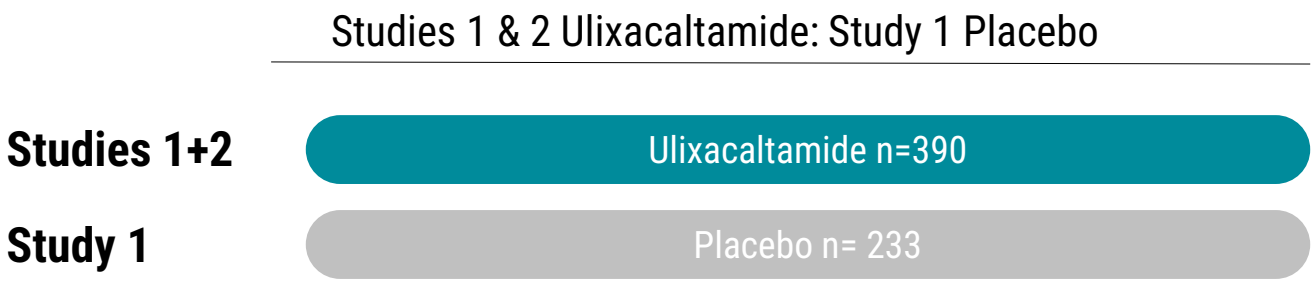



For primary endpoint, odds ratio, 95% confidence interval, and p-value were obtained from a logistic regression model including treatment group as the main effect and randomization strata (IT status, propranolol use, and family history of ET) as fixed effects.

# Hypothesis 3– Day 56 Parallel-group combined efficacy analysis

**Hypothesis 3**
**Studies 1+2 Ulixa / Study 1 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?*

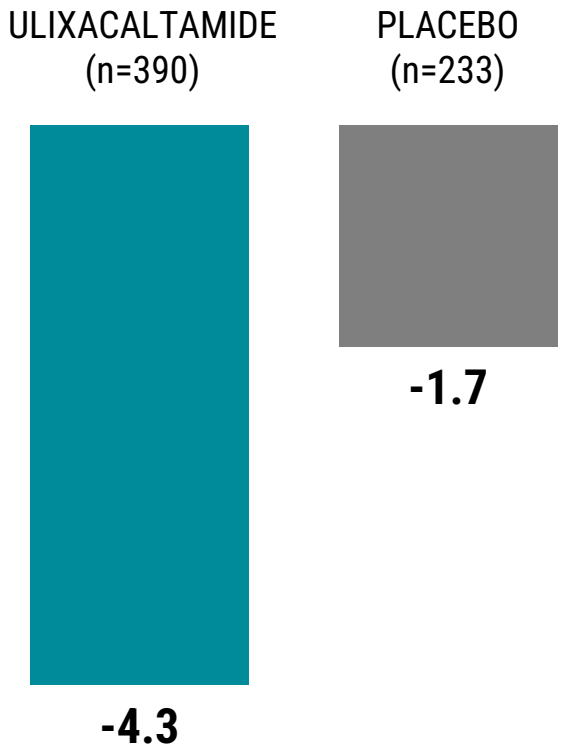



**Primary Endpoint:**

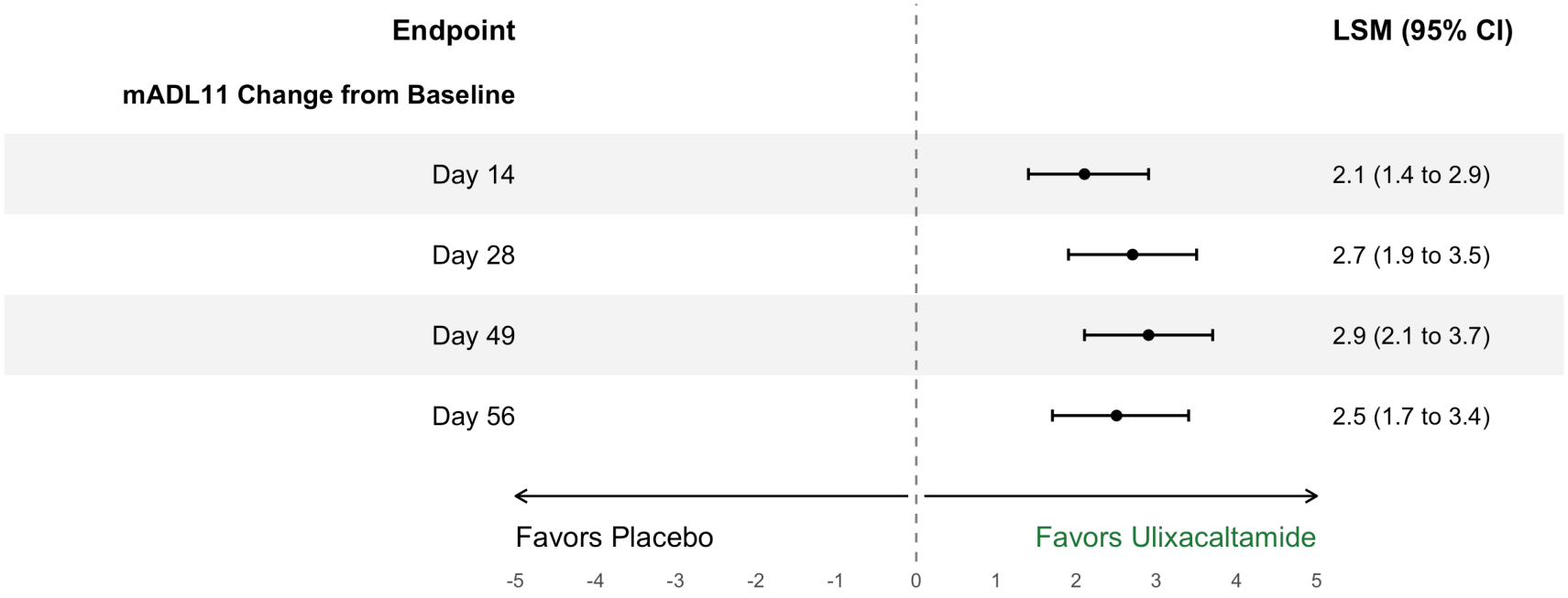
- mADL11 change from baseline to Day 56

# Hypothesis 3– Day 56 Parallel-group combined efficacy analysis

**Primary Endpoint**
**mADL11 CFB to Day 56**




**Parallel-group combined analysis - Studies 1+2 / Study 1**



# Hypothesis 4– Day 56 Parallel-group combined efficacy analysis

**Hypothesis 4**
**Study 2 Ulixa / Study 1 PBO**

*How do patients receiving ulixacaltamide in the RW study compare to placebo patients from the PD study after 56 days of intervention?*

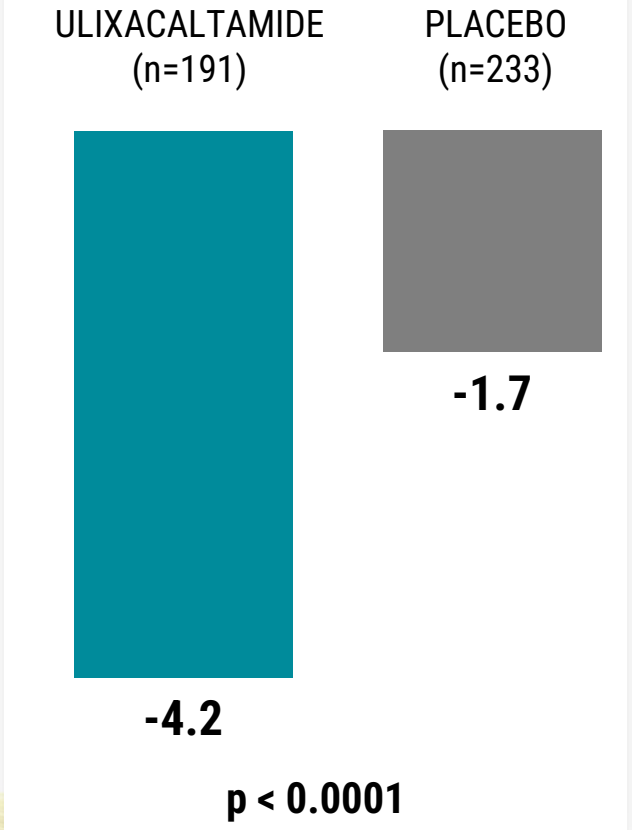
Study 1 Placebo: Study 2 ulixacaltamide


**Primary Endpoint:**

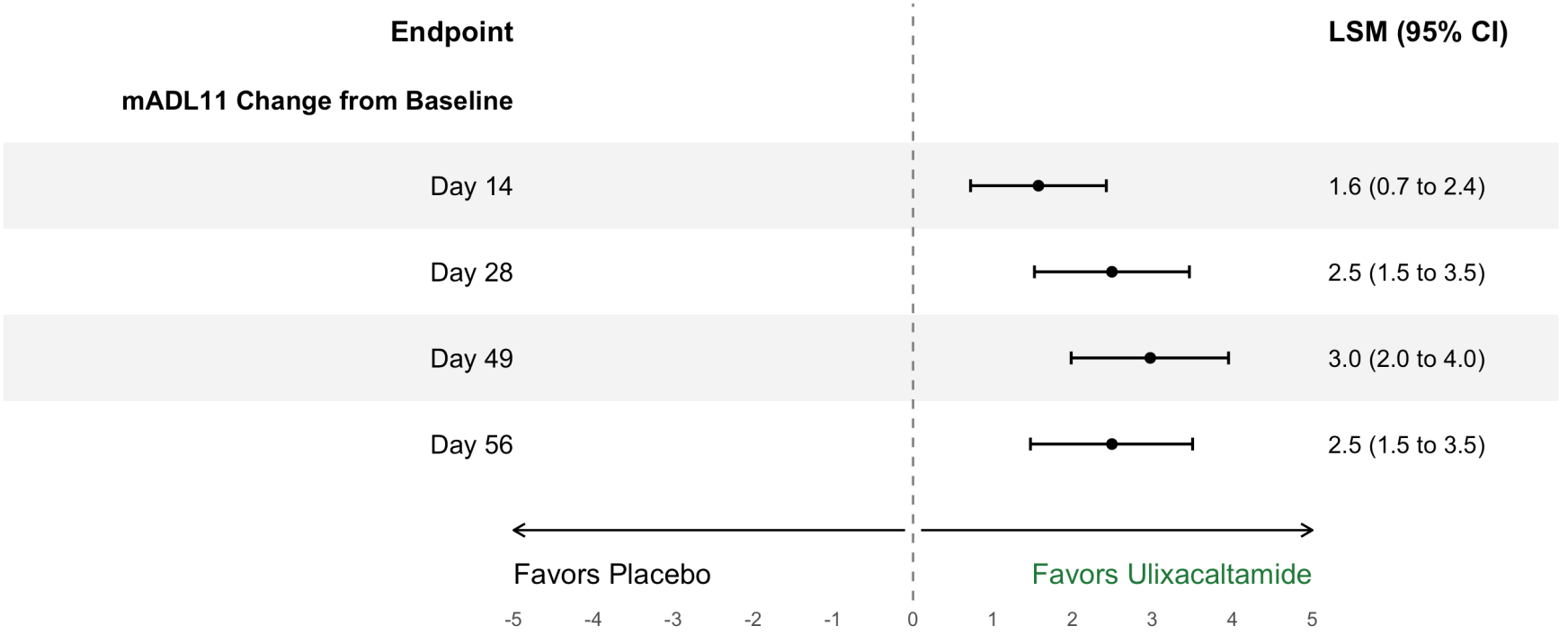
- mADL11 change from baseline to Day 56

# Hypothesis 4– Day 56 Parallel-group combined efficacy analysis

**Primary Endpoint**
**mADL11 CFB to Day 56**




**Day 56 Parallel-group placebo versus Study 2 analysis**



# Safety across studies remains consistent

- No change in overall safety profile and no new signals identified
- 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
- Majority of TEAEs were mild to moderate in severity
- No SAEs related to ulixacaltamide

# Essential3 Program: Study 1 and Study 2 disposition

## DISPOSITION STUDY 1

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

## DISPOSITION STUDY 2

| POPULATIONS | OVERALL |
|---|---|
| Enrolled | 238 (100%) |
| Population at Day 56 | 147 (61.8%) |
| Stable Responders (mITT) | 80 (54.4%) |
| Non-stable responders | 67 (45.6%) |

Study 1 Enrolled/ITT: All randomized participants
Study 2 Enrolled: All randomized participants
Safety: All participants who received at least one dose of study drug
Study 1 mITT: All randomized participants who received at least one dose and had at least one post-baseline efficacy assessment
Study 2 mITT/Stable responders: Participants with an average improvement of three or more points in mADL11 at Days 49–56, received at least one dose in RW and one post RW baseline efficacy assessment
Non-stable responders: Participants at Day 56 who did not meet the criteria for Responders

# Safety population – Overview of AEs

| OVERVIEW OF ADVERSE EVENTS | | | |
|---|---|---|---|
| | 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 (0.86%) | 8 (3.4%) | 4 (1.73%) |
| 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

# Safety population - Most common TEAEs

| TREATMENT EMERGENT ADVERSE EVENTS ≥10% OF PATIENTS | | | |
|---|---|---|---|
| | STUDY 1 | | STUDY 2 |
| **Preferred Term** | ULIXACALTAMIDE (N = 233) | PLACEBO (N = 234) | ULIXACALTAMIDE (N = 231) |
| Constipation | 57 (24.5%) | 16 (6.84%) | 68 (29.4%) |
| Dizziness | 56 (24.0%) | 27 (11.5%) | 59 (25.5%) |
| Euphoric mood | 30 (12.9%) | 3 (1.28%) | 15 (6.5%) |
| Brain fog | 27 (11.6%) | 8 (3.42%) | 44 (19.0%) |
| Paraesthesia | 23 (9.87%) | 5 (2.14%) | 27 (11.7%) |
| Fatigue | 22 (9.44%) | 26 (11.1%) | 22 (9.52%) |
| Headache | 19 (8.15%) | 20 (8.55%) | 29 (12.6%) |
| Insomnia | 18 (7.73%) | 9 (3.85%) | 27 (11.7%) |

# One step closer to delivering life-altering treatments to ET patients

First positive Phase 3 program for a drug in Essential Tremor

Praxis has submitted a pre-NDA meeting request to the FDA and, upon agreement with the agency, expect to file an NDA in early 2026

Will share additional data in upcoming medical conferences and scientific journals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