
# Assessing Clinically Meaningful Improvement Associated with Ulixacaltamide Treatment in Adults with Essential Tremor on Concomitant Propranolol: Findings from Essential1

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# Disclosure Information

Richard Able PhD is a current employee of Praxis Precision Medicines and is a Praxis stockholder.

# Essential Tremor (ET) is the Most Common Movement Disorder

Up to 7 million people in the United States may have ET[1]

Action tremors significantly disrupt daily living for people with ET

Hallmark feature is action tremor that primarily affects the hands[2,3]

Almost all ET patients suffer from at least one comorbid condition (e.g., depression, anxiety, sleep disorders, cognitive dysfunction)[4]

SOURCE: 1. GHOSH (2016) (P.231, C.1, PH.1, L.1-2), 2. Elble RJ. Curr Neurol Neurosci Rep. 2013 Jun;13(6):353. 3. Putzke JD, et al. J Neurol Neurosurg Psychiatry. 2006 Nov;77(11):1235-7.
4. Vetterick, C., Lyons, K.E., Matthews, L.G. et al. The Hidden Burden of Disease and Treatment Experiences of Patients with Essential Tremor: A Retrospective Claims Data Analysis. Adv Ther (2022). https://doi.org/10.1007/s12325-022-02318-8

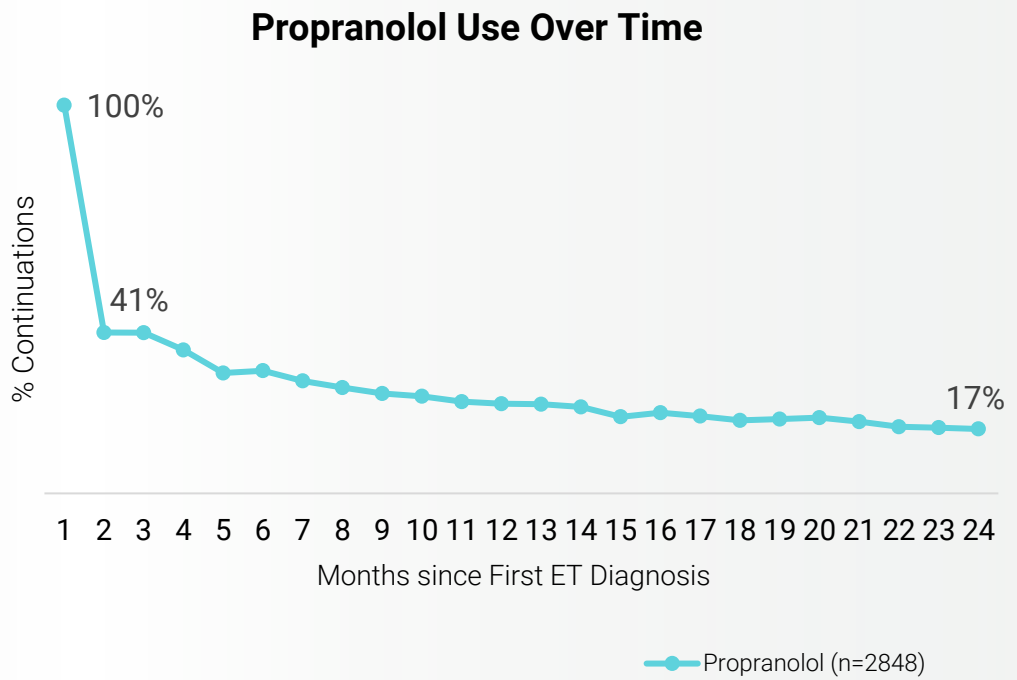
# ET Hidden Burden: High Treatment Discontinuation

**Propranolol is the only medication approved for ET ~40 years ago and is not widely used**

**1 million**

patients with ET remain untreated

- ~1 million people are diagnosed with ET and on treatment, while another 1 million are estimated to remain untreated
- <30% of patients are eligible to receive propranolol due to other medications/health conditions
- Of those who start propranolol
  - >50% discontinue after only 1 month
  - <20% still receive propranolol after 2 years




Source: Praxis Data on File; Vetterick C, et al. *Adv Ther*. 2022;39(12):5546-5567

# Ulixacaltamide is a Selective Small Molecule T-type Calcium Channel Modulator Addressing the Driver of ET

**Designed to block T-type calcium channels**

**Formulated as a once-daily oral medicine that can be taken any time of day, with or without food**

**Well-tolerated in clinical studies to date**

Source: Praxis data on file

# Our Journey to Develop a New ET Therapy


ESSENTIAL 1

- COMPLETE: Essential1 study
- 14-week results available: Essential1 open-label extension study

ESSENTIAL 3
AN AT-HOME RESEARCH STUDY

Now enrolling!

Ulixacaltamide is currently being studied in ET and is not approved by the U.S. Food & Drug Administration as safe or effective for use.

# Essential1 Phase 2b Study Evaluating the Efficacy and Safety of Ulixacaltamide for Essential Tremor

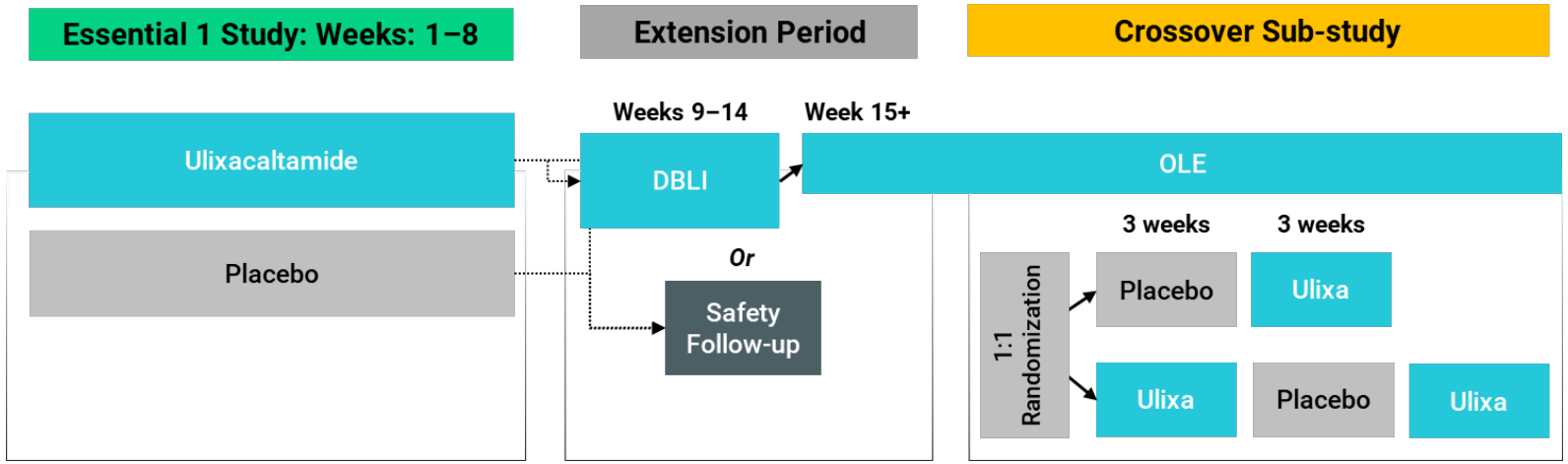
## Adults = 18 years or older with moderate to severe ET*

- Had ET symptoms for at least 3 years
- Willing to maintain stable doses of certain ET medications, but had to discontinue primidone
- Have not had surgery for ET


132 participants assigned to ulixacaltamide or placebo

8-week study (56 days)

## ESSENTIAL1 DESIGN




*Severity as defined by the TETRAS and CGI-S scales (clinical rating scales that quantify tremor)

DBLI – double blind lead-in, OLE = open label extension

ClinicalTrials.gov NCT05021991

# Essential1 Study Results Snapshot

## Primary study:
Essential1

- Ulixacaltamide showed clinically meaningful improvement
- Improvements seen across various activities of daily living (ADLs) and Patient Global Impression

## Sub-study:
Open-label extension

- Participants taking ulixacaltamide continued to benefit after 14 weeks of treatment

## Sub-study:
Randomized withdrawal

- Participants saw ADL scores worsen when they switched from ulixacaltamide to placebo

Results presented at IAPRD 2023 and MDS 2023 (posters available at https://praxismedicines.com/resources/)

# Pursuing Clinically Meaningful Benefit in ET

*Essential1 provided confidence in a **modified index of activities of daily living (mADL11)** as a robust endpoint for assessing meaningful benefit in ET, demonstrating early clinical benefit at 8 weeks, and long-term durable benefit.*

**mADL11**

***A modified index of activities of daily living, based on the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS)**, a clinical rating scale for measuring tremor impact.*[1]

***Comprises 11 key elements of the TETRAS Activities of Daily Living subscale (TETRAS-ADL),** reflecting typical daily activities impacted by tremor.*

***Focuses on elements determined to be most meaningful to patients with ET.** Essential1 findings highlighted mADL11 as a robust endpoint with greatest correlation with patient-reported outcomes.*[2,3]

[1]Elble et al. 2012; [2]Giroux et al. 2023 MDS Congress; [3]Giroux et al 2023 IAPRD Meeting

# Pursuing Clinically Meaningful Benefit in ET

## mADL11: A Modified Activities of Daily Living Scale

**11 Items from the TETRAS-ADL**

- Speaking
- Using Keys
- Pouring
- Writing
- Feeding with a spoon
- Carrying food trays, plates or similar items
- Overall disability with most affected task
- Dressing
- Hygiene
- Working
- Drinking from a glass

**Each measure is individually scored from 0-3**

0 = Slightly abnormal. Tremor is present but does not interfere with __.
1 = Mildly abnormal. Spills a little.
2 = Moderately abnormal. Spills a lot or changes strategy to complete task
3 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup

**TOTAL SCORE OF UP TO 33**

TETRAS = TRG Essential Tremor Rating Assessment Scale; ADL = Activities of Daily Living subscale

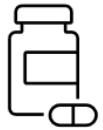
# Essential1 Propranolol Post-hoc Analysis

- *We sought to assess clinically meaningful change related to ulixacaltamide treatment in adults with ET able to maintain a stable dose of propranolol for the duration of the study.*

## *Approach*

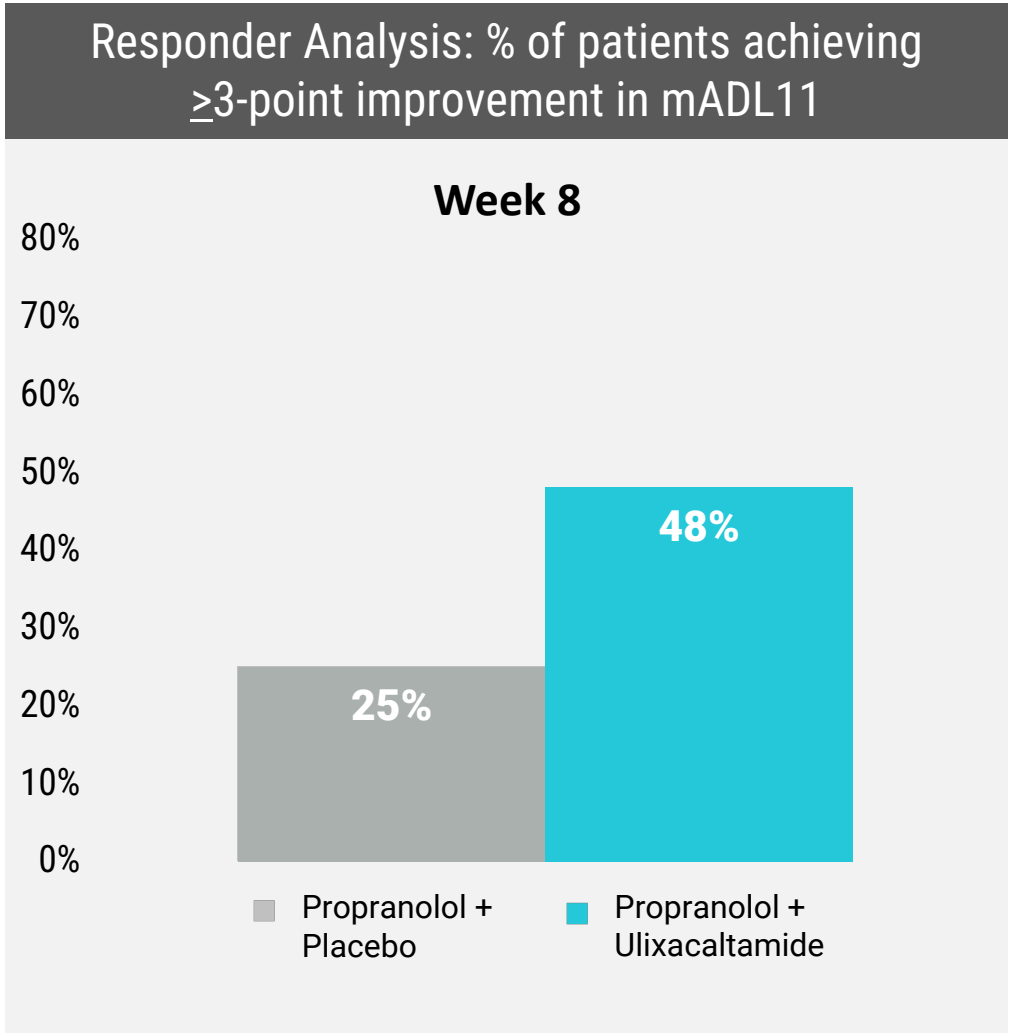
- mADL11 as a robust measure of clinically meaningful benefit in ET
- Clinically meaningful within-patient change in patients on propranolol receiving ulixacaltamide vs. placebo defined as a minimum 3-point improvement in mADL11

**Measuring Clinically Meaningful Benefit in ET Patients on Propranolol Receiving Ulixacaltamide**



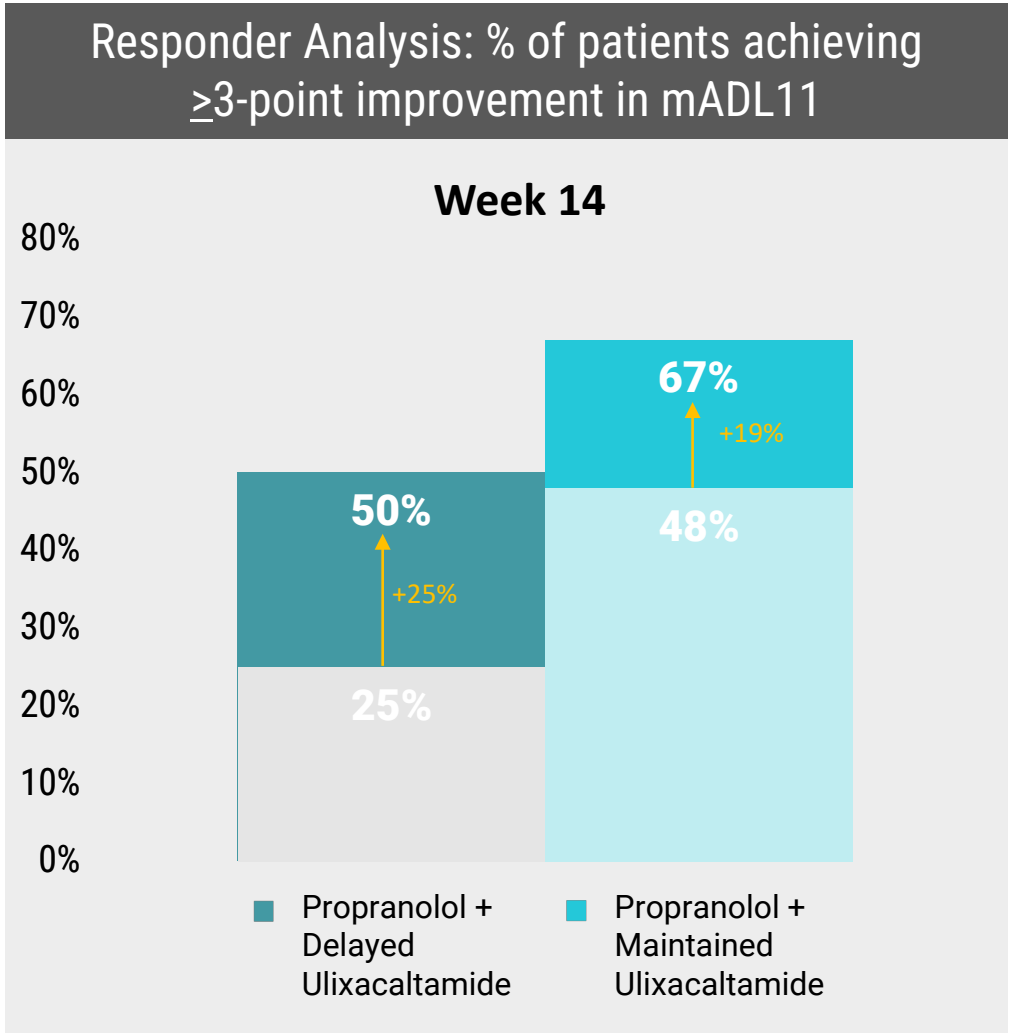
- Improvement based on regaining function
- Each point reduction provides benefit to a patient
- ADL assessment performed by a physician

# Adding Ulixacaltamide Benefited More Patients on Propranolol




Among patients who could tolerate propranolol, adding ulixacaltamide led to ~2-fold increase in the proportion achieving clinically meaningful change (ie. at least a 3-point change in mADL11)

# Rapid Improvement at Week 14 in Patients Transitioning from Placebo




Patients on propranolol transitioning from placebo to ulixacaltamide have a rapid efficacy response, consistent with earlier durability findings of sustained mADL11 improvement in propranolol-naive patients.

# Essential1 Phase 2b Set Foundation for Essential3 Phase 3 Program

*Building on findings from Essential1, and focusing on measures determined to be most meaningful to patients with ET, these results highlight the potential for ulixacaltamide to revolutionize the treatment of ET*

**Propranolol analysis further validated our clinical hypothesis**

- Strong efficacy signal with robust endpoint (mADL11)
  - Early clinical benefit in 8-week study
  - Long-term, durable benefit
  - **Meaningful improvement alone and in combination with chronic propranolol use**
- Well-tolerated with a differentiated safety profile
  - **Tolerability findings consistent with overall study**
- Tested Phase 3 design concepts

# Acknowledgements


- This work is presented on behalf of The Essential1 Study Team
- We thank the patients of the Essential1 trial, and our collaborators, clinical sites and investigators


ESSENTIAL 3

AN AT-HOME RESEARCH STUDY

**Now enrolling!**

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***P3003***

*An Innovative Multi-Study Phase 3 Program to Evaluate the Efficacy and Safety of Ulixacaltamide: The Future of Clinical Trial Design in Essential Tremor*