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

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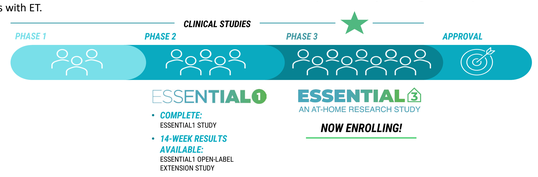
Background

- Essential tremor (ET) is characterized by involuntary progressive tremor especially in the hands and upper limbs, with patients experiencing significant disruption to their daily activities,[1-3] often alongside multiple comorbid conditions.[4]
- Existing treatment options are limited, with high discontinuation rates due to poor tolerability and modest efficacy.[5]
- Ulixacaltamide is a novel, selective T-type calcium channel blocker in clinical development for ET treatment.[6-9]
- Phase 2 studies showed improvement across TETRAS Activities of Daily Living (ADL) measures and Patient Global Impression, alongside favorable tolerability.[8,9]
- Incorporating learnings from Essential1 (NCT05021991) and FDA guidance, the ongoing Essential3 program addresses critical trial design considerations to facilitate definitive assessment of the safety and efficacy of 60 mg once-daily ulixacaltamide in adults with ET.



Innovative, Decentralized, Multi-Study Design

- Two simultaneous, 12-week, decentralized, pivotal studies will combine in-home and telehealth visits to assess efficacy of ulixacaltamide (60 mg QAM) vs. placebo, and maintenance and durability of effect in responders following randomized withdrawal (RW). Participants have the option to undergo a long-term safety study up to ~1 year.

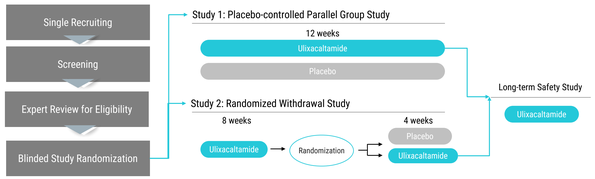


Figure 1. Essential3 Schema. *clinicaltrials.gov: NCT06087276*

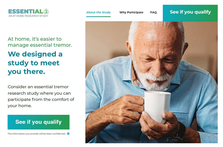
ESSENTIAL3 AN AT-HOME RESEARCH STUDY

A RESEARCH STUDY PATIENTS CAN PARTICIPATE IN FROM HOME

Expanding reach and reducing study burden

- Home health visits with a study nurse
- Telehealth visits with study physician
- An assigned study nurse to guide patient through study participation
- Digital app for completion of questionnaires

1 Patient completes online pre-screener at Essential3Study.com



2 Patient call with Study Coordinator ▶ 3 Telehealth visit ▶ 4 At-home nurse visit ▶ 5 At-home nurse + telehealth visits

Participant Eligibility

Table 1. Essential3 Study Eligibility

Key Inclusion Criteria
• Is between the age of 18 and 85 years (inclusive) at screening
• Clinical diagnosis of moderate to severe ET, as characterized by postural and action tremor, including tremor syndrome of bilateral upper limb action for at least 3 years
• If currently receiving medication prescribed for ET, must be on ≤1 medications, on a stable dose for at least 1 month prior to screening, and willing to maintain a stable dose throughout the study
• Has been assessed as an appropriate and suitable candidate by investigator and has a neurological exam and medical record(s) consistent with ET diagnosis, as confirmed by the ERC central reviewer
Key Exclusion Criteria
• Sporadic use of a benzodiazepine, sleep medication, or anxiolytic that would confound tremor assessment
• History of unilateral tremor or clinical evidence of other medical, neurological, or psychiatric condition that may explain or cause tremor, or medication-, food-, or supplement-induced movement disorder
• Prior magnetic resonance–guided focused ultrasound or surgical intervention for essential tremor, such as deep brain stimulation or thalamotomy
• Unwillingness or inability to discontinue primidone
• History of any suicide attempt or suicidal ideation with intent within 2 years before screening
• Positive alcohol or drug screening (including cannabis and cannabis-derived products). The participant can be enrolled in the study, if they are willing to stop use of cannabis or cannabis-related products after the Screening Visit and have a negative drug screen result at Baseline (Day 1).
• Neuropathy, muscle weakness, arthropathy or other musculoskeletal diagnosis of the upper extremity that impairs dexterity or function

Pursuing Clinically Meaningful Benefit in ET

Field-First Definition of Meaningful Benefit in ET[8] Provides Foundation for Phase 3 Program

*Essential1 Phase 2 study 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

PRIMARY ENDPOINT IN ESSENTIAL3 REGISTRATIONAL PROGRAM

***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.[10]*

***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.[8,9]*

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

Measuring Clinically Meaningful Benefit in ET

- Improvement based on regaining function
- Each point reduction provides benefit to a patient
- ADL assessment performed by a physician
- Aligned with FDA as primary endpoint for Essential3 studies

mADL11 Primary Endpoint is Well-Powered

Study	Study 1 Parallel Design	Study 2 Randomized Withdrawal
Participants	400	200
Primary Endpoint and Power	mADL11 Change from Baseline to Week 12 between ulixacaltamide and placebo **90% power to detect difference**	Difference in maintenance of response rate during the 4-week RW period between ulixacaltamide and placebo **90% power to detect difference**
Stratification	Intention tremor status, family history, and propranolol use	

Objectives and Endpoints

Table 3. Essential3 Study Objectives and Associated Endpoints

Study 1 – Parallel Design

Objective	Endpoint
Primary	
➢ To evaluate the efficacy of ulixacaltamide vs. placebo	• mADL11 change from baseline to Day 84
Secondary	

➢ To further evaluate the efficacy of ulixacaltamide vs. placebo over time	• Day 84
	  • Proportion of responders, defined by change in mADL11 score
	  • TETRAS-ADL; PGI-C; CGI-S; PGI-S
	• Day 14, Day 28, Day 56, Day 70
	  • Proportion of responders, defined by change in mADL11 score
	  • mADL11; TETRAS-ADL; PGI-C; CGI-S; PGI-S

Safety	
➢ To evaluate the safety of ulixacaltamide vs. placebo	• Incidence and severity of AEs, including discontinuation of study drug due to AEs • Vital sign measurements • Clinical laboratory results • 6-lead ECG parameters • C-SSRS measured suicidal ideation or behavior • BDI-II and BAI

Study 2 – Randomized Withdrawal

Objective	Endpoint
Primary	
➢ To evaluate the ulixacaltamide maintenance of response following RW	• Proportion of participants that maintained response following RW
Secondary	
➢ To further evaluate the efficacy of continued ulixacaltamide over time	• Day 70, Day 77, Day 84 • mADL11; TETRAS-ADL; PGI-C; CGI-S; PGI-S
Safety	
➢ To evaluate the safety of ulixacaltamide	• As for Study 1 above

Long-term Safety Study

Objective	Endpoint
Primary	
➢ To evaluate the long-term safety of ulixacaltamide	• Incidence and severity of AEs, including discontinuation of study drug due to AEs • Vital sign measurements • Clinical laboratory results • 6-lead ECG parameters • C-SSRS measured suicidal ideation or behavior

ADL=Activities of Daily Living; AE=adverse event; BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory – Second Edition; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; mADL11=modified TETRAS-ADL items 1 to 11 with modified score; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; TETRAS=The Essential Tremor Rating Assessment Scale; TETRAS-ADL=The Essential Tremor Rating Assessment Scale Activities of Daily Living subscale

Conclusions

- **Essential3, the Phase 3 program for ulixacaltamide, comprises two simultaneous Phase 3 studies including a 12-week, parallel design study and 12-week randomized withdrawal study for stable responders.**
- **Essential3 incorporates learnings from the Phase 2 Essential1 study including the use of a single 60 mg dose, using mADL11 as the primary endpoint, and conducting the study in a decentralized manner.**
- **3,000+ referrals received to date meet pre-qualifying criteria for ulixacaltamide in the Essential3 program, with topline results expected in 2024.**
- **In addition to providing evidence of ulixacaltamide safety and efficacy, the Essential3 program is expected to set the foundation for future clinical trial design in ET and other neurologic disorders.**

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