

Framework for Future Neurology Trials: Enhanced Scientific Rigor Through Innovative Decentralized Trial Methodology

Marcio Souza¹, Megan Sniecinski¹, Claudio Santos¹, Monique Giroux¹, Michael Steidle¹, Rodger Elble², Christine Cooper³, Alfonso Fasano^{4,5}, Alexander Shtilbans^{6,7}, Jill Farmer⁸, Salima Brillman⁹
¹Praxis Precision Medicines, Boston, MA, USA; ²Southern Illinois University School of Medicine Springfield, IL, USA; ³Department of Neurology, Medical University of South Carolina, Charleston, SC, USA;
⁴Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Division of Neurology, University of Toronto, Toronto, Ontario, Canada; ⁵Krembil Brain Institute, Toronto, Ontario, Canada; ⁶Hospital for Special Surgery, Department of Neurology, New York, NY, USA; ⁷Weill Cornell Medicine, Department of Neurology, New York, NY, USA; ⁸BoroNeuro, Hopewell, NJ, USA;
⁹Parkinson's Disease and Movement Disorders Center of Silicon Valley, Palo Alto, CA, USA

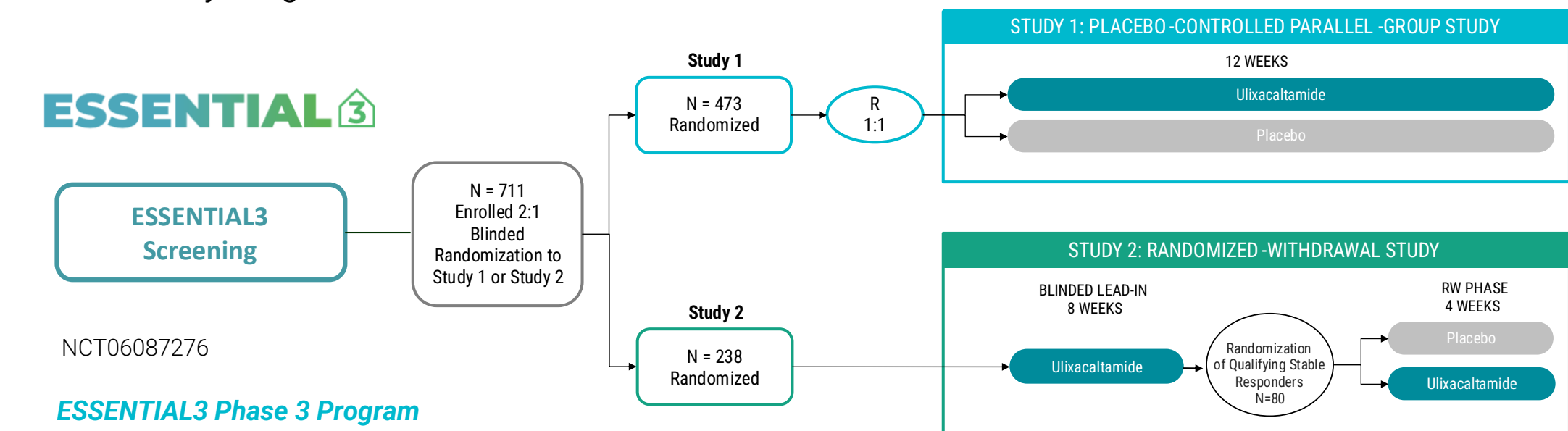
BACKGROUND

- Essential tremor (ET) affects ~7 million Americans, yet research participation remains limited by distance to specialty centers, mobility challenges, and visit burden.
- Traditional trials concentrate enrollment at tertiary centers, restricting access and introducing inter-site variability.
- ESSENTIAL3 evaluated ulixacaltamide HCl in ET using a decentralized (DCT) model designed to enhance rigor through centralized expert oversight, ecologically valid assessments, and a unified multi-study protocol.
- **Here we characterize feasibility and scientific rigor of a DCT Phase 3 trial in ET, emphasizing diagnostic standardization, real-world population access, centralized control, and real-time data integrity.**

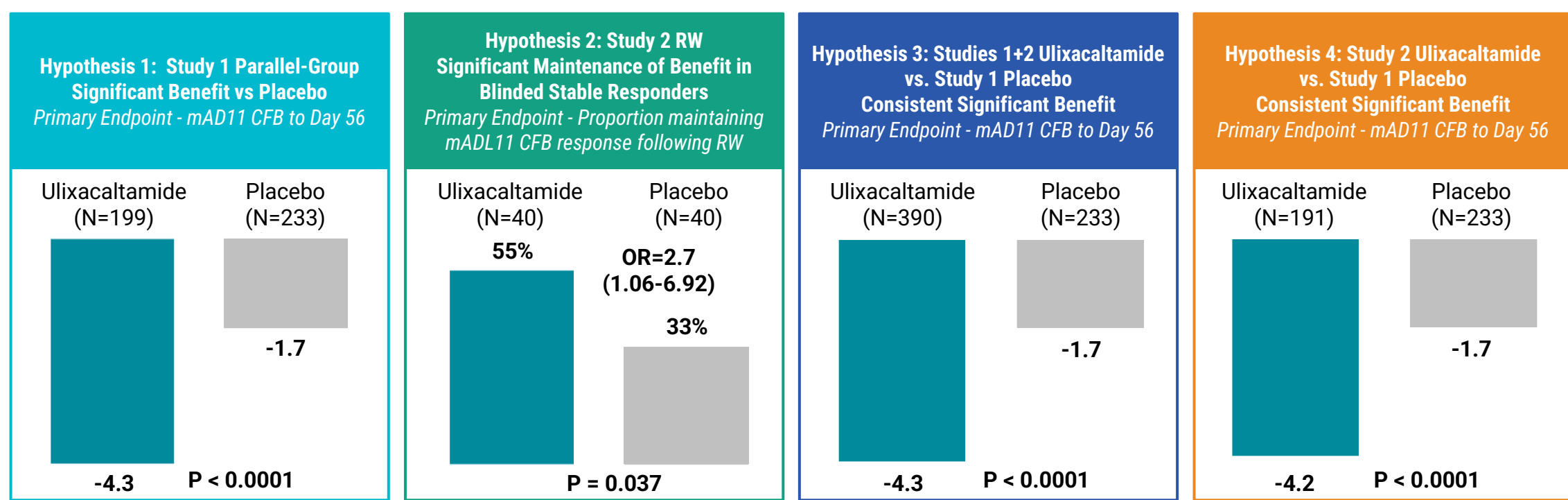
ESSENTIAL3: TWO POSITIVE PH 3 STUDIES UNDER A UNIFIED PROTOCOL

Two Simultaneous Blinded Designs: Complementary Randomized Controlled Trials

- Randomized, double-blind, placebo-controlled trial enrolling participants aged 18–85 years with ET (symptoms ≥3 years; if on permitted ET medication(s), stable dose for ≥28 days prior to screening).
- Pivotal Study 1 (parallel-group design) and Study 2 (randomized withdrawal, RW) were conducted concurrently under a single randomized, double-blind, placebo-controlled protocol with identical screening and assessments, enabling valid cross-study comparisons from one population. Pre-specified hypotheses evaluated overall treatment effect across studies.
- The Essential Tremor Rating Assessment Scale – Activities of Daily Living (TETRAS-ADL) subscale was collected, and mADL11 (TETRAS-ADL items 1–11, modified score) derived to capture real-world functional disability in the context of daily living.



ESSENTIAL3 – All Primary Endpoints Met



For hypotheses 1, 3 & 4, the primary endpoint was change from baseline (CFB) to Day 56 in mADL11. All primary 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. OR=odds ratio

ESSENTIAL3: AN INNOVATIVE, FULLY DECENTRALIZED PHASE 3 PROGRAM

Five Pillars of Methodological Rigor

PILLAR 1
Centralized Eligibility Review

PILLAR 2
Multi-Layer Blinding

PILLAR 3
Unified Protocol for Two Complementary Designs

PILLAR 4
Home-Based Ecologically Valid Assessment

PILLAR 5
Real-Time Centralized Data Oversight

- Comprehensive secondary pre-screening calls and medical records reviewed by MDs with movement disorder experience prior to referral to Central Coordinating Site
- 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

- Blinded study allocation and treatment arm allocation (in both Study 1 and Study 2)
- Investigators, site staff and participants blinded to enrollment criteria for threshold of disability and mADL11 stability, and threshold to qualify as a responder for RW phase in Study 2
- Blinded transformation from TETRAS-ADL to mADL11 total score

- Study 1 and Study 2 conducted concurrently under a single randomized, double-blind, placebo-controlled protocol
- Identical screening and assessments enabling valid cross-study comparisons from one population
- Standardized procedures coordinated by Central Coordinating Site, reducing inter-site variability

- Drug shipped and delivered to participant homes within 24 hours of randomization, nationwide – all 50 states
- In home assessments captured functional impact where it occurs, addressing unique access challenges of an ET patient population
- Standardized assessments and centralized eligibility review designed to reduce evaluator variability and potential bias from clinic-based assessment
- Home health visits staffed by trained research nurses under sub-investigator supervision
- Clinician-administered TETRAS-ADL collected (7-day look back) and mADL11 total score derived to capture real-world functional disability as the primary endpoint

- Three fellowship-trained movement disorder specialist PIs and >40 sub-investigators coordinated execution under standardized procedures
- Contemporaneous, centralized data entry at all visits
- Centralized, unified, 24/7 medical monitoring including cardiac monitoring and psychiatric safety surveillance
- Real-time data entry enabled site and sponsor oversight, including daily review of AEs, lab alerts, and data completeness

Blinding Integrity

Complementary Evidence

Diagnostic Standardization

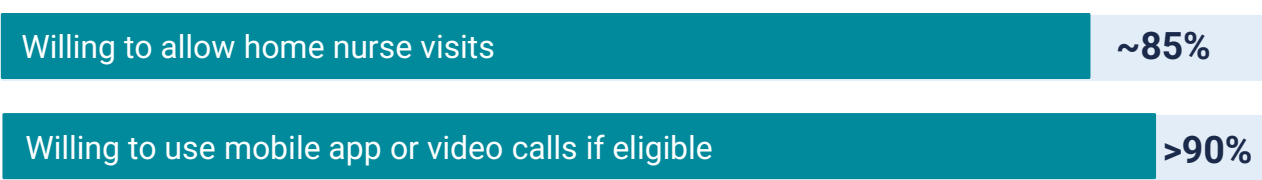
Ecological Validity

Data Integrity

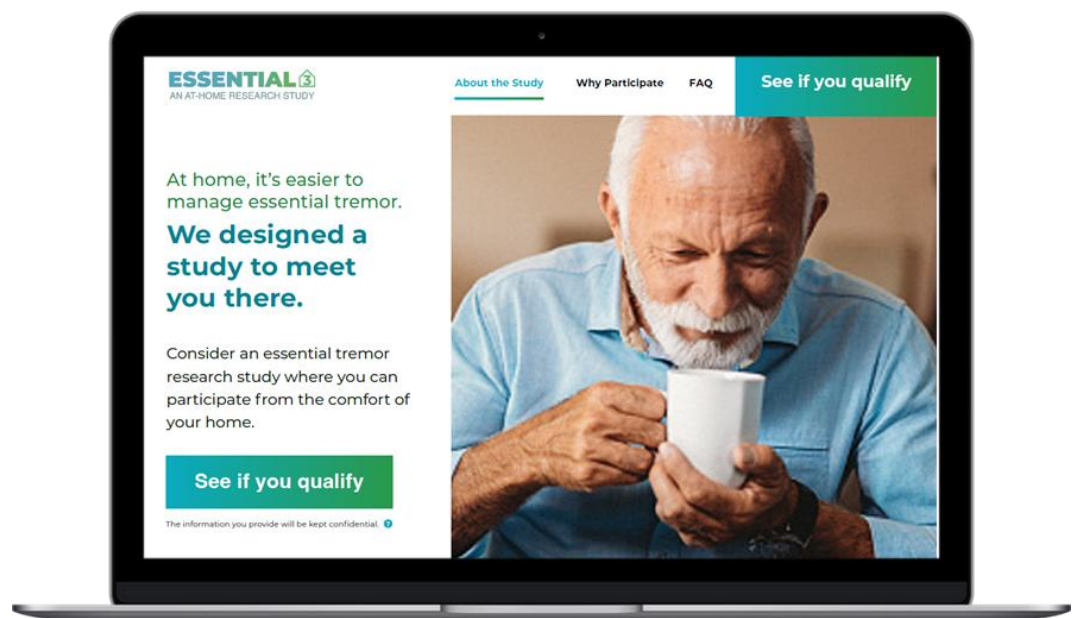
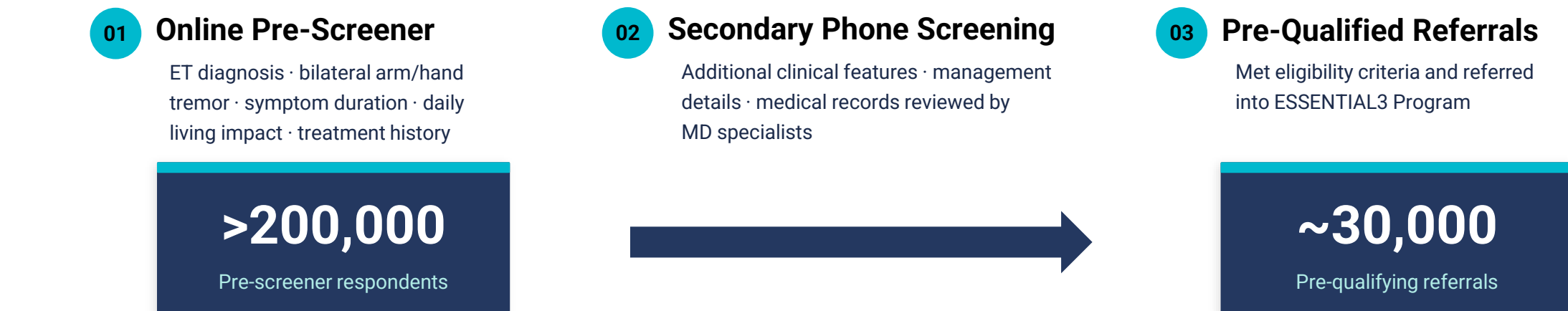
Characterizing the ET Population Seeking Trial Participation

ESSENTIAL3 Pre-Screener

PARTICIPANT WILLINGNESS – DECENTRALIZED MODEL

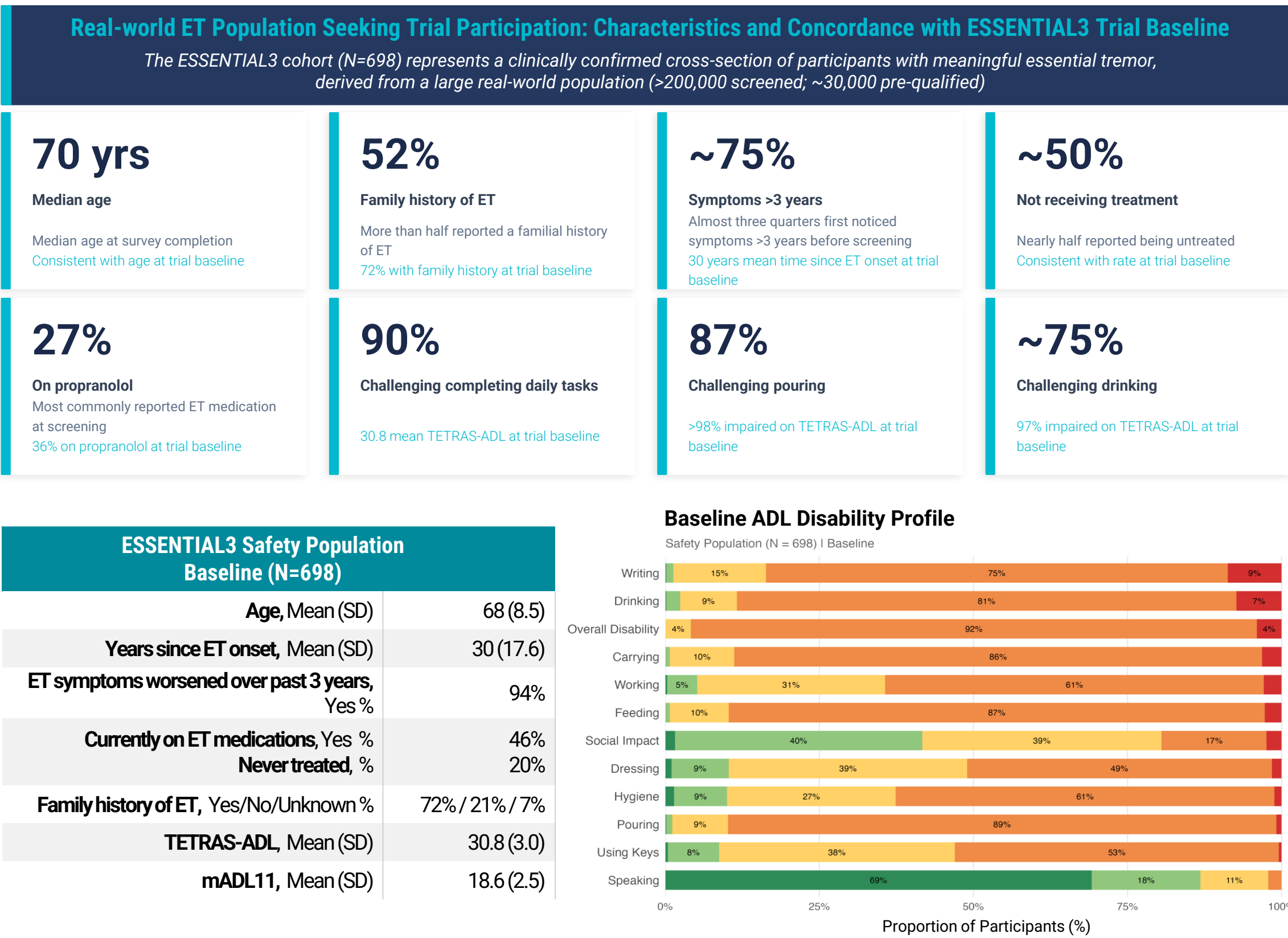


TWO-STAGE PRE-QUALIFICATION



ESSENTIAL3: BROAD REPRESENTATION OF ADULTS WITH ET

- A total of 2411 participants were assessed for eligibility nationwide, with 711 randomized, enabling broad representation of adults with long-standing ET (~30 yrs), on concomitant ET meds, and without access to specialty centers.



CONCLUSIONS

- ESSENTIAL3 demonstrates a DCT Phase 3 neurology trial is feasible, providing a scalable framework for future neurology trials.
- The DCT model enhanced rigor: centralized expert review standardized eligibility; complementary designs under one protocol enabled cross-study comparisons; home-based assessment increased ecological validity; centralized coordination reduced variability; and real-time monitoring ensured data completeness and oversight.
- Two studies conducted in parallel accelerated time to regulatory submission; the NDA for ulixacaltamide is under FDA review (PDUFA January 29, 2027).

REFERENCES

- Louis & Ottman 2014 *Tremor Other Hyperkinet Mov* (N Y)
- Jean-Louis & Seixas 2024 *Science*
- FDA 2025 Enhancing Participation in Clinical Trials – Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry
- FDA 2024 Conducting Clinical Trials With Decentralized Elements
- Lagelman et al. 2014 *Tremor Other Hyperkinet Mov* (N Y)
- Elble 2012 *Mov Disord*
- Farmer et al AAN 2026
- Brillman et al AAN 2026
- Shtilbans et al AAN 2026

Acknowledgments We thank the participants and their families, the ESSENTIAL3 Study Team, as well as our collaborators for their contributions to this work.

Funding All studies were funded by Praxis Precision Medicines. Medical writing and editorial assistance were provided by Lillian G. Matthews and Jamie Church in accordance with Good Publication Practice (GPP).

Disclosures RE has served as a Praxis consultant. CC has received honoraria from Praxis for participation in an advisory board. AF has received study funding from Praxis. AS, JF and SB have served as Praxis consultants and are Study Investigators. All other authors are current employees of Praxis Precision Medicines and may be Praxis stockholders.

- @PraxisMedicines
- Praxis Precision Medicines
- Praxismedicines.com
- clinicaltrials@praxismedicines.com



Presented at:
International Congress of Parkinson's Disease and Movement Disorders®
October 4–8, 2026
Seoul, Korea



International Parkinson and Movement Disorder Society