Background

Despite being the most common movement disorder, Essential Tremor (ET) remains underrecognized and poorly treated with almost half of patients who seek pharmacological therapy receiving medications due to limited efficacy and poor tolerability.1-4

Thus, there is an urgent need for novel therapies with improved efficacy and minimal side effects.

Ulixacaltamide (PRAXIS-944) is a differentiated, selective 1-type Ca2+ channel blocker in clinical development for movement disorders.

Phase 2b (Essential, NCT03251929) results in adult ET showed improvement on multiple endpoints including the TETRAS Activities of Daily Living (ADL) and Patient Global Impression of Change (PGIC) vs placebo at Day 56, alongside a well-tolerated safety profile.6,7

Notably, TETRAS-ADL, but not the Performance Subscale, correlated with patient-focused clinical outcome assessments (COA).6,7

Thus, there is an urgent need for novel therapies with improved efficacy and minimal side effects.

Field research question: what are the patient-focused outcome assessments that are most meaningful to patients with ET? And which endpoints are most clinically relevant to patients? Does ulixacaltamide meet these criteria?

Methods

Essential1 Study Design

- 122 adults with moderate to severe ET were enrolled in Essential1, an 8-week double-blinded, placebo-controlled study with optional Extension.

- Participants were randomized to ulixacaltamide OAM or placebo (Day 1-56), followed by blinded lead-in (DBI: Day 56-99) during which all participants were titrated to ulixacaltamide before transitioning to an unblinded open label period (Fig. 2).

Safety and efficacy measures were assessed including TETRAS-ADL (and derivate scales including mADL11 – comprising TETRAS-ADL and Individual Items). Overall, 65 were included in completer analysis.

- Of those eligible, 75 continued through the DBLI part of the study; 47 of which continued through the optional extension.

- 30% of patients who seek pharmacological therapy discontinuing medications due to limited efficacy and poor tolerability.1-5

- In 8-week DBLI period, ulixacaltamide-continuing participants and increased for those transitioning from placebo to ulixacaltamide (Fig. 5).

Safety and efficacy measures were assessed including TETRAS-ADL (and derivate scales including mADL11 – comprising TETRAS-ADL and Individual Items). Overall, 65 were included in completer analysis.

Ulixacaltamide Treatment Leads to Changes > MSD

- For mADL11, the MSD of 2 points was exceeded by 41 (60%) ulixacaltamide vs 14 (40%) placebo-treated participants, with significantly greater proportions of responders observed in treatment relative to placebo arms at higher cutoffs (Fig. 4).

- Sustained responder rates were observed during the DBI period for ulixacaltamide-continuing participants and increased for those transitioning from placebo to ulixacaltamide (Fig. 5).

Participant Disposition and Baseline Characteristics

- 122 adults were originally randomized and treated; 116 were included in mITT analysis of Essential1, all of whom reached at least 1 dose of study drug.

- Of those eligible, 75 continued through the DBI part of the study; 47 of which continued through the optional extension.

- Safety analysis population (N=132).

- With 18% receiving other concomitant medication during the study, predominantly for comorbidities.

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Conclusions

- This is the first time an MSD is defined in ET using a large patient dataset and a focus on measures determined to be most meaningful to patients.

- We highlight mADL11 as a reliable, patient-focused COA related to ulixacaltamide efficacy and durability of effect, with important decision-making implications for ET therapies.

- Following a successful End-of-Phase 2 meeting with the FDA in June 2023, we are initiating Essential3, the ulixacaltamide Phase 3 study for the treatment of ET, in Q4 23.