# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**Washington, D.C. 20549**

## FORM 8-K

**CURRENT REPORT**
**Pursuant to Section 13 or 15(d)**
**of the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported): March 3, 2023**

# PRAXIS PRECISION MEDICINES, INC.
**(Exact name of registrant as specified in its charter)**

| Delaware | 001-39620 | 47-5195942 |
|---|---|---|
| (State or other jurisdiction of incorporation) | (Commission File Number) | (I.R.S. Employer Identification No.) |

**Praxis Precision Medicines, Inc.**
**99 High Street, 30th Floor**
**Boston, Massachusetts 02110**
**(Address of principal executive offices, including zip code)**

**(617) 300-8460**
**(Registrant's telephone number, including area code)**

**Not Applicable**
**(Former Name or Former Address, if Changed Since Last Report)**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

| Title of each class | Trade Symbol(s) | Name of each exchange on which registered |
|---|---|---|
| **Common Stock, $0.0001 par value per share** | **PRAX** | **The Nasdaq Global Select Market** |

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

**Item 7.01. Regulation FD Disclosure.**

On March 3, 2023, Praxis Precision Medicines, Inc. (the "Company") published a corporate presentation announcing topline results from its Essential1 study. The presentation is available in the "Investors + Media" portion of the Company's website at investors.praxismedicines.com and a copy is furnished as Exhibit 99.1 to this Current Report on Form 8-K. As part of the presentation, the Company referenced certain communications between the Company and the U.S. Food and Drug Administration (the "FDA") related to endpoints for essential tremor studies. A copy of the communications dated March 12, 2021 is furnished as Exhibit 99.2 to this Current Report on Form 8-K.

The information in this Item 7.01 of this Form 8-K and Exhibits 99.1 and 99.2 attached hereto shall not be deemed filed for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall any of it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, except as expressly set forth by specific reference in such a filing.

**Item 8.01. Other Events.**

On March 3, 2023, the Company announced topline results from the Essential1 study evaluating the efficacy, safety and tolerability of ulixacaltamide (PRAX-944) for the treatment of essential tremor.

In Essential1, ulixacaltamide treated participants demonstrated improvement relative to placebo participants in the primary endpoint, change from baseline to Day 56 in the modified Activities of Daily Living ("mADL") score, that did not reach statistical significance. Nominal statistically significant improvement was observed in the TETRAS-ADL score secondary endpoint. Additional secondary endpoints were supportive of the ulixacaltamide efficacy profile, including nominal statistically significant improvements in the Clinical Global Impression-Severity ("CGI-S") and Patient Global Impression-Change ("PGI-C") scores. The Company intends to engage with the FDA in an end of Phase 2 meeting and initiate a Phase 3 study for the treatment of essential tremor in the second half of 2023 based upon the observed efficacy and safety profile.

***Essential1 Efficacy Results***

Essential1 is a randomized, double-blind, placebo-controlled, dose-range-finding Phase 2b trial evaluating the efficacy, safety and tolerability of once-daily daytime treatment of 60 or 100 mg of ulixacaltamide compared to placebo after 56 days. The primary endpoint for the study was the change from baseline to day 56 in the mADL score. A total of 132 patients with essential tremor were randomized and treated in the study. While improvements relative to placebo on the primary endpoint and nominal statistical significance on certain of the secondary endpoints were observed, the study did not meet the primary endpoint.

The primary analysis population was the modified intention to treat ("mITT"). mITT analysis is defined as all patients enrolled under Version 4 of the clinical protocol (or enrolled in a prior version and eligible for Version 4), who were randomized to treatment, and received at least one dose of study drug. In the mITT analysis (n=116), ulixacaltamide (n=78) showed numerical difference versus placebo (n=38) at day 56 in the mADL score (-3.01 points for ulixacaltamide treated participants, -1.44 for placebo participants (LS mean difference 1.58; 95% CI: -3.60, 0.45; p=0.126)) and nominal statistical significance versus placebo at day 56 in the TETRAS-ADL secondary endpoint (-3.60 points for ulixacaltamide treated participants, -1.07 for placebo participants (LS mean difference 2.53; 95% CI: -4.75, -0.31; p=0.026)). Consistent effect was observed across both the 60 mg and 100 mg dosing regimens. Observed changes across 10 of the 12 ADL scored items in the mITT favored ulixacaltamide treated participants relative to placebo and there were no items that favored placebo.

Patients and clinicians reported higher overall impression of improvement with ulixacaltamide relative to placebo. In the PGI-C, 47% of ulixacaltamide treated patients reported improvement, while 30% of placebo participants reported improvement ($p<0.05$, rank analysis). In the CGI-S, investigators reported that 42% of ulixacaltamide treated patients improved and 26% of placebo participants improved ($p<0.05$, rank ANCOVA).

Following study unblinding, *post hoc*, the Company explored the impact of treatment in the mADL without the addition of the TETRAS performance scale items, as well as potential prognostic factors relevant to the population studied. The Company expects that these *post hoc* analyses will be relevant for its Phase 3 plans.

***Essential1 Safety and Tolerability Results***

Ulixacaltamide was well-tolerated. No dose response relationship was observed between participants assigned to the 60 mg or the 100 mg dose regimens in effect or safety. Adverse events ("AEs") were generally consistent with the safety profile of ulixacaltamide seen to date, with no new safety findings.

The most commonly reported treatment emergent adverse events in ≥5% of all participants treated with ulixacaltamide (n=91) were dizziness (13, 14.3%), constipation (9, 9.9%), headache (8, 8.8%), fatigue (8, 8.8%), anxiety (6, 6.6%), feeling abnormal (6, 6.6%) and paraesthesia (6, 6.6%). There were no drug related serious adverse events ("SAEs"). Three SAEs were observed in two subjects, all deemed unrelated to treatment (exacerbation of chronic obstructive pulmonary disease in one patient; esophageal obstruction and gastric adenocarcinoma in one patient). The rate of discontinuations due to AEs in the mITT was 12% in ulixacaltamide treated participants and 3% in placebo participants.

**Forward-Looking Statements**

This Current Report on Form 8-K contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws, including statements regarding the clinical development of ulixacaltamide. The forward-looking statements included in this Current Report on Form 8-K are subject to a number of risks, uncertainties and assumptions, including, without limitation, uncertainties inherent in clinical trials, the expected timing of submission for regulatory approval or review by governmental authorities and other risks as described in the Company's Annual Report on Form 10-K for the year ended December 31, 2022 and its other filings with the Securities and Exchange Commission. These statements are based only on facts currently known by the Company and speak only as of the date of this Current Report on Form 8-K. As a result, you are cautioned not to rely on these forward-looking statements and the Company undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future developments or otherwise.

**Item 9.01. Financial Statements and Exhibits.**

(d) Exhibits

| Exhibit No. | Description |
|---|---|
| 99.1 | Praxis Precision Medicines March 2023 Corporate Presentation |
| 99.2 | Communications between the U.S. Food and Drug Administration and Praxis Precision Medicines, Inc., dated March 12, 2021 |
| 104 | Cover page from this Current Report on Form 8-K, formatted in Inline XBRL |

**SIGNATURE**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PRAXIS PRECISION MEDICINES, INC.

Date: March 3, 2023

By: /s/ Marcio Souza
Marcio Souza
Chief Executive Officer


# ULIXACALTAMIDE (PRAX-944) ESSENTIAL1 ESSENTIAL TREMOR TOPLINE RESULTS

March 2023

# Forward Looking Statements

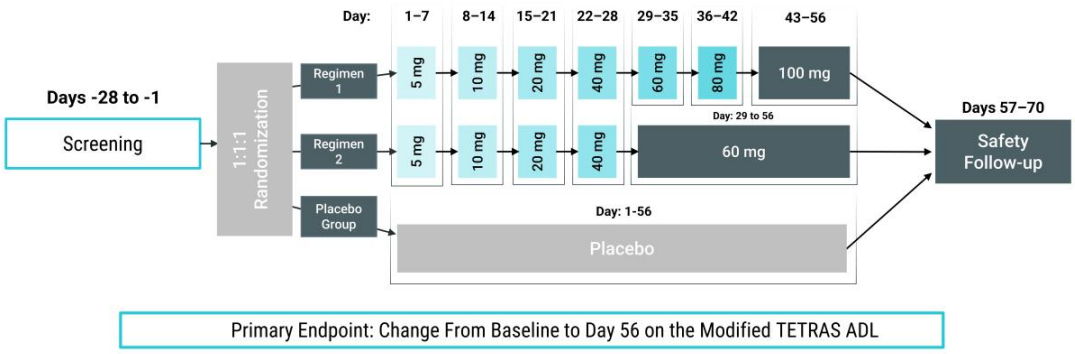
This presentation may contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial conditions, including but not limited to express or implied statements regarding the current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results and other future conditions. 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) 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 and our collaboration partners' abilities to manufacture our product candidates and scale production, and (viii) our ability to meet any specific milestones set forth herein. 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 filed for the year ended December 31, 2022 and other filings with the Securities and Exchange Commission.

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.

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

## ESSENTIAL1 DESIGN




Primary Endpoint: Change From Baseline to Day 56 on the Modified TETRAS ADL

ADL = activities of daily living.
ClinicalTrials.gov NCT05021991

# Topline Analysis: Essential1 Endpoints Measure Function and Quality of Life Improvements that Matter Most to Patients

## PRIMARY ENDPOINT

- Change from baseline to Day 56 on the TETRAS modified Activities of Daily Living (mADL)

## SECONDARY ENDPOINTS

- Incidence and severity of AEs, including discontinuation of study drug due to AEs
- Clinical Global Impression-Severity (CGI-S)
- Patient Global Impression-Change (PGI-C)
- TETRAS-ADL total score, TETRAS-UL score, TETRAS-CUL score, TETRAS-PS score

## POST-HOC ANALYSES

- Modified Activities of Daily Living score excluding the TETRAS-PS (mADL excluding PS)

ADL = activities of daily living; AE = adverse event; CUL = combined upper limb; PS = performance subscale; TETRAS = TRG Essential Tremor Rating Assessment Scale; UL = upper limb.

PRAXIS

## Essential1 Enrolled Adults with Moderate to Severe Essential Tremor

- CLINICAL DIAGNOSIS OF ET OF ≥3 YEARS
- MODERATE TO SEVERE FUNCTIONAL IMPAIRMENT DETERMINED USING TETRAS AND CGI-S
- COULD CONTINUE PROPRANOLOL AT A STABLE DOSE
- NO PRIOR SURGICAL INTERVENTION OR FOCUSED ULTRASOUND FOR TREATMENT OF ET

# Essential1 Patient Disposition


mITT ANALYSIS: Defined as all patients enrolled under Version 4 of Protocol (or enrolled in prior version and eligible for V4), who were randomized to treatment, and received 1 dose of study drug [n=116]
Excluded from mITT analysis are 16 patients enrolled under earlier protocol version and did not meet Version 4 inclusion/exclusion criteria and dose levels
Safety Analysis Population (N = 132)

PRAXIS

# Essential1 Demographics and Baseline Characteristics (mITT)

| | ULIXACALTAMIDE (n = 78) | PLACEBO (n = 38) |
|---|---|---|
| AGE, mean (min, max) | 70.4 (32, 86) | 67.7 (29, 88) |
| GENDER (Male / Female, %) | 59% / 41 % | 58% / 42% |
| FAMILY HISTORY OF ET | 59 (76%) | 23 (61%) |
| PROPRANOLOL USE | 27 (35%) | 9 (24%) |
| mADL SCORE, mean (min, max) | 20.6 (12, 32) | 20.8 (12, 34) |
| ADL SCORE, mean (min, max) | 29.0 (20, 38) | 28.6 (19, 39) |
| mADL EXCLUDING PS , mean (min, max) | 16.4 (9, 25) | 16.4 (8, 25) |
| ET PATIENTS WITH INTENTION TREMOR (%) | 18 (23%) | 15 (40%) |

# Ulixacaltamide was Generally Well-tolerated

| | ULIXACALTAMIDE (n=91) | PLACEBO (n=41) |
|---|---|---|
| *ANY TEAE* | *70 (76.9%)* | *21 (51.2%)* |
| **TEAEs > 5%** | | |
| DIZZINESS | 13 (14.3%) | 2 (4.9%) |
| CONSTIPATION | 9 (9.9%) | 0 |
| HEADACHE | 8 (8.8%) | 1 (2.4%) |
| FATIGUE | 8 (8.8%) | 1 (2.4%) |
| ANXIETY | 6 (6.6%) | 0 |
| FEELING ABNORMAL | 6 (6.6%) | 0 |
| PARAESTHESIA | 6 (6.6%) | 0 |

*3 SAEs in 2 subjects, all deemed unrelated to treatment (exacerbation of COPD in 1 patient; esophageal obstruction & gastric adenocarcinoma in 1 patient)

No clear dose response relationship for TEAEs

AEs were generally mild to moderate

No drug related SAEs*

PRAXIS

# Discontinuations – mITT Population

| | ULIXACALTAMIDE (n=78) | PLACEBO (n=38) |
|---|---|---|
| DISCONTINUATION | 13 (17%) | 4 (11%) |
| DISCONTINUATION DUE TO AEs | 9 (12%)<br>(1) Hallucination<br>(1) Restless Legs<br>(1) Anxiety<br>(2) Dizziness<br>(1) Feeling Abnormal<br>(1) Confusion<br>(1) Constipation<br>(1) Mental Impairment | 1 (3%)<br>(1) Adenocarcinoma, gastric |
| DAYS TO AE (MIN, MAX) | (3, 39) | (28, 28) |

# PRIMARY POPULATION: EFFICACY MEASURES

# Essential1 Efficacy Measures

## PRIMARY ENDPOINT

- Change from baseline to Day 56 on the TETRAS modified Activities of Daily Living (mADL)

## SECONDARY ENDPOINTS

- Clinical Global Impression-Severity (CGI-S)
- Patient Global Impression-Change (PGI-C)
- TETRAS-ADL total score, TETRAS-UL score, TETRAS-CUL score, TETRAS-PS score

ADL = activities of daily living; AE = adverse event; CUL = combined upper limb; PS = performance subscale; TETRAS = TRG Essential Tremor Rating Assessment Scale; UL = upper limb.

# Modified ADLs: A Modified Measure of TETRAS Activities of Daily Living (ADLs)

**TETRAS ADL measures observed:**

1. Speaking
2. Feeding with a spoon
3. Drinking from a glass
4. Hygiene
5. Dressing
6. Pouring
7. Carrying food trays, plates or similar items
8. Using keys
9. Writing
10. Working
11. Overall disability with most affected task
12. Social Impact

**Each measure is individually scored from 0-4:**

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

**TOTAL SCORE OF UP TO 48**

**Modified ADL measures observed:**

1. Speaking
2. Feeding with a spoon
3. Drinking from a glass
4. Hygiene
5. Dressing
6. Pouring
7. Carrying food trays, plates or similar items
8. Using keys
9. Writing
10. Working
11. Overall disability with most affected task
~~12. Social Impact~~
PS6. Spirals (Left, Right)
PS7. Handwriting

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

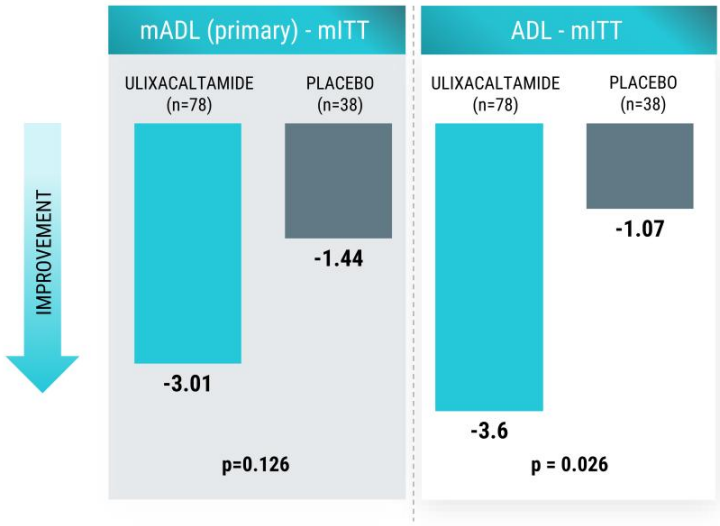
0 = Slightly abnormal. Tremor is present but does not interfere with __.
1 = Mildly abnormal. Spills a little.
2 = Moderately abnormal. Spills a lot or changes strategy to complete task.
3 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

**TOTAL SCORE OF UP TO 42**

PS = performance subscale

PRAXIS

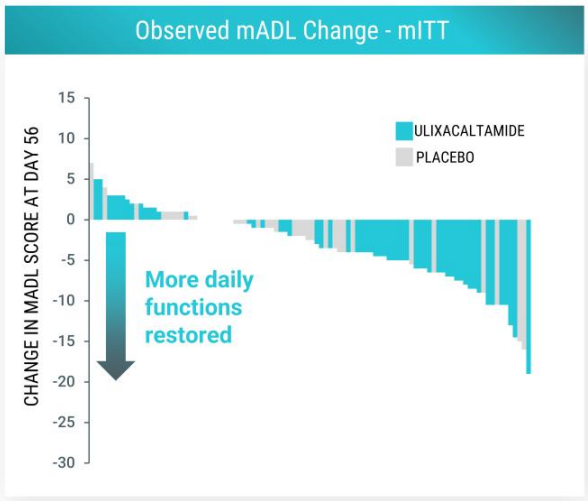
# mADL and ADL Improvement Over Placebo at Day 56

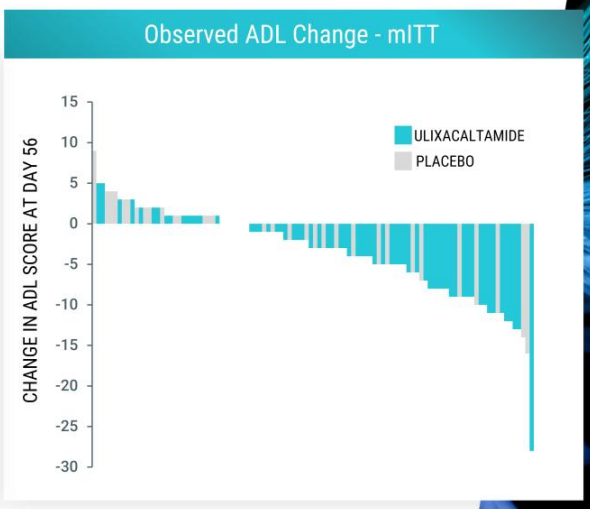



No dose related difference in efficacy between 60 mg and 100 mg groups

MMRM, Adjusted by baseline value, propranolol use and familial history of ET, all p values are nominal

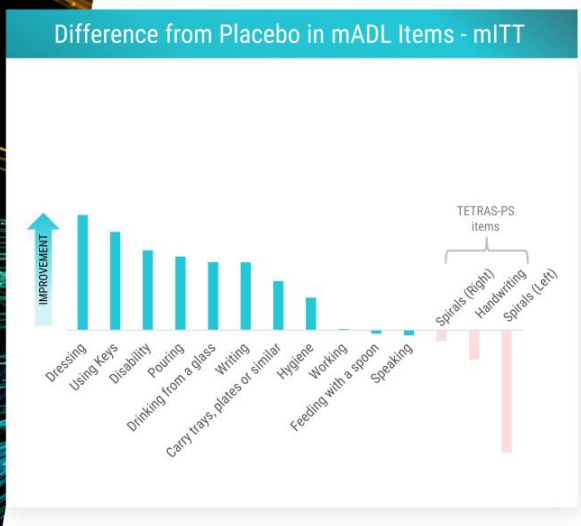
## More Patients Taking Ulixacaltamide Showed Improvements in ADL Scores Compared to Patients on Placebo

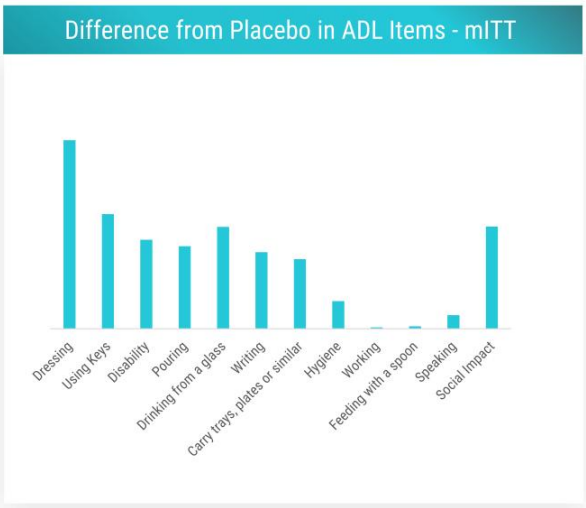


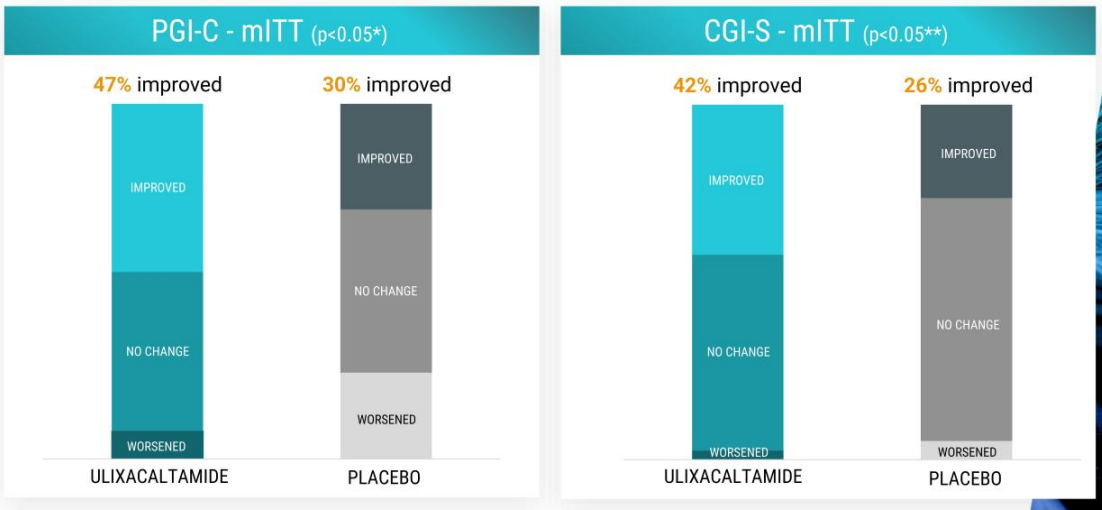

PRAXIS

# Ulixacaltamide Demonstrated Consistent Effect Relative to Placebo Across ADL Scored Items



# Patients and Investigators Reported Higher Overall Improvement in Status with Ulixacaltamide vs Placebo




CGI-S= clinical global impression improvement scale; PGI-C = patient global impression of change , all p-values are nominal
*RANK ANALYSIS
**RANK ANCOVA

PRAXIS

# POST-HOC ANALYSIS

# mADL Excluding PS - Definition and FDA Feedback

## TETRAS-ADL ITEMS FEEDBACK*

"In contrast, the Activities of Daily Living (TETRAS-ADL) subscale allows for assessment of meaningful change in patients' ability to function on activities of daily living (ADL) and has the potential to be an acceptable clinical endpoint. Therefore, we recommend that you include items 1-11 in the TETRAS-ADL subscale in your final endpoint. However, we recommend excluding Item 12 (Social Impact) of the TETRAS-ADL because the responses can be affected by factors unrelated to tremor."

## SCORING FEEDBACK*

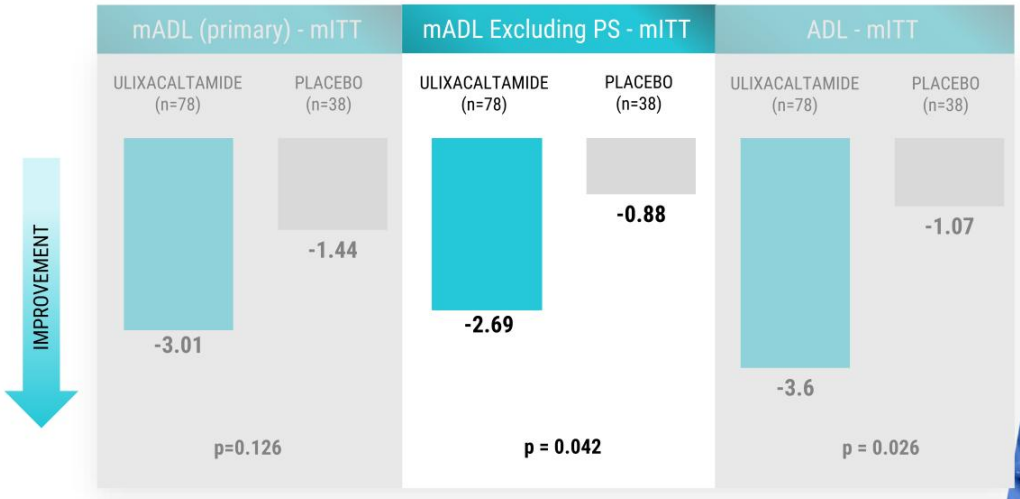
"The current response option 1 describes slight abnormalities that do not interfere with function; therefore, the change in score from 0 to 1 does not represent a meaningful change in function. The range of responses for Item 1 (Speaking) would be rescored as below (in red), and the other items would be rescored in a similar fashion.

0 0 = Normal.
0 1 = Slight voice tremulousness, only when "nervous".
1 2 = Mild voice tremor. All words easily understood.
2 3 = Moderate voice tremor. Some words difficult to understand.
3 4 = Severe voice tremor. Most words difficult to understand.

We note that you may collect scores for the TETRAS using standard scoring methods during the study and rescore as we have recommended for the purpose of the final analysis."

*Excerpts from Praxis communications with the FDA in relation to endpoints for ET studies. For full text, see item 7.01 of the Form 8-k filed with the Securities and Exchange Commission on March 3, 2023.

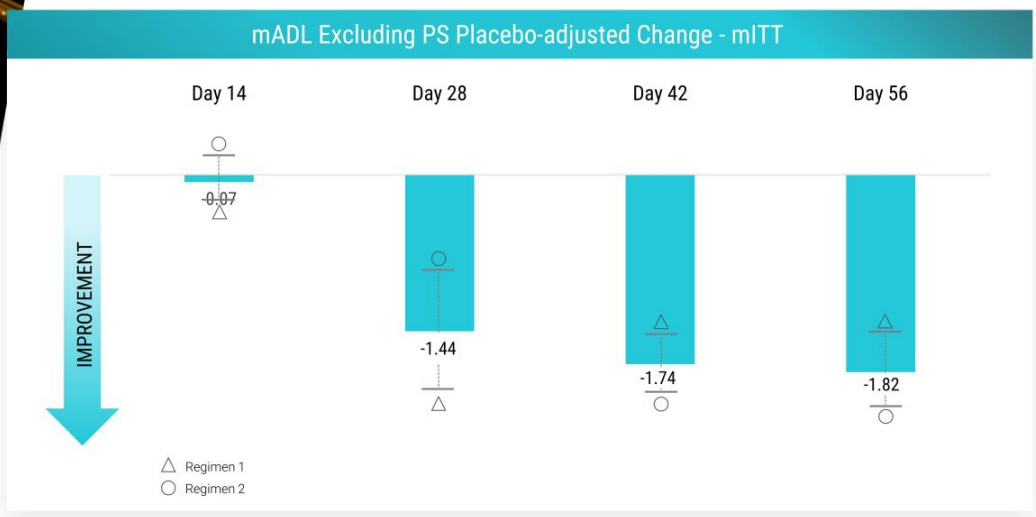
# Ulixacaltamide Demonstrated Improvement Over Placebo in the mADL Excluding PS at Day 56




MMRM, Adjusted by baseline value, propranolol use and familial history of ET, all p values are nominal

PRAXIS

# Consistent Effect Observed Across Both Dosing Regimens




MMRM, Adjusted by baseline value, propranolol use and familial history of ET

# PROGNOSTIC FACTORS EXPLORATION

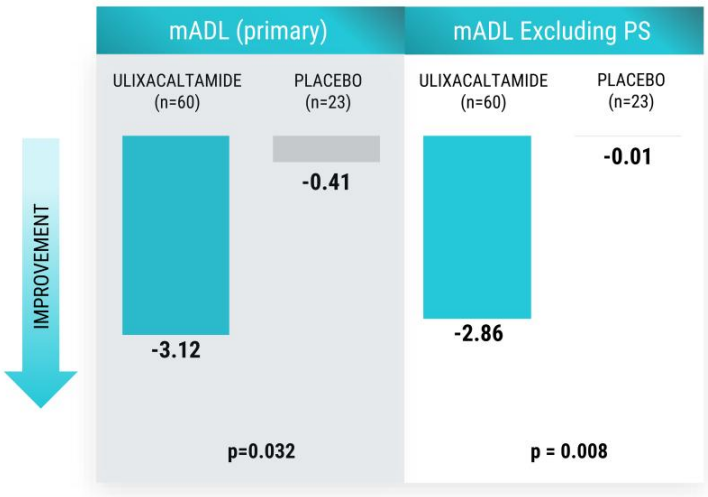
# Intention Tremor

Intention tremor is a type of tremor characterized by rhythmic and high amplitude oscillations during directed and purposeful motor movements, which worsen as the target is approached. It is often associated with dysfunction of the cerebellum, a brain structure responsible for motor coordination, posture, and balance. This tremor can affect the precision of coordinated movements of speech muscles and limbs. The underlying cause of intention tremor is thought to be impaired feedback mechanisms between the cerebellum, cortex, and brainstem, which leads to kinetic errors, particularly in fine motor skill tasks. Intention tremor is therefore a key clinical sign of cerebellar dysfunction and can have significant impact on the patient's ability to perform activities of daily living.


1. Treasure Island (FL): StatPearls Publishing; 2022 Jan
2. Louis ED. Tremor. Continuum (Minneap Minn). 2019 Aug;25(4):959-975.
3. Lenka A, Louis ED. Revisiting the Clinical Phenomenology of "Cerebellar Tremor": Beyond the Intention Tremor. Cerebellum. 2019 Jun;18(3):565-574.
4. Bötzel K, Tronnier V, Gasser T. The differential diagnosis and treatment of tremor. Dtsch Arztebl Int. 2014 Mar 28;111(13):225-35; quiz 236.
5. Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. Brain. 2000 Aug;123 ( Pt 8):1568-80.

# mADL and mADL Excluding PS Improvement Over Placebo at Day 56

*mITT Excluding ET Patients with Intention Tremor*



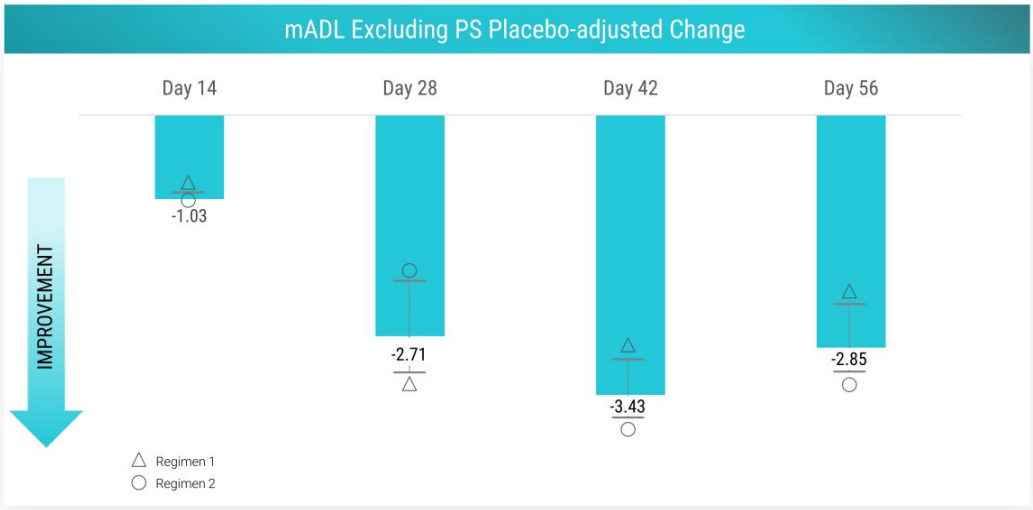

We intend to control for the presence of ET patients with intention tremor in future trials

MMRM, Adjusted by baseline value, propranolol use and familial history of ET, all p values are nominal

PRAXIS

# Consistent Effect Observed Across Both Dosing Regimens

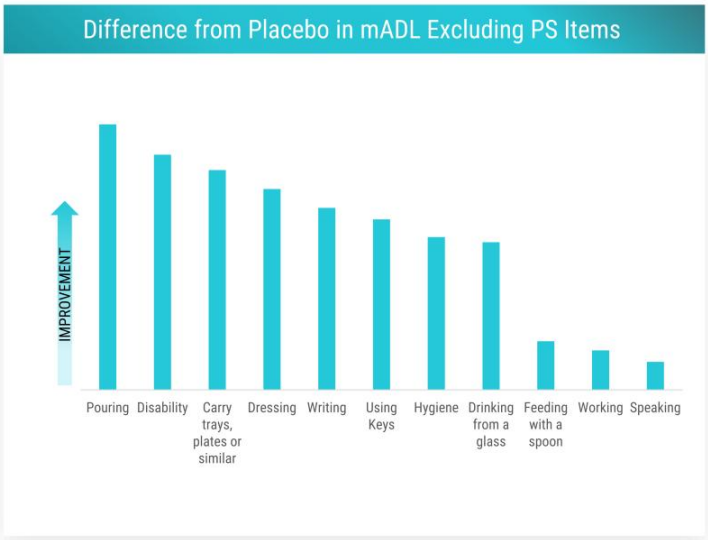
*mITT Excluding ET Patients with Intention Tremor*




MMRM, Adjusted by baseline value, propranolol use and familial history of ET

# *Post-hoc* Analysis of Observed mADL Scored Items

*mITT Excluding ET Patients with Intention Tremor*




PRAXIS

# Breaking Ground with Essential1 - Path Forward Towards Registration

## ESSENTIAL1 ENABLES PROGRESS

- Clinically meaningful effect observed in functional outcomes despite not achieving statistical significance in planned analysis
- Therapeutic drug levels achieved, suggesting individualized exposure response
- Well tolerated safety profile, no new safety signals identified
- TETRAS performance subscale not reliable due to variability
- Opportunity to further control for prognostic factors in subsequent clinical trials, including ET patients with intention tremor

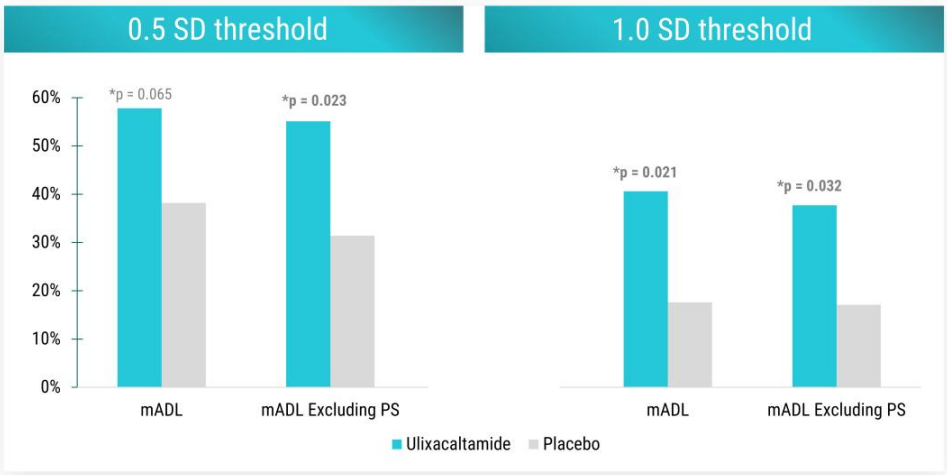
## NEXT STEPS

- Prepare and conduct an End of Phase 2 meeting with the FDA within ~100 days

- Preliminary elements of Phase 3 program planned to start in 2H23:
  - Parallel design with 60 mg and placebo treatment arms
  - Primary endpoint of mADL excluding PS
  - 6-week treatment duration

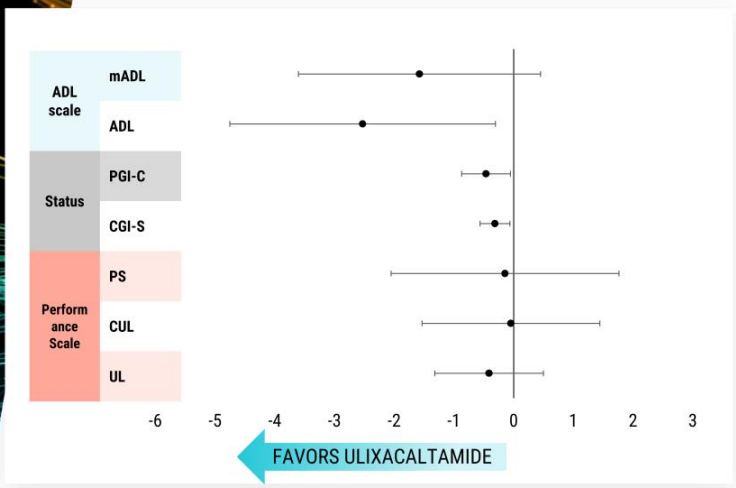

PRAXIS

# *Post-hoc* Responder Analysis Using MCID Distribution Method mITT Population




*Chi-sq comparisons in response rates between Ulixacaltamide and Placebo
One standard deviation equals 4.92 for mADL and 4.07 for mADL excluding PS
Mouelhi et al. Health and Quality of Life Outcomes (2020) 18:136

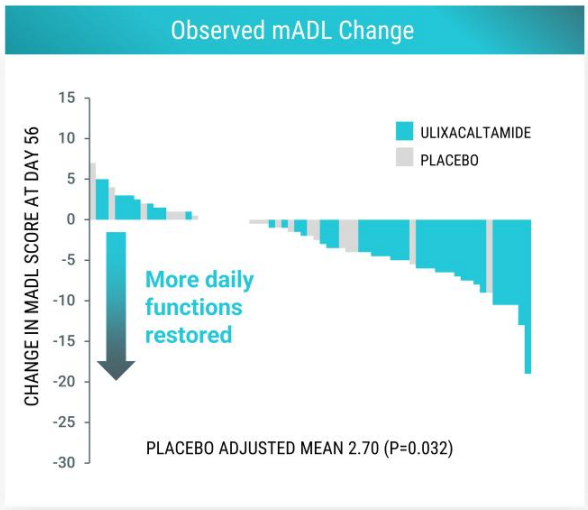
# Endpoints Analysis for mITT Population

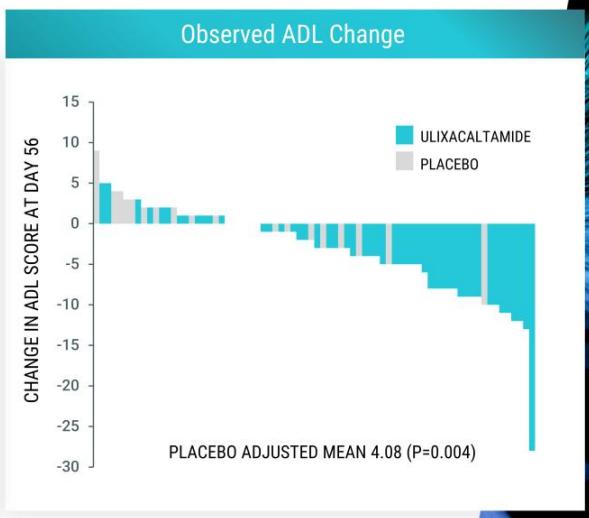



| | | LS MEANS DIFF | LOWER 95% CI | UPPER 95% CI |
|---|---|---|---|---|
| ADL scale | mADL | -1.576 | -3.604 | 0.451 |
| | ADL | -2.529 | -4.753 | -0.305 |
| Status | PGI-C | -0.462 | -0.871 | -0.053 |
| | CGI-S | -0.313 | -0.562 | -0.063 |
| Performance Scale | PS | -0.144 | -2.053 | 1.765 |
| | CUL | -0.046 | -1.535 | 1.444 |
| | UL | -0.412 | -1.321 | 0.497 |

mADL = modified ADLs; ADL = Activities of Daily Living; PS = Performance Subscale; CUL = Combined Upper Limb; UL = Upper Limb, PGI-C = Patient Global Impression – Change; CGI-S = Clinical Global Impression – Severity, MMRM

# *Post-hoc* Analysis Excluding ET Patients with Intention Tremor at Baseline



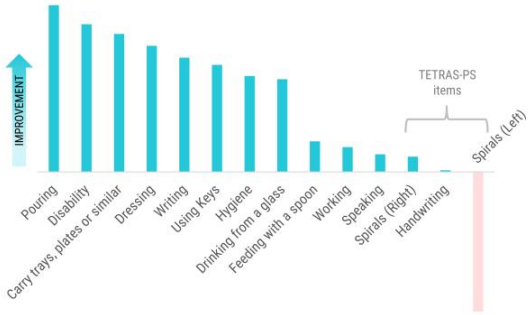




MMRM; all p values are nominal
Presence of intention tremor was assessed by investigator during screening

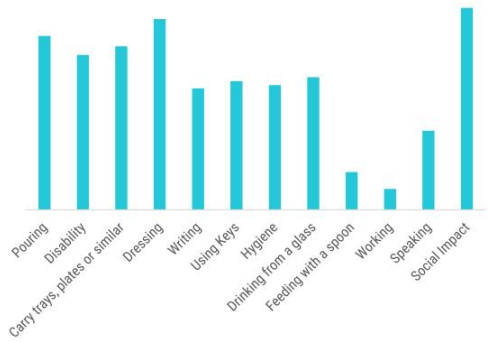
PRAXIS

# *Post-hoc* Analysis Excluding ET Patients with Intention Tremor at Baseline

## Difference from Placebo in mADL Items - mITT




## Difference from Placebo in ADL Items - mITT



b. *Does the Agency agree that the CUL score is an appropriate primary outcome measure?*

**FDA Response to Question 4b:**

The 2019 FDA Guidance for Industry – Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products[2], describes clinical endpoints accepted by the Agency to support approval as those that reflect patient benefit, i.e., how patients' function, feel (e.g., mood in the treatment of depression), or survive. There are components of The Essential Tremor Rating Assessment Scale (TETRAS) that do not adequately measure a clinically meaningful benefit for patients with ET; therefore, modification will need to be made to the TETRAS for it to be acceptable as a primary efficacy endpoint.

Specifically, many items of the Performance subscale of TETRAS do not provide a clinically meaningful measure of a patient's function and should not be included in the final endpoint. We understand that instruments based on the neurological examination developed to follow patients in clinical settings may include sensitive assessments of tremor. However, change measured on these selected components of the neurological exam (e.g., most of the TETRAS Performance subscale) cannot be directly interpreted as representing benefit in patients' ability to function in daily life.

As proposed, the TETRAS CUL (combined upper limb score: upper limb, spiral drawing, handwriting, dot approximation task) contains items of varying utility as efficacy

[2] https://www.fda.gov/media/133660/download





measurement. We note that Handwriting (Item 7 of the Performance Subscale) is a clinically meaningful task used in daily life and would be acceptable to include in the final endpoint. Although assessment of the ability to draw a spiral (Item 6, Archimedes spiral) is not a clinically meaningful function, it is less impacted by differences in written language and could be used with, or instead of, Handwriting as a repeatable assessment of patients' ability to write. However, Item 8 (Dot Approximation Task), which you have proposed to include in the assessment, does not evaluate an activity that measures function and should not be included in the primary efficacy endpoint.

Item 4 (upper limb tremor) of the TETRAS Performance subscale, is an exam-based measurement of tremor amplitude, where a change in score cannot be directly interpreted as being meaningful to patients. In addition, the response options rely on the visual estimate of change in tremor amplitude of less than a centimeter. The ability to accurately measure changes in tremor amplitude of a fraction of a centimeter on a component of the neurological exam is difficult and raises doubts about the accuracy of the estimate and the meaningfulness of a change in score.

In contrast, the Activities of Daily Living (TETRAS-ADL) subscale allows for assessment of meaningful change in patients' ability to function on activities of daily living (ADL) and has the potential to be an acceptable clinical endpoint. Therefore, we recommend that you include items 1-11 in the TETRAS-ADL subscale in your final endpoint. However, we recommend excluding Item 12 (Social Impact) of the TETRAS-ADL because the responses can be affected by factors unrelated to tremor.

In summary, we recommend that the final TETRAS endpoint be composed of items 1-11 of the TETRAS-ADL subscale, as well as Handwriting (Item 7) and Archimedes spiral (Item 6) from the Performance subscale.

Additionally, we recommend that the response options 0 and 1 for items 1-11 in the TETRAS- ADL subscale, as well as Handwriting and Archimedes spirals, be collapsed into a single response of "0 = Normal." The current response option 1 describes slight abnormalities that do not interfere with function; therefore, the change in score from 0 to 1 does not represent a meaningful change in function. The range of responses for Item 1 (Speaking) would be rescored as below (in red), and the other items would be rescored in a similar fashion.

0 0 = Normal.
0 1 = Slight voice tremulousness, only when "nervous".
1 2 = Mild voice tremor. All words easily understood.
2 3 = Moderate voice tremor. Some words difficult to understand.
3 4 = Severe voice tremor. Most words difficult to understand.

We note that you may collect scores for the TETRAS using standard scoring methods during the study and rescore as we have recommended for the purpose of the final analysis.