STATISTICAL ANALYSIS PLAN

Protocol Number: PRAX-944-221

Protocol Title: A Phase 2 Clinical Trial Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of PRAX-944 in Adults with Essential Tremor

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TABLE OF CONTENTS

APPROVALS 5
DEFINITIONS AND ABBREVIATIONS 6
1 OVERVIEW 8
2 STUDY DETAILS 9
2.1 Study Objectives 9
2.2 Study Design 11
2.3 Determination of Sample Size 13
3 ANALYSIS SETS 14
3.1 Enrolled Analysis Set 14
3.2 Safety Analysis Set 14
3.3 Randomized Withdrawal Safety Analysis Set 14
3.4 Full Analysis Set 14
3.5 Randomized Withdrawal Analysis Set 14
3.6 Pharmacokinetic Analysis Set 15
4 DEFINITION OF STUDY VARIABLES 16
4.1 Participant Disposition 16
4.2 Protocol Deviations 17
4.3 Demographic and Baseline Characteristics 17
4.3.1 Age 17
4.3.2 Sex 17
4.3.3 Ethnicity 18
4.3.4 Race 18
4.3.5 Dominant Hand 18
4.3.6 Height 18
4.3.7 Weight 18
4.3.8 Body mass index 18
4.4 Other Variables 18
4.5 Medical History 18
4.6 Essential Tremor Medical History 19
4.7 Prior and Concomitant Medications 19
4.8 Study Drug Exposure 20
4.9 Efficacy Variables 20
4.9.1 TETRAS 20

[redacted]
[redacted]
4.9.4 Quality of Life in Essential Tremor Questionnaire (QUEST) 23
[redacted]
[redacted]
4.10 Safety Variables 24
4.10.1 Adverse Events 24
4.10.2 Laboratory Test Results 27
4.10.3 Vital Sign Results 27
4.10.4 Electrocardiogram Results 28
4.10.5 Physical Examination 29
4.10.6 Columbia–Suicide Severity Rating Scale 29
4.11 Pharmacokinetic Variables 30
5 ANALYSIS METHODS 31
5.1 Participant Disposition 32
5.2 Protocol Deviations 32
5.3 Demographics and Other Baseline Characteristics 32
5.4 Medical History 32
5.5 Essential Tremor Medical History 32
5.6 Prior and Concomitant Medications 33
5.7 Efficacy Analyses 33
5.7.1 Primary efficacy analysis 33
5.7.2 Secondary Efficacy Analysis 34
5.7.3 Exploratory Efficacy Analysis 35
5.7.4 Subgroup Analyses 37
5.8 Safety Analyses 37
5.8.1 AEs 37
5.8.2 Laboratory Test Results 38
5.8.3 Vital Sign Results 38
5.8.4 ECG Results 38
5.8.5 C-SSRS 39
5.9 Pharmacokinetic Analyses 39
5.9.1 Plasma Concentrations 39
5.9.2 Plasma PK Parameters 39
6 INTERIM ANALYSES 40

7 CHANGES TO PLANNED ANALYSES 41
7.1 Changes to Analysis as Described in Protocol 41
7.2 Changes to Approved Version of the SAP 41
8 REFERENCES 42

APPROVALS

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DEFINITIONS AND ABBREVIATIONS

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}tau}$	area under the concentration vs time curve from the time of dosing through the dosing interval
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
[redacted]	
CI	confidence interval
CL/F	apparent systemic clearance following oral administration
C_{max}	maximum observed concentration
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
ET	essential tremor
FSH	follicle-stimulating hormone
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
ICH	International Council for Harmonisation
KDIGO	Kidney Disease Improving Global Outcomes
[redacted]	

MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
[redacted]	[redacted]
PK	pharmacokinetic
PS	performance subscale
PT	preferred term
QAM	every morning
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SoA	Schedule of Activities
SOC	system organ class
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
T_{max}	time to maximum observed concentration
ULN	upper limit of normal
Vd/F	apparent volume of distribution after non-intravenous administration
WBC	white blood cell

1 OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Protocol PRAX-944-221 (A Phase 2 Clinical Trial Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of PRAX-944 in Adults with Essential Tremor), Final Version 6.0 dated 11 August 2021.

The statistical analyses and summaries described in this SAP will follow the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for Statistical Principles for Clinical Trials (ICH E9 Expert Working Group, 1999) and will form the basis of the results sections of the clinical study report (CSR) in accordance with the ICH guideline for Structure and Content of Clinical Study Reports (ICH Harmonised Tripartite Guideline E3, 1995). This SAP will be finalized and fully executed before database lock and unblinding of treatment codes. Any changes to the analyses that are not included in this SAP will be documented in the CSR.

2 STUDY DETAILS

2.1 Study Objectives

A list of the specific protocol objectives for each study part along with their respective endpoints are listed in the tables below:

Part A

Objective	Endpoint
Primary	
To evaluate the efficacy of PRAX-944 on upper limb tremor in participants with ET	• Change from Baseline to Day 7 and Day 14 in The Essential Tremor Rating Assessment Scale (TETRAS) upper limb score (bilateral sum of items 4a, 4b, and 4c)
Secondary	
To evaluate the efficacy of PRAX-944 on other measures of tremor severity in participants with ET	• Change from Baseline to Day 7 and Day 14 in: • TETRAS performance subscale total score • Accelerometer-based upper limb score (bilateral sum of items 4a, 4b, and 4c) • TETRAS performance subscale individual item scores
To evaluate the safety and tolerability of PRAX-944 in participants with ET	• Incidence and severity of adverse events (AEs) • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in electrocardiogram (ECG) parameters • Incidence of Columbia-Suicide Severity Rating Scale (C-SSRS) measured suicidal ideation or behavior
Exploratory	
[redacted]	

[redacted]

Part B

Objective	Endpoint
Primary	
To evaluate the safety and tolerability of PRAX-944 in participants with ET	• Incidence and severity of AEs • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in ECG parameters • Incidence of C-SSRS measured suicidal ideation or behavior
Secondary	
To evaluate the efficacy of PRAX-944 on upper limb tremor in participants with ET	• Change from Baseline to Day 42 in TETRAS Upper Limb score (bilateral sum of items 4a, 4b, and 4c)
To evaluate the efficacy of PRAX-944 on other measures of tremor severity in participants with ET	• Change from Baseline to Day 7 and Day 21 in TETRAS Upper Limb score (bilateral sum of items 4a, 4b, and 4c) • Change from Baseline to Day 7, Day 21, and Day 42 in the following: • TETRAS Performance subscale total score • Accelerometer-based upper limb score (bilateral sum of items 4a, 4b, and 4c) • TETRAS Performance individual item scores
To evaluate the efficacy of PRAX-944 on measures of disease impact in participants with ET	• Change from Baseline to Day 7, Day 21, and Day 42 in the following: • TETRAS ADL subscale score • Quality of Life in Essential Tremor Questionnaire (QUEST) total and subscale scores
Exploratory	
[redacted]	

2.2 Study Design

This multi-center clinical trial will assess the efficacy, safety, tolerability, and PK of PRAX-944 in participants aged 18 years or older who have had signs and symptoms consistent with ET for at least 3 years with onset before age 65. The clinical trial will be conducted in 2 parts (Part A and Part B).

- Part A of the clinical trial is open-label and will assess the safety and tolerability of PRAX-944, as well as the overall magnitude and pattern of change in ET severity. Daily dose levels will be titrated from 20 mg to 40 mg.
- Part B of the clinical trial consists of both an open-label titration phase and a randomized, double-blind, placebo-controlled withdrawal phase. Part B will assess the safety and tolerability of PRAX-944, as well as the overall magnitude and pattern of change in ET severity and the duration of that effect. Daily dose levels will be titrated from 20 mg to up to 120 mg during the open-label phase. In the randomized, double-blind, placebo-controlled withdrawal phase, participants will either be maintained on their final open-label dose or switched to placebo.

Both parts will consist of 3 periods: Screening/Baseline, Intervention, and Safety Follow-up.

Screening/Baseline Period

The Screening period for Part A and Part B will be up to 28 days (Day -28 to Day -1). Fourteen additional days (ie, 42 days total) will be allowed in the Screening period for participants who are discontinuing primidone.

Prior to any clinical trial procedures, participants will provide their consent to participate in the clinical trial. Screening assessments are as noted in the study Schedule of Activities (SoA; see Appendix 1).

Part A:

Following confirmation of eligibility, including review by the Sponsor or designee, participants will complete Baseline assessments (Day 0). Day 0 (Baseline) activities may be combined with Day 1 activities, provided that Baseline activities are completed before dosing and that dosing occurs in the morning of Day 1. Baseline efficacy assessments should either be conducted on Day 0 or Day 1 pre-dose.

Part B:

For participants in Part B, [redacted] will also be completed with accelerometry at Screening and via telehealth on Day -2 of the Screening period. Additional assessments added to Part B screening include [redacted] Following confirmation of eligibility, including review by the Sponsor or designee, participants will complete Baseline assessments (Day 1). Some Baseline assessments (as indicated in SoA; see Appendix 1) may be completed on Day -1.

Intervention Period

Part A:

On Day 1, participants will receive a 20 mg dose of PRAX-944, administered in the morning. Participants will remain in a clinical setting under medical observation for approximately 6 hours. TETRAS performance assessments will be performed before dosing and 6 hours post-dose. After the first dose, participants will continue QAM dosing at home through Day 7. On Day 8, the dose will increase to 40 mg QAM from Day 8 to Day 14. Participants will return to the clinic on Day 14.

Safety and efficacy assessments will be obtained as described in the SoA (see Appendix 1). Participants who agree to optional additional PK sampling will remain overnight in the clinic on Day 1, Day 7, and Day 14.

Part B:

The open-label titration phase will begin on Day 1, participants will receive a 20 mg dose of PRAX-944 on an empty stomach. Participants will remain in a clinical setting under medical observation for approximately 6 hours. TETRAS Performance assessments will be performed before dosing and 6 hours (±2) post-dose.

For dosing on Day 2 through Day 41, participants will be instructed to dose QAM at home. On Day 4, participants will escalate to 40 mg QAM through Day 7; on Day 8, participants should escalate to 60 mg QAM through Day 14; on Day 15, participants should escalate to 80 mg QAM through Day 21; on Day 22, participants should escalate to 100 mg QAM through Day 28; and on Day 29, participants will escalate to 120 mg QAM through Day 42, when they will return to the clinic for safety assessments and efficacy testing. On Day 41, participants will complete a TETRAS Performance Upper Limb assessment via a telehealth visit. Safety and efficacy assessments will be obtained during the open-label titration phase as indicated in the SoA (see Appendix 1).

If at any point during the open-label titration phase a participant does not tolerate escalation and the Investigator returns the participant to a lower dose level, the participant will continue according to the schedule outlined above, but no further dose changes will be allowed.

On Day 42, participants will complete the final clinic visit of the open-label titration phase. After Day 42, participants will begin the double-blind randomized withdrawal phase and either continue receiving PRAX-944 at their current dose or switch to placebo, depending on their randomization. Randomization in a 1:1 fashion may be completed at any time on Day 37 through 42. On Day 43 through Day 56, participants will take their assigned dose QAM and return to clinic on Day 56 for safety assessments and efficacy testing.

Safety Follow-up Period

Part A:

The Safety Follow-up period will take place from Day 15 to Day 21. At the end of the Safety Follow-up period, participants will return to the clinic on Day 21 for the final clinical trial assessments.

[redacted]

2.3 Determination of Sample Size

Up to 12 participants are planned to be administered PRAX-944 in Part A. Approximately 12 participants are planned to be administered PRAX-944 in Part B. Up to 12 additional participants may be enrolled at the discretion of the Sponsor to ensure inclusion of a broad range of tremor severity.

The sample size of each part is a convenience sample. The sample size was not selected according to any statistical power calculation. Instead, the sample size was determined according to feasibility and is thought to provide sufficient efficacy and safety data to inform the development of future controlled studies with PRAX-944 in participants with ET. In the open-label phases of the trial (Part A and Part B, open-label titration), a sample size of at least 10 participants would provide an 80% probability of observing at least 1 AE with an underlying incidence of 15% or greater. In addition, 10 participants should also provide approximately 80% power to detect an effect size of 1.0 on the primary endpoint of change from baseline in TETRAS Upper Limb score.

3 ANALYSIS SETS

An analysis data set will be created for efficacy, safety, and PK assessment. In addition to raw data values, each analysis data set will include derived variables as specified in Section 4 (eg, baseline, total, and change from baseline values). All analysis data sets will also include key demographic information (including, but not limited to: study, center, subject identifier, age, gender, race, ethnic group, randomization number, analysis set eligibility flags, study treatment start and stop dates, reason for treatment discontinuation, randomized treatment [where applicable], and actual treatment received).

All data analyses will be performed using at least one of the below specified analysis sets. Participant eligibility for each analysis set will be finalized before database lock and unblinding of the data, where applicable.

3.1 Enrolled Analysis Set

The enrolled analysis set includes all participants who sign informed consent and are provided with an enrollment number. The enrolled analysis set will be used for all participant disposition analyses.

3.2 Safety Analysis Set

The safety analysis set includes all participants who received at least 1 dose of study drug. Participants will be classified according to actual treatment received. The safety analysis set will be used for all demographic, baseline characteristics, prior/concomitant medication, study drug exposure, and safety analyses.

3.3 Randomized Withdrawal Safety Analysis Set

The randomized withdrawal safety analysis set includes all participants who received at least 1 dose of blinded study drug in the randomized withdrawal phase of Part B. Participants will be classified according to actual treatment received. The randomized withdrawal safety analysis set will be used for all demographic, baseline characteristics, prior/concomitant medication, study drug exposure, and safety analyses for the randomized withdrawal phase of Part B.

3.4 Full Analysis Set

The full analysis set includes all participants who took at least 1 dose of study drug and have a valid baseline TETRAS assessment and at least 1 valid post-baseline TETRAS assessment. The full analysis set will be used for the analysis of all efficacy data, unless otherwise indicated.

3.5 Randomized Withdrawal Analysis Set

The randomized withdrawal analysis set is a subset of the full analysis set and includes all participants who were randomized into the double-blind, randomized withdrawal phase of Part B and have a valid Day 42 TETRAS assessment and at least 1 valid TETRAS assessment after Day 42. The randomized withdrawal analysis set will be used for the analysis of all efficacy data collected during the randomized withdrawal phase.

3.6 Pharmacokinetic Analysis Set

The pharmacokinetic (PK) analysis set includes all participants that received at least 1 dose of study drug and have sufficient PK concentration data for analysis. The PK Analysis set will be used for the descriptive statistical analysis of plasma concentrations and PK parameters.

4 DEFINITION OF STUDY VARIABLES

The following definitions will be used throughout the analysis plan for this study:

Study Day

Study day calculations (ex. study day of an event or a visit) will be defined as follows, assuming non-missing dates:

- Study Day = Date of event – Reference date + 1, when the date of interest occurs on or after the reference date;
- Study Day = Date of event – Reference date, when the date of interest occurs before the reference date;

If either date is missing, study day calculations will not be performed.

For this study, the reference date used will be the treatment start date. Based on the calculations above, there will be no study day zero.

Baseline and Change from Baseline

Unless otherwise specified, the baseline value is defined as the last non-missing value collected prior to receiving first dose of study drug. Values collected after the time of treatment start will be excluded from the calculation of baseline as applicable. Post-baseline values will be defined as those collected after the treatment start date (and time, as applicable).

Change from baseline will be defined as: assessment value – baseline value. Change from baseline values will only be derived for post-baseline assessments.

Randomization Baseline and Change from Randomization

The randomization baseline value, used as the reference value for double-blind randomized withdrawal phase efficacy endpoints, is defined as the Day 42 post-dose value. If the Day 42 post-dose value is unavailable, the randomization baseline value will be considered missing.

Change from randomization will be defined as: assessment value – randomization baseline value. Change from randomization values will only be derived for assessments conducted after the randomized treatment start date (and time, as applicable).

4.1 Participant Disposition

The participant number, informed consent date, and protocol version at time of consent (if applicable) will be recorded in the electronic case report form (eCRF).

In addition, study completion status, the date of study completion or early withdrawal, reason for early withdrawal, adverse event number (if applicable), and description of primary reason will be recorded in the eCRF. Study completion status will be recorded as “Yes” or “No”. The reason for early withdrawal will be recorded as “Adverse Event”, “Withdrawal of consent”, “Lost to follow-up”, “Safety reasons”, “Investigator’s decision”, “Non-compliance to protocol”, or “Other”.

The duration of time in study, in days, will be calculated as (Study Completion or Discontinuation Date) - (Informed Consent date) + 1.

The following durations within the clinical trial are expected as follows, per the protocol:

- Part A: ≤49 days (63 days if on primidone)
- Part B: ≤98 days (112 days if on primidone)

4.2 Protocol Deviations

The failure to meet any eligibility criteria and the specific criteria not met will be recorded in the eCRF.

All participant data will be reviewed for the occurrence of protocol deviations. The Sponsor project team will review all protocol deviations and their major/minor classifications prior to database lock. Deviation categories will include the following:

- Procedure / Assessment outside protocol window
- Procedure / Assessment not done
- Order of Procedure / Assessment
- Missed Visit
- Visit outside protocol window
- Inclusion / Exclusion
- Informed Consent
- Study Drug Administration
- Documentation
- Study Restrictions
- COVID-19: Visit missed
- COVID-19: Assessment not performed
- COVID-19: Other
- Other

4.3 Demographic and Baseline Characteristics

The following variables are captured and/or derived for this study.

4.3.1 Age

The age in years at informed consent will be recorded in the eCRF.

4.3.2 Sex

Sex will be recorded in the eCRF as “Male” or “Female”.

4.3.3 Ethnicity

Ethnicity will be recorded in the eCRF as “Hispanic or Latino”, “Not Hispanic or Latino”, “Not reported”, or “Unknown”.

4.3.4 Race

Race will be recorded in the eCRF as one or more of the following: “Black or African American”, “American Indian or Alaska Native”, “Asian”, “Native Hawaiian or Other Pacific Islander”, "White", “Other”, or “Not reported”. Multiple race categories can be selected.

4.3.5 Dominant Hand

Dominant hand will be recorded in the eCRF as “Right” or “Left”.

4.3.6 Height

Height in centimeters (cm) will be recorded in the eCRF.

4.3.7 Weight

Weight in kilograms (kg) will be recorded in the eCRF.

4.3.8 Body mass index

Body mass index (BMI; kg/m^2) will be derived in the eCRF, provided that weight and height are available.

4.4 Other Variables

Drug screen and alcohol results will be collected at Screening. The assessment date, time, and result will be recorded in the eCRF. The result will be recorded as "Positive" or "Negative". For positive drug screen results, those drugs of abuse testing positive will also be captured in the eCRF. Categories for positive drug tests include the following: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Methadone, Opiates, Phencyclidine, and Other.

4.5 Medical History

For those participants reporting medical history, the medical condition, onset date, ongoing indicator (Yes/No), end date (if applicable), and treatment indicator (Yes/No) will be recorded in the eCRF. Each medical history condition will be coded using Medical Dictionary for Regulatory Affairs (MedDRA) version 22.0.

4.6 Essential Tremor Medical History

Details on essential tremor medical history will be recorded in the eCRF including year of tremor onset, ET diagnosis, prior and current medications for ET (Yes/No), family history (Yes/No), ET worsening over the past 3 years (Yes/No), and effect of alcohol on ET symptoms: if symptoms decrease (Yes/No), by how much (Minimal decrease/Moderate decrease/Substantial decrease), and how many standard alcohol containing cause symptoms to decrease (<1, 1, 2, 3, >3).

4.7 Prior and Concomitant Medications

For each prior and concomitant medication, the medication name, indication, dose, frequency, route, start date, ongoing indicator, stop date (for those medications not ongoing) will be recorded in the eCRF. Each medication will be coded using the World Health Organization Drug Dictionary (WHODrug) version March 2019.

Each medication will be classified according to the study period in which its use occurred (ie, Prior, Concomitant). Prior medications are those that started and ended before the initiation of study drug. Concomitant medications are (i) those that started before initiation of study drug and continued after initiation of study drug or (ii) those that started after initiation of study drug. Any medications starting on the same day as the initiation of study drug will be considered concomitant.

For Part B, medications will be further classified as concomitant for the double-blind randomized withdrawal phase following initiation of randomized study drug. Concomitant medications from the open-label titration phase will not include events occurring within the randomized withdrawal phase. Concomitant medications taken within the safety follow-up period for a participant will be classified as occurring during his/her last phase of participation (ie, if a participant does not enter the double-blind randomized withdrawal phase any post-treatment medications will be reported as part of the open-label titration).

If the start date (or stop date) of a medication is completely unknown (ie, the day, month, and year are all missing) or only the study day is known, then the start date (or stop date) will not be imputed. Unless the stop date is before the start date of study drug, then the medication will be considered concomitant.

For a partial start date of medication, the following conventions will be used for imputing the start date:

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the first day of the month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the stop date of medication.

For a partial stop date of medication, the following conventions will be used for imputing the stop date:

- If the year is present and the month and day are missing, then the month and day will be set to December 31.

- If the year and day are present and the month is missing, then the month will be set to December.
- If the year and month are present and the day is missing, then the day will be set to the last day of the month.

4.8 Study Drug Exposure

For study drug exposure, date of administration, time of administration, and dose recorded in the eCRF. The overall duration of exposure to study drug (in days) will be calculated for Study Part, by dose level and overall, as follows:

- Duration of Exposure to study drug (days) = Date of Last Dose – Date of First Dose + 1

Overall percent compliance will be calculated as the total number of days drug was received divided by the total number days drug was expected to be received during the subject's participation in the study. In addition, overall compliance will also be categorized as:

- Compliance < 80%
- 80% ≤ Compliance ≤ 120%
- Compliance >120%

In Part B, separate compliance estimates will be calculated for the open-label titration phase and the double-blind, randomized withdrawal phase.

4.9 Efficacy Variables

4.9.1 TETRAS

The TETRAS is a scale used to quantify essential tremor severity and its impact on activities of daily living (ADLs). The full scale consists of 2 components, the Performance and ADL subscales which are highly correlated. Upper extremity action tremor is the main focus of both parts of this scale since it is the main source of disability. However, action tremor is also assessed in the head, face, voice, and lower limbs.

4.9.1.1 Performance subscale

The performance subscale consists of 9 items covering different body regions. Each item is rated on a scale of 0 to 4, including 0.5 increments if a rating cannot be reconciled between two whole numbers, with higher scores indicating higher tremor amplitude. Item 4 of the performance subscale is the upper limb item. It is comprised of 6 sub-items (4a, 4b, and 4c assessed for both the right and left upper limbs). The upper limb total score is the sum of these 6 items and ranges from 0 to 24. The timepoint, blinded TETRAS code, date and time of assessment, rater ID, an indicator of whether the assessment was performed (Yes/No), and the individual item scores will be recorded in the eCRF.

The full performance subscale score is calculated as the sum of item 1 (head), item 2 (face), item 3 (voice), each of the 6 sub-items for item 4 (upper limb), the maximum of the 4 sub-items for item 5 (lower limb), 2 sub-items (right and left side) for item 6 (Archimedes spirals), item 7 (handwriting), 2

sub-items (right and left side) for item 8 (dot approximation), and item 9 (standing) for a total score ranging from 0 to 64 from 16 sub-items.

The TETRAS performance subscale will be collected at the following timepoints:

Part A:

- Screening, Day 0 and Day 21: completed anytime
- Day 1: pre-dose and 6 (±2) hours post-dose
- Day 7 and Day 14: 6 (±2) hours post-dose

Part B:

- Screening and Day 70: completed anytime
- Day 1: pre-dose and 6 (±2) hours after a 20 mg qAM dose
- Day 7: 6 (±2) hours after a 40 mg qAM dose
- Day 21: 6 (±2) hours after an 80 mg (or highest tolerated dose) qAM dose
- Day 42: pre-dose and 6 (±2) hours after a 120 mg (or highest tolerated dose) qAM dose
- [redacted]

4.9.1.2 Upper limb item

The upper limb item will be assessed via clinician (ie, site rater), Kinesia ONE (accelerometer), and video rating by an independent rater. In Item 4 of the performance subscale, the clinician will assess 3 tasks performed on each side of the body: 4a) postural tremor with upper limbs held forward and horizontally ("outstretched" position), 4b) postural tremor with upper limbs extended laterally and horizontally, with the elbows flexed and hands positioned close to each other near the chin ("wing beating position"), and 4c) kinetic tremor during finger-nose (or chin)-finger movements. As each of the upper limb items is rated independently for the right and left side of the body, the upper limb item is comprised of 6 sub-items. Each sub-item is rated on a scale from 0 to 4 including 0.5 increments, with higher scores indicating higher tremor amplitude of the upper limb. The upper limb total score is the sum of these 6 sub-item scores and ranges from 0 to 24. The baseline TETRAS upper limb score will be categorized as <10 or ≥ 10.

4.9.1.3 Combined upper limb

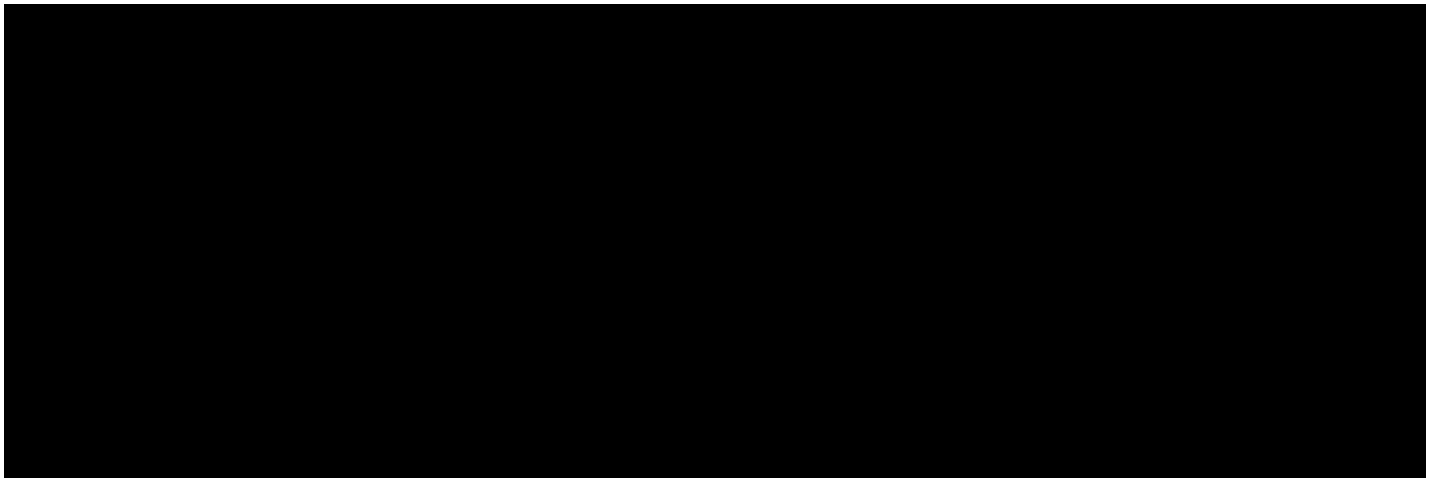
The combined upper limb score is the sum of the 6 sub-item scores of the upper limb item and the handwriting and spirals scores. The combined upper limb score ranges from 0 to 32.

4.9.1.4 Accelerometer

After the TETRAS Performance Subscale is performed by the clinician, the participant will then perform the TETRAS upper limb tasks while wearing a Kinesia ONE accelerometer. The accelerometer will record coordinates and accelerations in the 3D space over time. All 3 maneuvers in the upper limb assessments will be completed for both arms, first for the right arm and then for the left. Kinesia ONE assessments should be completed twice at each timepoint with the 2 assessments separated by at least 30

minutes. The timepoint, date and time of both assessments, and an indicator of whether the accelerometer assessment was performed (Yes/No) will be recorded in the eCRF.

Each upper limb sub-item is scored on a scale from 0 to 4 including to 0.1 increments and will be provided by the Kinesia ONE accelerometer vendor. The accelerometer upper limb total score, ranging from 0 to 24, is the sum of these 6 sub-items and ranges from 0 to 24. For each timepoint, the average score of the two Kinesia ONE assessments will be calculated to be used for analysis. If only one assessment is performed, the single score will be used for analysis.

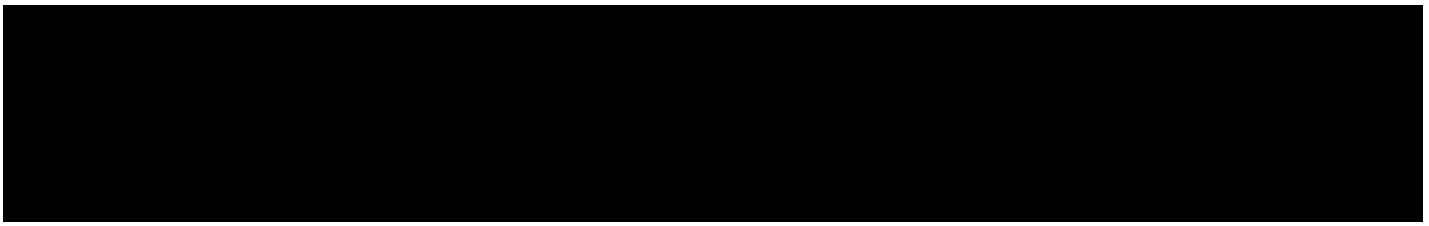


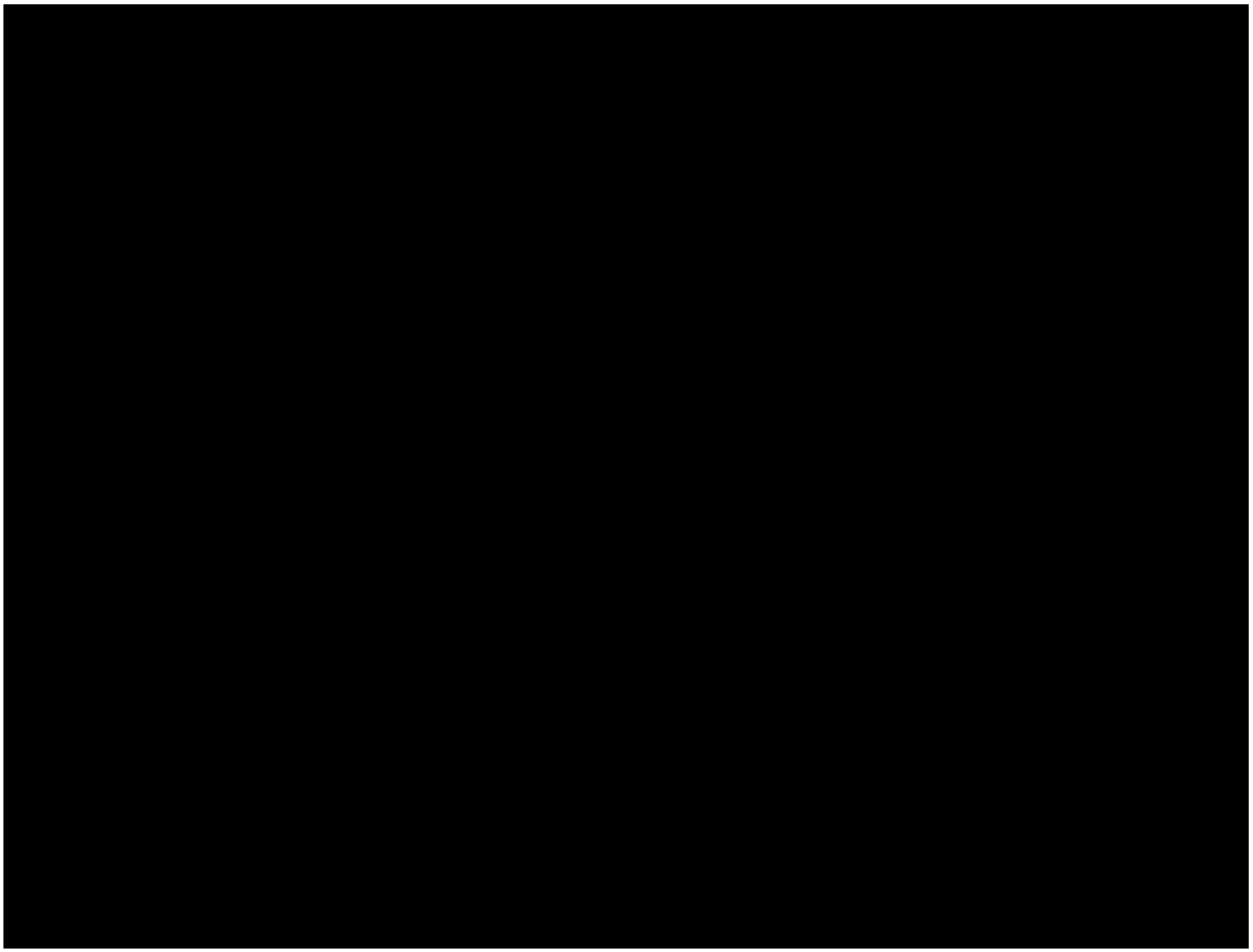
4.9.1.6 Teleheath Assessment

The TETRAS Performance Subscale upper limb item (item #4) will be conducted by the site rater using televideo technology while the participant is at home. The date and time of telehealth assessment, rater ID, an indicator of whether the assessment was performed (Yes/No), and the individual item scores will be recorded in the eCRF. The upper limb score will be calculated as the sum of all 6 sub-items.

4.9.1.7 Activities of Daily Living (ADL)

The TETRAS ADL subscale is a 12-item assessment of typical daily activities that are impacted by tremor that will be collected for Part B only. Activities are assessed in the following functional domains: speaking, feeding, drinking, personal hygiene, dressing, writing, and social activity. The impact to each function is rated on a 5-point Likert scale from 0 to 4. The ADL subscale score is calculated as the sum of all 12 items and ranges from 0 to 48 with higher scores reflecting higher impact. The date and time of the ADL subscale, rater ID, an indicator of whether the assessment was performed (Yes/No), and the individual item scores will be recorded in the eCRF. The subscale score will be derived directly in the eCRF.





4.9.4 Quality of Life in Essential Tremor Questionnaire (QUEST)

The QUEST is a patient-reported ET-specific quality of life scale that will be collected for Part B only. The scale contains 5 subscales that cover physical, psychosocial, communication, hobbies/leisure, and work/finance dimensions. The individual items are rated either on a 5-level Likert scale from 0 to 4 (Never, Rarely, Sometimes, Frequently, Always) or a 2-level scale from 0 (No) to 4 (Yes) relative to the respondent's current situation. Five items could also be rated as not applicable. The QUEST total and subscale scores are calculated as the sum of all applicable items divided by the number of applicable items times 100. The subscale scores will be derived directly in the eCRF.

Participants are also asked to rate their overall health status and quality of life on scale from 0 to 100 by 5 point increments, if tremor has interfered with their sexual satisfaction (Yes/No), if they have had side effects from tremor medication (Yes/No), if they are satisfied by tremor control achieved by tremor medication (Yes/No), and to describe their work status (Never Worked, Not working, retired because of tremor, Not working, retired NOT due to tremor, Working full time, Working part time). Additionally, the participant is asked to report how many hours in a typical day they experience tremor in any body part (0 to 24) and the severity of tremor in the head, voice, right arm/hand, left arm/hand, right leg/foot, and left leg/foot on a scale from 0 to 4 (None, Mild, Moderate, Marked, Severe).

An indicator of whether the QUEST was performed (Yes/No), the date and time of assessment, rater ID, and individual item scores will be recorded on the eCRF.

4.10 Safety Variables

4.10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial participant, temporally associated with the use of study drug, whether or not considered related to the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

AEs are collected from the time the informed consent form is signed until study participation is completed. For each AE, the following data will be recorded in the eCRF: verbatim text, start date, stop date (or ongoing), outcome, investigator's assessment of severity, relationship to study drug, relationship to study procedures, relationship to disease under study, action taken with study drug, administration of concomitant therapy, concomitant therapy type, assessment of seriousness, and criteria for seriousness. For any AEs leading to death, the date of death and assessment cause of seriousness. death will also be recorded in the eCRF. The verbatim text will be coded using MedDRA version 22.0.

- Action taken with study drug will be recorded as "None", "Study drug interrupted", "Study drug withdrawn", "Study drug dose changed" or "Not applicable";

- Outcome will be recorded as “Recovered”, “Recovered with sequelae”, “Not recovered”, “Fatal”, or “Unknown”;
- Relationship to study procedures and study drug will be recorded as “Not Related” or “Related”;
- Investigator’s assessment of severity will be recorded as “Mild”; “Moderate”; or “Severe”;
- Assessment of seriousness will be recorded as “Y” or “N”.

A flag for AEs of special interest (AESIs) will be defined to include any event of seizure, seizure-like phenomena, loss of consciousness, or altered state of consciousness as defined in Section 8.4.5 of the protocol. As a result of an FDA request documented in a study note to file, these additional events will also be included as AESIs: tardive dyskinesia, acute dystonic reactions, akathisia, and Parkinsonian symptoms (bradykinesia, tremor, cogwheel rigidity, mask-like facies). Search criteria for defining these AESIs according to MedDRA preferred terms are included in Appendix 2. In accordance with these search criteria, a flag will be created to indicate whether or not the event was an AESI (Y/N).

A flag for AEs leading to study drug withdrawal will be calculated as:

- IF the action taken with study drug is “Study drug withdrawn”, THEN set the AE leading to study drug withdrawal flag equal to “Y”.
- OTHERWISE, set the AE leading to study drug withdrawal flag equal to “N”.

Treatment emergent AEs (TEAEs) are defined as those AEs occurring or worsening after the first dose of study drug. If an AE start date is completely missing (ie, in which the day, month, and year are all unknown), then the AE start date will be set to the date of first dose of study drug. For a partial AE start date, the following conventions will be used for imputing the AE start date:

- When the year is present and the month and day are missing:
  - If the year of AE start = the year of first dose of study drug, then the month and day will be set to the month and day of first dose of study drug.
  - If the year of AE start < the year of first dose of study drug, then the month and day will be set to December 31st.
  - If the year of AE start > the year of first dose of study drug, then month and day will be set to January 1st.

- When the year and day are present and the month is missing:
  - If the year of AE start = the year of first dose of study drug, then the month will be set to the month of first dose of study drug.
  - If the year of AE start < the year of first dose of study drug, then the month will be set to December.
  - If the year of AE start > the year of first dose of study drug, then the month will be set to January.

- When the month and year are present and the day is missing:
  - If the year of AE start = the year of first dose of study drug and

- the month of AE start = the month of first dose of study drug, then the day will be set to the day of first dose of study drug.
- the month of AE start < the month of first dose of study drug, then the day will be set to the last day of the month.
- the month of AE start > the month of first dose of study drug, then the day will be set to the 1st day of the month.
- If the year of AE start < the year of first dose of study drug, then the day will be set to the last day of the month.
- If the year of AE start > the year of first dose of study drug, then the day will be set to the 1st day of the month.
- If the imputed AE start date is after the AE stop date, then the AE start date will be set to the AE stop date.

For Part B, AEs will be identified as TEAEs for the double-blind randomized withdrawal phase based on the first dose of randomized study drug. AEs reported during the open-label titration period will not include events occurring within the randomized withdrawal phase. Events occurring within the safety follow-up period for a participant will be classified as occurring during his/her last phase of participation (ie, if a participant does not enter the double-blind randomized withdrawal phase any post-treatment AEs will be reported as part of the open-label titration).

If an AE is imputed for Part B and is attributed to the open-label titration or double-blind randomized withdrawal phase, it should be checked for plausibility. If an imputed AE onset date could potentially have started during a subsequent phase (eg, if the onset date had been imputed as the 1st of a particular month falling into the open-label titration phase, but it plausibly could have started later in the month during the double-blind randomized withdrawal phase), the AE should be identified as TEAE for any plausible phases.

For each AE, a treatment emergent flag will be calculated using the recorded AE start date (or imputed start date, where applicable). Additional treatment emergent flags will be created for each dose level.

Adverse events occurring during PRAX-944 titration will be assigned to a dose level based on the onset date/time of the adverse event relative to the first dose date/time of study drug administration at each dose level. Specifically, if an AE occurs after the first dose of study drug at a participant's actual dose level and prior to the first dose at the next dose level, the AE will be assigned within a participant's actual dose level in the adverse event summary. If the date was imputed and could plausibly occurred during a subsequent dose level, the AE should be identified as TEAE for subsequent and plausible dose levels.

If the time is missing (either for the adverse event or study drug administration), then the AE date (and relative study day) will be used to determine in which dose level the AE should be assigned, assuming that the AE occurred after the dose taken on the specified day. An adverse event will only be reported within the dose level in which the AE started (eg, an adverse event that starts within the 40 mg dose level and continues into the 80 mg dose level will only be reported in the 40 mg dose level).

In addition, each AE will also be categorized into the study period in which it started: prior to first dose (ie, Screening/Baseline period), during the Intervention period (Part A), open-label titration phase (Part

B), double-blind randomized withdrawal phase (Part B), or during the Safety Follow-up period. AEs categorized under multiple study periods will be identified as needed. AEs starting during the Safety Follow-up period will be defined as any event with a start date occurring after the last date in the Intervention Period, according to the SoAs for each respective study part. AEs with an onset after Day 56 will be reported based on the last dose level received during the study and last phase of participation (open-label titration or double-blind randomized withdrawal phase).

4.10.2 Laboratory Test Results

Blood and urine samples will be collected by site staff for clinical laboratory testing. Urine pregnancy tests will be performed at the site and will be recorded in the eCRF as "Positive" or "Negative". All other samples will be analyzed at the central laboratory. For all samples collected, the following data will be recorded in the eCRF: test category (ie, Chemistry, Hematology, Urinalysis, Coagulation, Pregnancy Test, Viral Serology or Urine Drug Screen), sample collection date, and sample time. For urine pregnancy tests, the result will also be recorded in the eCRF as "Positive" or "Negative". An indicator for whether a repeat sample was taken (Yes/No) will also be recorded in the eCRF for each sample collected.

Collected laboratory samples will then be processed at the central laboratory for the calculation of reported values for the laboratory tests listed in Appendix 3. Central laboratory data will include test category, lab test name, reported result, reported unit, reported reference range (ie, low and high), and abnormal indicator. Data from the central laboratory will be combined with the laboratory eCRF data prior to analysis.

Change from baseline values to each post-baseline assessment will be calculated for all continuous laboratory tests.

4.10.3 Vital Sign Results

The following vital sign data will be recorded in the eCRF: assessment date, height, weight, BMI, as well as standing and supine temperature, pulse rate, respiratory rate, supine systolic blood pressure (BP), and diastolic BP. An indicator for whether a repeat assessment was taken (Yes/No) will also be recorded in the eCRF for each assessment.

Change from baseline values to each post-baseline assessment will be calculated for pulse rate, respiratory rate, systolic BP, and diastolic BP. In addition, potentially clinically important flags will be derived for systolic BP, diastolic BP, pulse rate, and respiratory rate (see Table 1).

Table 1: Potentially Clinically Important Criteria for Vital Sign Results

ECG measure	Lower PCI criterion	Upper PCI criterion
Pulse rate	≤50 bpm	≥130 bpm
Systolic BP	<90 mmHg	>130 mmHg
Diastolic BP	<50 mmHg	>85 mmHg
Change in systolic BP	decrease ≥30 mmHg	increase ≥30 mmHg
Change in diastolic BP	decrease ≥30 mmHg	increase ≥30 mmHg

BP = blood pressure; PCI = potentially clinically important

4.10.4 Electrocardiogram Results

Standard 12-lead electrocardiograms (ECGs) will be performed after the participant has been supine for approximately 5 minutes. All ECGs will be performed using the equipment supplied by the central ECG vendor. For all ECGs performed, the following data will be recorded in the eCRF: assessment date, triplicate timepoint, timepoint performed indicator (Yes/No), and time of assessment.

Electronic ECG tracings will be analyzed for the calculation of reported values for the following ECG tests: heart rate, RR interval, PR interval, QRS duration, QT interval, corrected QT interval using the Bazett formula (QTcB), corrected QT interval using the Fridericia formula (QTcF), evaluator interpretation, and abnormal findings. ECG vendor data will include ECG test name, reported result/finding, reported unit, standard result/finding, standard unit, and lead location. The evaluator interpretation result will be recorded as “NORMAL”, “ABNORMAL”, or “UNABLE TO EVALUATE”. Data from the ECG vendor will be combined with the ECG eCRF data prior to analysis.

Change from baseline values to each post-baseline assessment will be calculated for heart rate, RR interval, PR interval, QRS duration, QT interval, and QTcF interval. In addition, potentially clinically important flags will be calculated for heart rate, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval, change from baseline in heart rate, and change in QT, QTcB, and QTcF intervals (see Table 2).

Table 2: Potentially Clinically Important Criteria for ECG Results

ECG measure	Lower PCI criterion	Upper PCI criterion
Heart rate	≤50 bpm	≥130 bpm
PR interval		≥180 msec
QRS duration		≥100 msec
QT interval		≥450 msec
QTcB interval		≥450 msec
QTcF interval		≥450 msec
Change in QTcB		increase ≥30 msec
Change in QTcF		increase ≥30 msec

ECG = electrocardiogram; PCI = potentially clinically important

4.10.5 Physical Examination

Physical examinations will be performed per the SOA. The date of the physical exam will be recorded in the eCRF. Any significant findings from physical examinations should be reported as either medical history or adverse events.

4.10.6 Columbia–Suicide Severity Rating Scale

The Columbia–Suicide Severity Rating Scale (C-SSRS; available at www.cssrs.columbia.edu) is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior has occurred. The C-SSRS has a "Screening/Baseline" version that will be completed at the Screening Visit (Visit 1) and a "Since Last Visit" version that will be completed at all other visits. Both versions contain all 11 categories of suicidal ideation and behavior defined in the Food and Drug Administration (FDA) guidance document on suicidal behavior and ideation (FDA, 2012). Each category is assessed using a single question requiring a "Yes" or "No" response with follow-up questions for any "Yes" responses. The assessment date and each C-SSRS response will be recorded in the eCRF.

In addition, three C-SSRS composite indicator variables will be calculated as follows:

4.10.6.1 C-SSRS Suicidal Ideation Indicator

A composite indicator of C-SSRS suicidal ideation will be calculated as:

- If the response to any one of the five suicidal ideation questions is "Yes", THEN set the suicidal ideation indicator equal to 1.
- OTHERWISE, set the suicidal ideation indicator equal to 0.

4.10.6.2 C-SSRS Suicidal Behavior Indicator

A composite indicator of C-SSRS behavior ideation will be calculated as:

- IF the response to any one of the five suicidal behavior questions is "Yes", THEN set the suicidal behavior indicator equal to 1.
- OTHERWISE, set the suicidal behavior indicator equal to 0.

4.10.6.3 C-SSRS Suicidal Ideation or Behavior Indicator

A composite indicator of C-SSRS suicidal ideation or behavior will be calculated as:

- IF the response to any one of the 5 suicidal ideation questions or any of the 5 suicidal behavior questions is "Yes", THEN set the suicidal ideation or behavior indicator equal to 1.
- OTHERWISE, set the suicidal ideation or behavior indicator equal to 0.

4.11 Pharmacokinetic Variables

Plasma samples will be collected by site staff for PK testing. For all PK samples collected, the following data will be recorded in the eCRF: scheduled timepoint, sample collection date, and sample collection time. A validated bioanalytical method will be utilized for the determination of plasma concentrations of PRAX-944 and its metabolites, as applicable. For Part A, PK parameters of parent drug and primary metabolites (M15, M23, and M32) will be estimated from concentration-time data using noncompartmental methods as described in a separate PK analysis plan.

5 ANALYSIS METHODS

Analysis will be carried out using SAS® (version 9.4 or newer, SAS Institute Inc, Cary, NC). Templates for the summary tables, figures, and participant data listings will be available separately. Data listings will include all data recorded for all enrolled participants; where captured, data entered for screen failure participants will be flagged in the listings.

For all data displays, separate summaries will be generated for each part and phase (open-label titration and double-blind randomized withdrawal) of the clinical trial.

- Part A: All summaries except those for adverse events will use a single "PRAX-944 Overall" column. Summaries of adverse events will use the following columns: "PRAX-944 20 mg qAM", "PRAX-944 40 mg qAM ", and "PRAX-944 Overall".

- Part B: Summaries of disposition and PK will be presented for all of Part B (i.e., not by phase) and will use a single “PRAX-944” column.

- Part B Open-label Titration: Summaries of demographics, baseline characteristics, medical history, prior and concomitant medications, study drug exposure, efficacy, and all safety except adverse events will include a "PRAX-944 Overall" column. Summaries of adverse events will include columns for "PRAX-944 20 mg qAM", "PRAX-944 40 mg qAM ", "PRAX-944 60 mg qAM ", "PRAX-944 80 mg qAM ", "PRAX-944 100 mg qAM ", "PRAX-944 120 mg qAM ", and "PRAX-944 Overall".

- Part B Randomized Withdrawal: Summaries of demographics, baseline characteristics, medical history, prior and concomitant medications, study drug exposure, efficacy, and all safety except adverse events will include the columns "Placebo" and "PRAX-944” for the randomized withdrawal phase. Summaries of adverse events will include columns for "Placebo" and "PRAX-944".

Descriptive statistics for continuous data will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Summaries of change from baseline variables will include only participants who have both a baseline value and corresponding value at the timepoint of interest. Descriptive statistics for categorical data will include frequency and percentage. Where appropriate, descriptive statistics may be presented with 95% confidence intervals (CIs).

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the recorded data. Measures of location (eg, mean and median) will be reported to 1 degree of precision more than the recorded data, and measures of spread (eg, standard deviation) will be reported to 2 degrees of precision more than the recorded data.

Any changes to the analyses that are not included in this SAP will be documented in the CSR.

5.1 Participant Disposition

All participants in the enrolled analysis set will be included in disposition summaries. The number of participants screened, screen failed, randomized, completed, and discontinued from the study, as well as reason for discontinuation, will be summarized by treatment group and overall. The number of participants in each analysis set will also be summarized. All disposition data will be listed by participant.

5.2 Protocol Deviations

Major protocol deviations will be summarized by treatment group and overall using the safety analysis set. All inclusion/exclusion criteria and protocol deviation data will be listed by participant.

5.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be provided by treatment group and overall using the safety analysis set and randomized withdrawal safety analysis set. These tabulations will include the following variables:

- Age
- Sex
- Ethnicity
- Child-bearing potential
- Race
- Dominant Hand
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Baseline TETRAS upper limb score category (<10, ≥ 10)

All demographics and other baseline characteristics data will be listed by participant.

5.4 Medical History

Descriptive summaries of medical history will be provided by treatment group and overall using the safety analysis set and randomized withdrawal safety analysis set. Medical history will be displayed by MedDRA system organ class (SOC) and preferred term. All medical history data will be listed by participant.

5.5 Essential Tremor Medical History

Descriptive summaries of essential tremor medical history will be provided by treatment group and overall using the safety analysis set and randomized withdrawal safety analysis set. ET medical history data will also be listed by participant.

5.6 Prior and Concomitant Medications

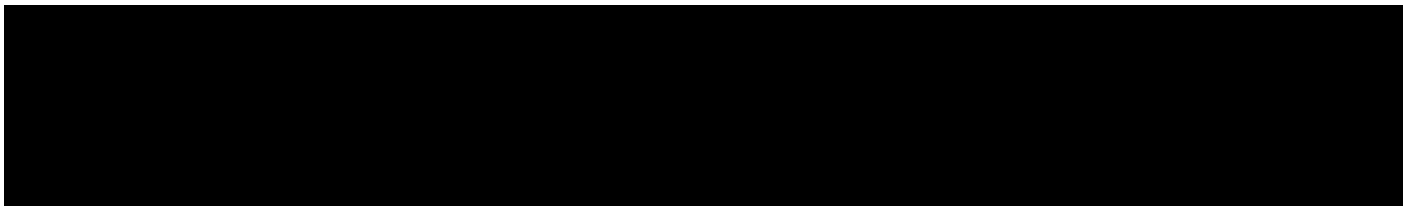
Descriptive summaries of prior medications will be provided by treatment group and overall using the safety analysis set and randomized withdrawal safety analysis set. Both prior and concomitant medications will be displayed by Anatomical Therapeutic Chemical (ATC) classification level 3 and preferred term. All prior and concomitant medication data will be listed by participant.

5.7 Efficacy Analyses

Unless otherwise indicated, all efficacy data will be analyzed by part using the full analysis set. In summaries of change from baseline variables, only participants with both baseline and change from baseline values will be included. Summaries based on the full analysis set will include all timepoints, regardless of period, and will include changes from baseline where appropriate. Unless stated otherwise, summaries of efficacy endpoints will additionally include displays based on the randomized withdrawal analysis set, including randomization baseline and change from randomization, where applicable, to report data collected after receipt of randomized treatment. Summaries based on the randomized withdrawal set will also include open-label titration results and changes from baseline. All efficacy data will be listed; the listings will include all reported and derived values as well as rater ID, where applicable. Analysis of TETRAS scores may be performed for dominant hand only.

5.7.1 Primary efficacy analysis

For Part A, the change from baseline in TETRAS upper limb score to each post-dose timepoint will be analyzed using Mixed Model Repeated Measures (MMRM) methods using the full analysis set. The model will include timepoint as a fixed effect and the baseline TETRAS upper limb score as a covariate. Within subject variability will be modeled using an unstructured covariance pattern. In case of convergence problems, a banded Toeplitz structure for the covariance pattern will be used. Model based point estimates (ie, least square [LS] means), standard error, 95% confidence interval, and p-value will be reported for each timepoint. Reported p-values will test the LS mean for each timepoint versus zero. Similar MMRM methods will be used for the open-label titration phase of Part B. The SAS code to be used for the MMRM analysis is provided below:



Line-plots of the estimated LS means will be used to graphically illustrate the TETRAS upper limb scores over time.

For Part A and both phases of Part B, the TETRAS upper limb score as measured by the clinician will be summarized using descriptive statistics for the reported, change from baseline, and change from randomization (where applicable) values by timepoint. TETRAS upper limb data will be listed by study part, participant, and visit.

5.7.2 Secondary Efficacy Analysis

5.7.2.1 Accelerometer-based upper limb score

For each timepoint, the average score of the two Kinesia ONE assessments will be used for analysis.

For Part A and both phases of Part B, the Kinesia ONE upper limb score will be summarized using descriptive statistics for the reported, change from baseline, and change from randomization (where applicable) values by timepoint. MMRM methods similar to those described in Section 5.7.1 will be used for the change from baseline and change from randomization in Kinesia ONE upper limb scores. Kinesia ONE data will be listed by study part, participant, and visit.

Line-plots of the estimated LS means will be used to graphically illustrate the Kinesia ONE upper limb scores over time.

5.7.2.2 TETRAS combined upper limb score

For Part A and both phases of Part B, the TETRAS combined upper limb score as measured by the clinician will be summarized using descriptive statistics for the reported, change from baseline, and change from randomization (where applicable) values by timepoint. MMRM methods similar to those described in Section 5.7.1 will be used for the change from baseline and change from randomization in

TETRAS combined upper limb scores. TETRAS combined upper limb data will be listed by study part, participant, and visit.

Line-plots of the estimated LS means will be used to graphically illustrate the TETRAS combined upper limb scores over time.

5.7.2.3 TETRAS performance subscale total score

For Part A and both phases of Part B, the TETRAS performance subscale total score as measured by the clinician will be summarized using descriptive statistics for the reported, change from baseline, and change from randomization (where applicable) values by timepoint. MMRM methods similar to those described in Section 5.7.1 will be used for the change from baseline and change from randomization in TETRAS performance subscale scores. TETRAS performance subscale data will be listed by study part, participant, and visit.

[redacted]

5.7.2.5 TETRAS ADL subscale score

In Part B, the TETRAS ADL subscale total score as measured by the clinician will be summarized using descriptive statistics for the reported, change from baseline, and change from randomization (where applicable) values by timepoint. MMRM methods similar to those described in Section 5.7.1 will be used for the change from baseline and change from randomization in TETRAS ADL subscale scores. TETRAS ADL data will be listed by study part, participant, and visit.

5.7.2.6 QUEST total and subscale score

In Part B, the QUEST total and subscale scores will be summarized using descriptive statistics for the reported, change from baseline, and change from randomization (where applicable) values by timepoint. MMRM methods similar to those described in Section 5.7.1 will be used for the change from baseline and change from randomization in QUEST scores. QUEST data will be listed by study part, participant, and visit.

[redacted]

[redacted]

5.7.3.3 Telehealth Assessments

In Part B, the TETRAS upper limb score as assessed by telehealth will be summarized using descriptive statistics for reported and change from baseline values at Day 41. Telehealth assessment data will not be summarized for the randomized withdrawal analysis set as no telehealth assessments were performed during the randomized withdrawal phase. TETRAS telehealth data will be listed by participant and visit.

[redacted]

[redacted]

[redacted]

5.7.4 Subgroup Analyses

In Part B, subgroup analyses for patients having a baseline TETRAS upper limb score of 10 or higher will be performed for primary and secondary efficacy endpoints, as well as the TETRAS modified total score.

5.8 Safety Analyses

For all safety variables, descriptive statistics will be presented by study part, treatment group, and visit (where applicable) using the safety analysis set and randomized withdrawal safety analysis set. In summaries of change from baseline safety variables, only participants with both baseline and change from baseline values will be included. No formal hypothesis testing will be performed for any safety variable.

5.8.1 AEs

The overall incidence of participants having at least one AE in each of the following categories will be summarized by treatment group and dose level, as defined in Section 5:

- Any TEAE
- Any serious adverse event (SAE)
- Any AE leading to death
- Any AESI
- Any TEAE leading to study drug withdrawal
- Any related TEAE

The overall AE incidence summary, as well as summaries identified in subsequent sections, will be reported by part and phase. Part A and Part B open-label titration phase summaries will be based on the safety analysis set. Part B double-blind randomized withdrawal phase summaries will be based on the randomized withdrawal analysis set.

All AE data will be listed by study part and participant. Separate listings will be presented for SAEs, AEs leading to death, and TEAEs leading to study drug withdrawal.

5.8.1.1 TEAEs

The incidence of TEAEs will be summarized by SOC and preferred term. Each participant will be counted only once per SOC and preferred term. The incidence of TEAEs by preferred term will also be summarized.

5.8.1.2 TEAEs Leading to Study Drug Withdrawal

The incidence of TEAEs leading to study drug withdrawal will be summarized by SOC and preferred term. Each participant will be counted only once per SOC and preferred term.

5.8.1.3 TEAEs Related to Study Drug

The incidence of TEAEs related to study drug will be summarized by SOC and preferred term. Each participant will be counted only once per preferred term.

5.8.1.4 TEAEs by Maximum Severity

The incidence of TEAEs will be summarized by maximum severity, SOC, and preferred term, where Severe > Moderate > Mild. Each participant will be counted only once per preferred term and most severe category reported. If missing, severity will be categorized as Severe for summary purposes.

5.8.2 Laboratory Test Results

Descriptive statistics for all reported and change from baseline values will be summarized by test category, laboratory test, and visit. Only the original assessment for each visit day will contribute to descriptive statistics; repeat or unscheduled assessments will not be included in the calculation of descriptive statistics by visit. All laboratory test results data (including pregnancy test and urine drug screen data and any repeat or unscheduled assessments) will be listed by study part, participant, and visit.

Descriptive statistics for all reported and change from baseline values for KIM-1, urine creatinine, and KIM-1 per urine creatinine ratio will be summarized by test and visit. Results will be listed by study part, participant, and visit.

5.8.3 Vital Sign Results

Descriptive statistics for all reported and change from baseline values will be summarized by visit. Only the original assessment for each timepoint will contribute to these summaries; repeat or unscheduled assessments will not be included in the calculation of descriptive statistics by timepoint. The number and percentage of participants with PCI values at any time will be tabulated by treatment group. Summaries of PCI values will include all assessments regardless of whether an original, repeat, or unscheduled assessment. All vital sign results data will be listed by study part, participant, and visit.

5.8.4 ECG Results

Descriptive statistics for all reported and change from baseline values will be summarized by visit. Only the original assessment for each visit will contribute to these summaries; repeat or unscheduled assessments will not be included in the calculation of descriptive statistics. The number and percentage of participants with PCI values at any time will be tabulated by treatment group; the number and percentage of participants with abnormal ECG findings will be presented similarly. Summaries of PCI values and abnormal ECG findings will include all assessments regardless of whether an original, repeat, or unscheduled assessment. All ECG results data will be listed by study part, participant, and visit.

5.8.5 C-SSRS

The C-SSRS will be evaluated based on methods described by Nilsson et al. (2013). The number and percentage of participants with any suicidal ideation and/or suicidal behavior following the first dose of study drug will be tabulated.

For the composite endpoint of suicidal ideation, the number and percent of participants who experience any one of the five suicidal ideation events at least once during dosing through follow-up will be tabulated.

For the composite endpoint of suicidal behavior, the number and percent of participants who experience any one of the five suicidal behavior events at least once during dosing through follow-up will be tabulated.

For the composite endpoint of suicidal ideation or behavior, the number and percent of participants who experience any one of the ten suicidal ideation or behavior events at least once during dosing through follow-up will be tabulated.

5.9 Pharmacokinetic Analyses

5.9.1 Plasma Concentrations

For each study part, plasma concentrations will be summarized by visit and nominal sampling time using descriptive statistics. For concentration summaries, plasma concentrations below the level of quantification (BLQ) will be set to zero. Descriptive statistics for plasma concentrations will include n, number of participants with concentrations below the level of quantification (BLQ), mean, SD, coefficient of variation (CV%), geometric CV%, geometric mean, median, minimum, and maximum. All plasma concentration data will be listed by study part, participant, and visit.

Plasma concentrations will also be presented graphically.

5.9.2 Plasma PK Parameters

PK parameters will not be estimated for this study as no participants from Part A agreed to participate in the optional overnight PK sampling.

6 INTERIM ANALYSES

No formal interim analysis is planned for this clinical trial.

7 CHANGES TO PLANNED ANALYSES

7.1 Changes to Analysis as Described in Protocol

The protocol specifies an exploratory objective "to characterize the pharmacokinetic (PK) profile of PRAX-944 following multiple dose administration" for Part A. This objective will not be assessed as no participants from Part A agreed to participate in the optional overnight PK sampling.

The order of the endpoints supporting the objective "to evaluate the duration of PRAX-944 effect on upper limb tremor, other measures of tremor severity, measures of disease impact, mood, and global measures of disease state in participants with ET" as specified in the protocol has been updated to reflect the importance of direct measures of movement (ie, accelerometry) and activities of daily living.

[redacted]

The protocol includes a Day 0 (Baseline) visit in the SoA for Part A. However, for simplicity and consistency across both parts of the study, the derived study day variable as defined in Section 4 will not include a study day 0.

The TETRAS combined upper limb score (derived as the sum of the 6 TETRAS upper limb sub-items, the handwriting item, and the spirals item scores) has been included as another TETRAS based measure of upper limb tremor.

7.2 Changes to Approved Version of the SAP

Not applicable.

8 REFERENCES

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APPENDIX 1 SCHEDULE OF ACTIVITIES

Schedule of Activities for Part A

Visit Days	Day -28 to Day -1 (Screening)	Day 0* (Baseline)	Day 1	Day 7 (±1)	Day 14 (±1)	Day 21 (±1) End of Clinical Trial or Early Termination
CLINICAL TRIAL ENTRY AND GENERAL ASSESSMENTS						
Informed Consent	X					
Inclusion/ Exclusion	X	X				
Demographic Data	X					
Medical History	X					
Body Weight/ Height	X					
Drug/ Alcohol Screen [a]	X	X				
Pregnancy test	X *(serum)*	X *(urine)*				X *(urine)*
SAFETY ASSESSMENTS						
Vital Signs [b]	X	X	X	X	X	X
Physical Examination	X	X				X
Clinical Laboratory Tests [c]	X	X		X	X	X

12-lead ECG [d]	X	X		X	X	
C-SSRS (Baseline/Screening)	X					
C-SSRS (Since Last Visit)		X		X	X	X
AE Monitoring	X					
Concomitant Meds/ Procedures	X					
EFFICACY ASSESSMENTS						
TETRAS Performance [e]	X	X	X	X	X	X
[redacted]						
PHARMACOKINETICS						
Blood Collection for Study Drug Concentration (sparse sampling) [h]			X	X	X	
Blood Collection for Study Drug Concentration (serial sampling) [i]			O	O	O	
STUDY DRUG						
Study Drug Administration [j]			X			

AE=adverse event; [redacted] C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; O=optional; [redacted] TETRAS=The Essential Tremor Rating Assessment Scale.

D

* Day 0 (Baseline) activities may be combined with Day 1 activities, provided that Baseline activities are completed before dosing in the morning.

[a] Urine sample for assessment of selected drugs and a breath sample for alcohol screen.

[b] Vital signs (pulse rate, respiratory rate, temperature, and blood pressure [after the participant has been supine for at least 5 minutes and standing for at least 2 minutes]). On Day 1, should be performed 2 and 6 hours after dosing (±30 min).

[c] Including CBC, clinical chemistry, coagulation factors, viral serology screen, exploratory urine biomarkers, urinalysis and urine albumin. Coagulation factors and viral serology screen collected at Screening only.

[d] Triplicate measurement will be taken at Screening only; for all other timepoints, single measurement is acceptable.

[e] Screening, Day 0 and Day 21: completed anytime; Day 1, pre-dose and 6 (±2) hours post-dose; Day 7 and Day 14 6 (±2) hours post-dose.

[f] The TETRAS Performance assessment will be captured on video for central reading. The local rater will rate the same TETRAS Performance assessment that is captured on video. The Screening video will be independently assessed for eligibility.

[g] To be performed 2 consecutive times separated by at least 30 minutes, the first time immediately after the post-dose TETRAS Performance assessment. All 3 maneuvers in the upper limb item (sub- items 4a, 4b, and 4c) will be completed for both arms, first for the RIGHT arm and then for the LEFT.

[h] Day 1: 0 (pre-dose); post-dose immediately after completion of the 2nd accelerometer-based upper limb assessment; When PK sampling timepoints coincide with the TETRAS Performance timepoints or accelerometer-based assessment timepoints the PK sample is to be obtained last.

[i] Optional samples collected at sites that have capabilities to perform serial sample collection: Day 1, 7 and 14: 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours post-dose. All collection times up to 4 hours post-dose have a ±15 min window and a ±30 min window thereafter. 24-hour timepoint samples are to be taken prior to the AM dose. When PK sampling timepoints coincide with the TETRAS Performance timepoints or accelerometer-based assessment timepoints the PK sample is to be obtained last.

[j] Administered in clinic on Day 1. All other days it should be taken in the morning, within 30 minutes after breakfast. On Day 1 participant should be observed in clinic for approximately 6 hours before discharge. Study drug is dispensed (20 mg QAM for Day 1 to Day 7; 40 mg QAM for Day 8 to Day 14).

Schedule of Activities for Part B

Study Phase	Screening			Open-label Titration								[redacted]
Visit Days (Visit Window)	Day -28 to Day -1	Day -2 (-2)	Day 1 (Baseline)	Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Day 42	
CLINICAL TRIAL ENTRY AND GENERAL ASSESSMENTS												
Informed Consent	X											
Inclusion/Exclusion	X		X*									
Demographic Data	X											
Medical History	X											
Body Weight/Height	X											
Drug/Alcohol Screen [a]	X		X*									
Pregnancy test	X *(serum)*		X *(urine)**									
SAFETY ASSESSMENTS												
Vital Signs [b]	X		X		X		X				X	

Study Phase	**Screening**			**Open-label Titration**								[redacted]
Visit Days (Visit Window)	**Day -28 to Day -1**		**Day 1 (Baseline)**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 41**	**Day 42**	
		Day -2 (-2)										
Physical Examination	X		X*									
Clinical Laboratory Tests [c]	X		X*		X		X				X	
12-lead ECG [d]	X		X*		X		X				X	
C-SSRS (Baseline/Screening)	X											
C-SSRS (Since Last Visit)			X*		X		X				X	

Study Phase	Screening			Open-label Titration								[redacted]
Visit Days (Visit Window)	**Day -28 to Day -1**		**Day 1 (Baseline)**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 41**	**Day 42**	
		Day -2 (-2)										
SAFETY ASSESSMENTS												
Phone Call Check-in				X		X		X	X			
AE Monitoring	X											
Concomitant Meds/ Procedures	X											
EFFICACY ASSESMENTS												
TETRAS Performance [e]	X		X		X		X				X	[redacted]
[redacted]												

Study Phase	Screening			Open-label Titration								[redacted]
Visit Days (Visit Window)	Day -28 to Day -1	Day -2 (-2)	Day 1 (Baseline)	Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Day 42	
[redacted]												
QUEST			X		X		X				X	[redacted]

Study Phase	Screening			Open-label Titration								[redacted]
Visit Days (Visit Window)	Day -28 to Day -1	Day -2 (-2)	Day 1 (Baseline)	Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Day 42	
EFFICACY ASSESMENTS												
[redacted]												
PHARMACOKINETICS												
Blood Collection for Study Drug Concentration[i]			X		X		X				X	[redacted]

Study Phase	Screening			Open-label Titration								[redacted]
Visit Days (Visit Window)	Day -28 to Day -1	Day -2 (-2)	Day 1 (Baseline)	Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Day 42	
STUDY DRUG												
Randomization[j]											X	
Study Drug Dispensing			X		X		X				X	
Study Drug Administration[k]				X *(open label)*								

ADL=Activities of Daily Living; AE=adverse event; [redacted] CBC=complete blood count; [redacted] C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; Meds=Medications; [redacted]; PK=pharmacokinetics; QAM=every morning; QUEST=Quality of Life in Essential Tremor Questionnaire; TETRAS=The Essential Tremor Rating Assessment Scale.

* May be performed on Day -1.

a Urine sample for assessment of selected drugs and a breath sample for alcohol screen.

b Vital signs include pulse rate, respiratory rate, temperature, and blood pressure. Blood pressure must be measured once after the participant has been supine for at least 5 minutes and once after the participant has been standing for at least 2 minutes. On Day 1, vital signs should be measured pre-dose, 2 hours post-dose (±30 min), and 6 hours post-dose (±30 min).

c Including CBC, clinical chemistry, coagulation factors, viral serology screen, urinalysis, and urine albumin. Coagulation factors and viral serology screen collected at Screening only.

d A triplicate measurement must be taken at Screening only; for all other timepoints, a single measurement is acceptable.

e TETRAS can be completed anytime at Screening and Day 70. On other days, the following timing should be followed: Day 1: pre-dose and 6 (±2) hours after a 20 mg QAM dose Day 7: 6 (±2) hours after a 40 mg QAM dose Day 21: 6 (±2) hours after an 80 mg (or highest tolerated dose) QAM dose Day 42: pre-dose and 6 (±2) hours after a 120 mg (or highest tolerated dose) QAM dose Day 56: 6 (±2) hours post-dose

f The TETRAS Performance assessment will be captured on video for central reading. The local rater must rate the same TETRAS Performance assessment as that which is captured on video for central reading. The Screening video will also be independently assessed for eligibility.

Study Phase	Screening			Open-label Titration								[redacted]
Visit Days (Visit Window)	Day -28 to Day -1		Day 1 (Baseline)	Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 41	Day 42	
		Day -2 (-2)										

g Kinesia ONE assessments must be completed immediately after the TETRAS Performance assessments (including both pre-dose and post-dose assessments on Day 1 and Day 42). After each TETRAS Performance assessment, Kinesia ONE assessments should be completed twice separated by at least 30 minutes. All 3 maneuvers in the upper limb item (sub-items 4a, 4b, and 4c) will be completed for both arms, first for the RIGHT arm and then for the LEFT.

h For visits with multiple TETRAS assessments, the TETRAS ADL subscale should only be assessed once. On Day 1, the ADL subscale should be completed pre-dose. On day 42, the ADL subscale should be completed 6 (±2) hours after the QAM dose.

i On Day 1 and Day 42 blood samples should be collected at the following timepoints: pre-dose and 0.5, 1, 2, 4, and 6 hours post-dose. The 6-hour post-dose sample will be collected immediately after completion of the second Kinesia ONE assessment. When PK sampling timepoints coincide with the TETRAS Performance timepoints or accelerometer-based assessment timepoints, the PK sample is to be obtained last. On Days 7, 21, and 56; samples should be collected 2 hours post-dose. Blood collection can be completed anytime on Day 70.

j Participants will be randomized (1:1) to receive either placebo or PRAX-944 from Day 43 to Day 56. Randomization can occur on Day 37 through Day 42.

k On Day 1 and 42, study drug must be administered in the clinic on an empty stomach (at least 1 hour before breakfast, which will be provided at the site) and the participant should be observed in the clinic for approximately 6 hours before discharge. On all other days, participants should be instructed to take study drug at least 1 hour before breakfast in the morning at home. The escalation schedule is as follows: 20 mg, Day 1 through Day 3; 40 mg, Day 4 through Day 7; 60 mg, Day 8 through Day 14; 80 mg, Day 15 through Day 21; 100 mg, Day 22 through Day 28; and 120 mg, Day 29 through Day 42. Participants will receive blinded study drug on Days 43 to 56. During blinded treatment period, participants should take the same number of tablets per day as taken during Days 36 to 42.

APPENDIX 2 ADVERSE EVENTS OF SPECIAL INTEREST

FDA Requested AESI Terms	MedDRA Preferred Term Search Criteria for Defining AESI
Any event of seizure, seizure-like phenomena	Seizure Seizure like phenomena Generalised tonic-clonic seizure Seizure cluster Simple partial seizures Focal dyscognitive seizures Seizure anoxic Petit mal epilepsy Atonic seizure Clonic convulsion Febrile convulsion Tonic convulsion Autonomic seizure Partial seizures Generalised onset non-motor seizure Partial seizures with secondary generalisation
Loss of consciousness and altered state of consciousness	Loss of consciousness Depressed level of consciousness Consciousness fluctuating Slow response to stimuli Hyporesponsive to stimuli Unresponsive to stimuli Stupor Syncope
Tardive dyskinesia	Tardive dyskinesia
Acute dystonic reactions	Dystonia Oromandibular dystonia Torticollis Blepharospasm Pharyngeal dystonia Writer’s cramp Early onset primary dystonia Oculogyric crisis Opisthotonus Trismus Tic Emprosthotonus
Akathisia	Akathisia
Acute Parkinsonian symptoms	Parkinsonism Parkinsonian gait Tremor Parkinsonian rest tremor Bradykinesia

FDA Requested AESI Terms	MedDRA Preferred Term Search Criteria for Defining AESI
	Cogwheel rigidity Reduced facial expression

APPENDIX 3 CLINICAL LABORATORY EVALUATIONS

The tests detailed in Table 3 will be performed by a central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the clinical trial as determined necessary by the Investigator or required by local regulations.

Table 3 Protocol-Required Laboratory Assessments

Clinical Chemistry	Hematology	Urinalysis
Alanine aminotransferase (ALT) Alkaline phosphatase Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) Calcium Creatinine Glucose Potassium Sodium Total and direct bilirubin Total protein	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential (absolute): • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Bilirubin Glucose Ketones Leukocyte esterase Nitrite Blood pH Specific gravity Protein Urobilinogen Microscopic exam including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

Drug Screen	**Coagulation Factors (Screening only)**	**Other Tests**
Including but not limited to: Amphetamines Barbiturates Benzodiazepines (Stable use of ≤2 mg of lorazepam/day is allowed) Cannabinoids (THC) Cocaine (metabolite) Methadone Opiates Phencyclidine	Activated partial thromboplastin time Prothrombin time and international normalized ratio	Serum and urine pregnancy, (women of childbearing potential only) Viral Serology Screen (at Screening only): Hepatitis B surface antigen (HBsAg) and Hepatitis C (HCV) antibody and HIV antibody/antigen Urinary albumin Urinary creatinine (Part A only) [redacted]