CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE	A Phase 2 Clinical Trial Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of PRAX-944 in Adults with Essential Tremor
PROTOCOL NUMBER	PRAX-944-221
COMPOUND NUMBER	PRAX-944
CLINICAL TRIAL PHASE	Phase 2
SPONSOR NAME	Praxis Precision Medicines Australia Pty Ltd
SPONSOR ADDRESS	727 Collins Street Docklands Vic 3008, Australia
REGULATORY AGENCY IDENTIFIER NUMBER(S)	N/A
CURRENT VERSION DATE	Version 6.0 – 11 August 2021

NCT Number- NCT05021978

SIGNATURE PAGE FOR SPONSOR

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

Clinical Trial No: PRAX-944-221

Current Version Date: Version 6.0 – 11 August 2021

This clinical trial protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the study drug.
- The ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the principles of the International Council for Harmonisation (ICH), and local country regulations.

The Investigator will be supplied with details of any significant or new findings, including adverse events (AEs), relating to treatment with the study drug.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 15-Aug-2021 | 21:36:04 EDT
5DDDBD5AC0464A0B814E683880247E02

[redacted] MD, MS

15-Aug-2021 | 21:36:08 EDT

Date

INVESTIGATOR'S AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor. I agree to conduct this clinical trial in accordance with the requirements of this protocol, and also to protect the rights, safety, privacy, and well-being of clinical trial participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations.
- This document contains confidential information from the Sponsor, which may not be disclosed to anyone other than clinical trial staff and members of the IRB/IEC.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACT INFORMATION IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Clinical Trial	Name	Address and Telephone Number
Responsible Physician	[redacted], MD, PhD	One Broadway, 16th Floor Cambridge, MA 02142, USA Telephone: +1 617 504 3087

PROTOCOL SUMMARY TABLE

DOCUMENT HISTORY	DATE
Version 1.0	11 January 2019
Version 2.0	07 November 2019
Version 3.0	18 July 2020
Version 4.0	20 October 2020
Version 5.0	13 July 2021
Version 6.0	11 August 2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
$AUC_{0\text{-}tau}$	area under the concentration vs time curve from the time of dosing through the dosing interval
[redacted]	[redacted]
[redacted]	[redacted]
BMI	body mass index
BUN	blood urea nitrogen
Ca^{2+}	Calcium
CBC	complete blood count
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent systemic clearance following oral administration
C_{max}	maximum observed concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
ET	essential tremor

Abbreviation	Definition
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KDIGO	Kidney Disease Improving Global Outcomes
KIM-1	kidney injury molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
MR	modified release
NREM	non-rapid eye movement
P-gp	P-glycoprotein
[redacted]	[redacted]
PK	pharmacokinetic
PT	preferred term
QAM	every morning
QUEST	Quality of Life in Essential Tremor Questionnaire
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCr	serum creatinine
SD	standard deviation
SoA	Schedule of Activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
T_{max}	time to maximum observed concentration

Abbreviation	Definition
TRG	Tremor Research Group
ULN	upper limit of normal
Vd/F	apparent volume of distribution after non-intravenous administration
WBC	white blood cell

1. PROTOCOL SUMMARY

1.1. Synopsis

This is a brief summary of the clinical trial. For complete details, refer to the body of the protocol.

PROTOCOL TITLE

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

RATIONALE

Essential Tremor (ET) is one of the most common neurological disorders with a prevalence of nearly 1%. It is characterized by a 6 to 12 Hz postural and kinetic tremor. Tremor typically occurs in the hands, arms, head, and voice, and is less common in the face, legs, and trunk. ET, by definition, is not associated with other neurological signs, although a resting tremor and impairments in balance, particularly tandem gait, have been described. The diagnosis of ET is based on medical history and neurological exam as described in The International Parkinson and Movement Disorders Society Consensus Statement on the Classification of Tremors.

There is a range in the severity of ET; some patients require no treatment, whereas others have severe disability with impairment in activities of daily living (ADLs) such as dressing and eating. Treatments for ET include pharmacological therapies, regional injection of botulinum toxin (off-label usage), and surgical therapies for those with severe disability. The most effective pharmacological therapies are propranolol and primidone. They have limited efficacy, with about 50% of patients having a durable yet incomplete response. Dose-limiting side effects are common and include bradycardia for propranolol, and sedation and dizziness for primidone. Surgical therapies, including deep brain stimulation and ablation of the nucleus ventralis intermedius of the thalamus, are effective but they are reserved for medically refractory patients due to the risks associated with brain surgery. Many patients who are eligible for surgical therapies do not elect to have these procedures. Thus, there is a high unmet need for efficacious and well-tolerated pharmacological therapies for ET.

While the genetics and pathophysiology of ET is not fully understood, it is thought to involve abnormal activity of cerebellar afferent and efferent pathways. This network consists of input from the inferior olive to the cerebellar cortex, and outflow through deep cerebellar nuclei to the ventral thalamus and cortex. Low voltage, T-type calcium (Ca^{2+})-channels in the inferior olive and thalamus may play a role in the pathogenesis and treatment of ET. The T-type Ca^{2+}-channel family is comprised of 3 different isoforms: $Ca_V3.1$, $Ca_V3.2$, and $Ca_V3.3$. These channels are involved in generation of physiological and pathophysiological rhythms in the brain. In the harmaline rodent model of ET, synchronous neuronal discharges which are associated with T-type Ca^{2+}-channels are increased. The abnormal discharges were attenuated in mice lacking the gene that encodes for $Ca_V3.1$, and in wildtype mice, selective knockdown of $Ca_V3.1$ in the inferior olive by shRNA suppressed the harmaline-induced tremor. The non-selective Ca^{2+} channel blocker ethosuximide was found to suppress tremor in the harmaline model and in a genetic model of ET, in a dose-dependent fashion.

PRAX-944 is an orally active, small molecule that belongs to the class of T-type Ca^{2+}-channel blockers. PRAX-944 blocks all 3 T-type Ca^{2+}-channel subtypes with high potency and is therefore being studied for the treatment of ET. Different formulations of PRAX-944 have been studied in 4 single and multiple ascending dose trials in healthy volunteers. The modified-release (MR)7 formulation (80% of drug product released within 7 hours), which will be used in this trial, was well tolerated at doses of up to 120 mg per day when administered in a titration regimen.

In a human electroencephalogram (EEG)/polysomnography clinical trial, PRAX-944 showed robust suppression of the sigma frequency band during non-rapid eye movement (NREM) sleep, a marker of sleep spindle activity, at the 20 mg, 40 mg, and 60 mg dose levels. Sleep spindles are prominent oscillations of 11 to 15 Hz observed in the human scalp EEG during NREM sleep that are mediated by activation of T-type Ca^{2+} channels in the thalamus. Thus, these data suggest that PRAX-944 blocks T-type Ca^{2+} channels in the central nervous system (CNS) at well tolerated doses.

The aim of this development program is to evaluate whether oral administration of PRAX-944 can provide therapeutic benefit to patients with ET. The study is divided into 2 parts: Part A is designed to study the dose titration from 20 to 40 mg every morning (QAM) (ie, 2 weeks with 7 days at each dose level) and Part B is designed to study the dose titration from 20 to up to 120 mg QAM with at least 14 days of dosing at the highest tolerated dose for each participant.

OBJECTIVES AND ENDPOINTS

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: o TETRAS Performance subscale total score o Accelerometer-based upper limb score (bilateral sum of items 4a, 4b, and 4c) o 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

Objective	Endpoint
	• Changes in electrocardiogram (ECG) parameters • Incidence of Columbia-Suicide Severity Rating Scale (C-SSRS) measured suicidal ideation or behavior
Exploratory	
[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: o TETRAS Performance subscale total score o Accelerometer-based upper limb score (bilateral sum of items 4a, 4b, and 4c) o 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: o TETRAS ADL subscale score o Quality of Life in Essential Tremor Questionnaire (QUEST) total and subscale scores
Exploratory	
[redacted]	[redacted]

Objective	Endpoint
[redacted]	

OVERALL DESIGN

This multi-center clinical trial will assess the efficacy, safety, tolerability, and PK of PRAX-944 in participants aged 18 years of age or older who have had signs and symptoms consistent with ET for at least 3 years, with an onset before age 65.

The clinical trial will be conducted in 2 parts (Part A and Part B). Both parts will consist of 3 periods: Screening/Baseline, Intervention, and Safety Follow-up.

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.

Participants who received study drug in Part A are not eligible for Part B (see Exclusion Criterion #19).

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 procedures, participants will provide written informed consent to participate in the clinical trial. Key Screening assessments will include medical history, demographics, physical examination, drug screen, clinical laboratory evaluations and serum pregnancy for women of childbearing potential, 12-lead ECG, vital signs, C-SSRS, assessment of ET severity using the TETRAS Performance subscale (including a video for independent review of eligibility), and a review of concomitant medications. To be eligible, potential participants who are taking prohibited medications will need to successfully discontinue these medications for at least 5 half-lives or 14 days prior (whichever is the longer period of time) before the first dose of study drug.

For those participants requiring the 14 additional days in the Screening period to discontinue primidone, all or some of the Screening assessments may need to be repeated, pending approval by the Sponsor's Medical Monitor.

For participants in **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. In addition, Baseline efficacy assessments should either be conducted on Day 0 or Day 1 pre-dose, but not both to avoid learning effects.

For participants in **Part B**, TETRAS Upper Limb items will also be completed with accelerometry at Screening and via telehealth on Day -2 of the Screening period. The Screening telehealth visit is needed to ensure participants can complete the TETRAS Upper Limb assessment successfully via telehealth and to provide a pre-dose measure. Additional assessments added to Part B screening include TETRAS ADL and [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 Table 3) 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 after breakfast through Day 7. Participants will return to the clinic on Day 7 for efficacy testing at the 20 mg dose level. On Day 8, the dose will increase to 40 mg QAM after breakfast through Day 14 for efficacy testing at the 40 mg dose level. Participants will return to the clinic on Day 14 for efficacy testing at the 40 mg dose level. Participants who agree to optional additional PK sampling will remain overnight in the clinic on Day 1, Day 7, and Day 14.

Key safety measures will include clinical laboratory evaluations, 12-lead ECG, C-SSRS, and vital signs (Table 2). Key efficacy assessments will include the TETRAS Performance subscale, [redacted] (Table 2). Blood samples will be obtained for the determination of PRAX-944 plasma concentrations using a validated bioanalytical method and may also be used for exploratory method development and/or metabolite characterization.

Part B

Open-label Titration Phase

On Day 1, participants will receive a 20 mg dose of PRAX-944 on an empty stomach (at least 1 hour before breakfast). 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 least 1 hour before breakfast at home.

Participants will continue taking PRAX-944 20 mg QAM at home through Day 3.

On Day 3, participants will receive a telephone call from site staff to inquire about AEs and concomitant medications, confirm dose escalation, and remind the participant about the number of study drug tablets to take on Day 4 through Day 7.

On Day 4, participants will escalate to 40 mg QAM through Day 7, when they will return to the clinic for safety assessments and efficacy testing. On Day 8, participants should escalate to 60 mg QAM through Day 14.

On Day 14, participants will receive a telephone call from site staff to inquire about AEs and concomitant medications, confirm dose escalation, and remind the participant about the number of study drug tablets to take on Day 15 through Day 21.

On Day 15, participants should escalate to 80 mg QAM through Day 21, when they will return to the clinic for safety assessments and efficacy testing. On Day 22, participants should escalate to 100 mg QAM through Day 28.

On Day 28, participants will receive a telephone call from site staff to inquire about AEs and concomitant medications, confirm dose escalation, and remind the participant about the number of study drug tablets to take on Day 29 through Day 42.

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. The dose on Day 42 will be taken in the clinic (see Double-blind Randomized Withdrawal Phase below).

On Day 35, participants will receive a telephone call from site staff to inquire about AEs and concomitant medications.

On Day 41, participants will complete a TETRAS Performance Upper Limb assessment via a telehealth visit.

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. The Investigator should discuss the decision to continue at a lower dose level with the Sponsor and Medical Monitor. Participants can only change to a lower dose level once, and no dose changes may occur after Day 36.

Double-blind Randomized Withdrawal Phase

On Day 42, participants will complete the final clinic visit of the open-label titration phase. Participants will receive their dose of PRAX-944 in the clinic on an empty stomach (at least 1 hour before breakfast). 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.

After Day 42, participants will 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.

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 (±1 day) for the final clinical trial assessments (Table 2).

Part B

The Safety Follow-up period will take place from Day 57 to Day 70. At the end of the Safety Follow-up period, participants will return to the clinic on Day 70 for the final clinical trial assessments (Table 3).

Safety Monitoring

The Sponsor will review ongoing safety data. The clinical trial may be stopped, or clinical trial enrollment suspended if:

- The Sponsor, in consultation with the Principal Investigators, consider that the number and/or severity of AEs justify discontinuation of the clinical trial
- The Sponsor makes a decision to do so

Critical safety endpoints are listed in Section 8.2. AEs and concomitant medication and procedures use will be monitored from the time of informed consent to Day 21 (±1 day) in Part A and to Day 70 in Part B. At that time, participants will have completed the clinical trial.

Renal function monitoring will be based on the KDIGO criteria for acute kidney injury (AKI) as outlined in Section 8.2.4.1. If a participant's laboratory values exceed these thresholds, dosing of that participant will be stopped, and the laboratory tests repeated.

NUMBER OF PARTICIPANTS

Part A

Up to 12 participants are planned to be administered PRAX-944.

Part B

Approximately 12 participants are planned to be administered PRAX-944 for the first 42 days followed by randomization (1:1) to 2 additional weeks on the highest tolerated dose of PRAX-944 or placebo. Up to 12 additional participants may be enrolled at the discretion of the Sponsor to ensure inclusion of a broad range of tremor severity.

Participant Replacement

Participants who withdraw from either Part A or Part B prior to completion of the clinical trial may be replaced at the discretion of the Sponsor. No more than 6 participants in either part of the study will be replaced.

DURATION OF CLINICAL TRIAL

Participants will be part of the clinical trial for the following time intervals:

Part A

Screening/Baseline Period	Up to 28 days (+14 days if on primidone)
Intervention Period	14 days
Safety Follow-up Period	7 days

Total Participation	Up to 49 days (63 days if on primidone)

Part B

Screening/Baseline Period	Up to 28 days (+14 days if on primidone)
[redacted]	
Safety Follow-up Period	14 days
Total Participation	Up to 98 days (112 days if on primidone)

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

A participant must meet the following criteria at Screening and Baseline (unless otherwise specified) to be eligible to participate in this clinical trial:

I 1. Male or non-pregnant, non-lactating female aged 18 years or older.

I 2. Willing and able to understand and sign an informed consent document indicating that he/she understands the clinical trial purpose, the clinical trial procedures, and that he/she is willing to participate in the clinical trial and comply with the protocol.

I 3. Body mass index (BMI) at Screening between 18 and 40 kg/m^2, inclusive.

I 4. Clinical diagnosis of ET consistent with Movement Disorders Society Criteria, a duration of ET of at least 3 years and with onset before the age of 65.

I 5. Moderate to severe ET as defined by the following:

a. A combined bilateral score of ≥10 on the TETRAS Upper Limb items 4 a, b, c. (UL tremor severity at Screening will be confirmed by central video review, for eligibility)

OR

b. A score of ≥2 on 2 or more of the following TETRAS activities of daily living (ADL) subscale items: (2) Feeding with a spoon, (3) Drinking from a glass, (5) Dressing, (6) Pouring, (9) Writing

OR

c. A score of ≥2 on 1 of the following TETRAS ADL subscale items: (2) Feeding with a spoon, (3) Drinking from a glass, (5) Dressing, (6) Pouring, or (9) Writing AND a score of ≥2 on both of the following TETRAS ADL subscale items: (10) Working and (12) Social Impact

Note: ET severity at Baseline will be confirmed by the Investigator at the clinical trial site.

I 6. Those currently receiving any medication for their ET must be willing and able to discontinue all but 1 tremor medication and be on a stable dose for at least 28 days.

I 7. Willing to comply with medically acceptable method of contraception as defined in Section 5.4.3.

Exclusion Criteria

A participant who meets any of the following criteria at Screening or Baseline (unless otherwise specified) will be excluded from this clinical trial:

E 1. Known hypersensitivity to any component of the formulation of PRAX-944.

E 2. Unwilling or unable to refrain from episodic use of medication(s)/substance(s) that might interfere with the evaluation of tremor during the trial. Stable use of medication(s)/substance(s) that might impact tremor, including beta-agonist bronchodilators, is allowed so long as the tremor is judged by the investigator to be primarily due to the participant's ET diagnosis.

E 3. Trauma to the nervous system within 3 months preceding the onset of tremor.

E 4. Clinical evidence of psychogenic tremor as ascertained by the Investigator.

E 5. History of other medical, neurological or psychiatric condition that may explain or cause tremor, including but not limited to Parkinson's disease, dystonia, cerebellar disease, family history of Fragile X syndrome, traumatic brain injury, alcohol abuse or withdrawal, benzodiazepine abuse or withdrawal, multiple sclerosis, polyneuropathy, and endocrine states such as hyperthyroidism.

E 6. Prior magnetic resonance-guided focused ultrasound or surgical intervention for ET such as deep brain stimulation or thalamotomy.

E 7. Botulinum toxin injection for ET in the 6 months prior to Screening.

E 8. Unwilling or unable to discontinue primidone.

E 9. Unwilling or unable to refrain from alcohol 24 hours before and during clinical trial visits. Or regular use of alcohol that would preclude abstinence from alcohol in this period, in the judgement of the Investigator.

E 10. Substance use disorder in the judgement of the Investigator

E 11. Sporadic use of a benzodiazepine, sleep medication or anxiolytic, that in the judgement of the Investigator or Sponsor would confound the assessment of tremor. Stable use at a consistent dose not exceeding the equivalent of 2 mg/day of lorazepam (see Section 6.5.2) is allowed as long as tremor persists against the background of regular medication use.

E 12. Use of prescription or non-prescription products and food known to be strong inhibitors or inducers of CYP3A4 or known to be a P-gp substrate (see Section 6.5.1) which cannot be discontinued at least 5 half-lives or 14 days prior (whichever is the longer period of time) to Baseline and withheld throughout the clinical trial, including primidone.

E 13. The participant has any of the following at the Screening visit: a serum total bilirubin value >1.5×ULN; a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2×ULN. As an exception, participants that present

with elevated bilirubin in the absence of elevations in ALT or AST that fits the pattern of Gilbert's syndrome may be enrolled after discussion with the medical monitor if their conjugated bilirubin is within the ULN.

E 14. Criterion removed from protocol in Version 5.0.

E 15. History of any suicide attempt within the past 2 years.

E 16. History of structural heart disease (eg, congestive heart failure, depressed ejection fraction or left ventricular hypertrophy) or clinically significant cardiac arrhythmias (eg ventricular tachycardia) excluding sinus arrhythmia.

E 17. History of cancer treated with chemotherapy

E 18. Any other significant disease, disorder, laboratory abnormalities, or environmental factor that, in the opinion of the Investigator or Sponsor, may either put the participant at risk due to participation in the clinical trial, may influence or confound the result of the clinical trial, or affect the participant's ability to participate in the clinical trial.

E 19. Has previously received treatment with PRAX-944 in any clinical trial (including Part A of the current trial for participants enrolling in Part B)

TEST PRODUCT, REFERENCE THERAPY, AND ADMINISTRATION

20 mg PRAX-944 MR7 tablets or matching placebo will be administered orally and provided in pre-packaged containers to the participants.

DOSE/ROUTE/REGIMEN

Part A

All participants will receive PRAX-944 orally, 20 mg QAM for 7 days and 40 mg QAM for 7 days.

Part B

Open-label Titration

The planned titration schedule for PRAX-944 is as follows:

- 20 mg QAM for 3 days
- 40 mg QAM for 4 days
- 60 mg QAM for 7 days
- 80 mg QAM for 7 days
- 100 mg QAM for 7 days
- 120 mg QAM for 14 days

[redacted]

SAMPLE SIZE

The sample size of each part (up to 12 participants) 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. Part B sample size may be increased to up to 24 participants to ensure inclusion of a broad range of tremor severity. 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.

STATISTICAL METHODS

For all data displays, separate summaries will be generated for each part of the clinical trial. For the randomized portion of Part B, data will be summarized by the randomized continuation treatment. Safety, tolerability, PK, and efficacy variables will be summarized using descriptive statistics. Descriptive summaries for categorical variables will include counts and percentage. Descriptive summaries for continuous variables will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Where appropriate, 95% confidence intervals (CIs) may be reported. Summaries will be presented by time point, where appropriate.

Unless specified otherwise, all data recorded will be listed by participant.

Reported values and change from baseline values in TETRAS Upper Limb score, TETRAS Performance subscale total and individual scores, [redacted]

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

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

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.

The PK Analysis Set includes all participants who received at least 1 dose of study drug and have at least 1 evaluable plasma concentration. The PK Analysis Set will be used for the analysis of plasma concentrations and PK parameters.

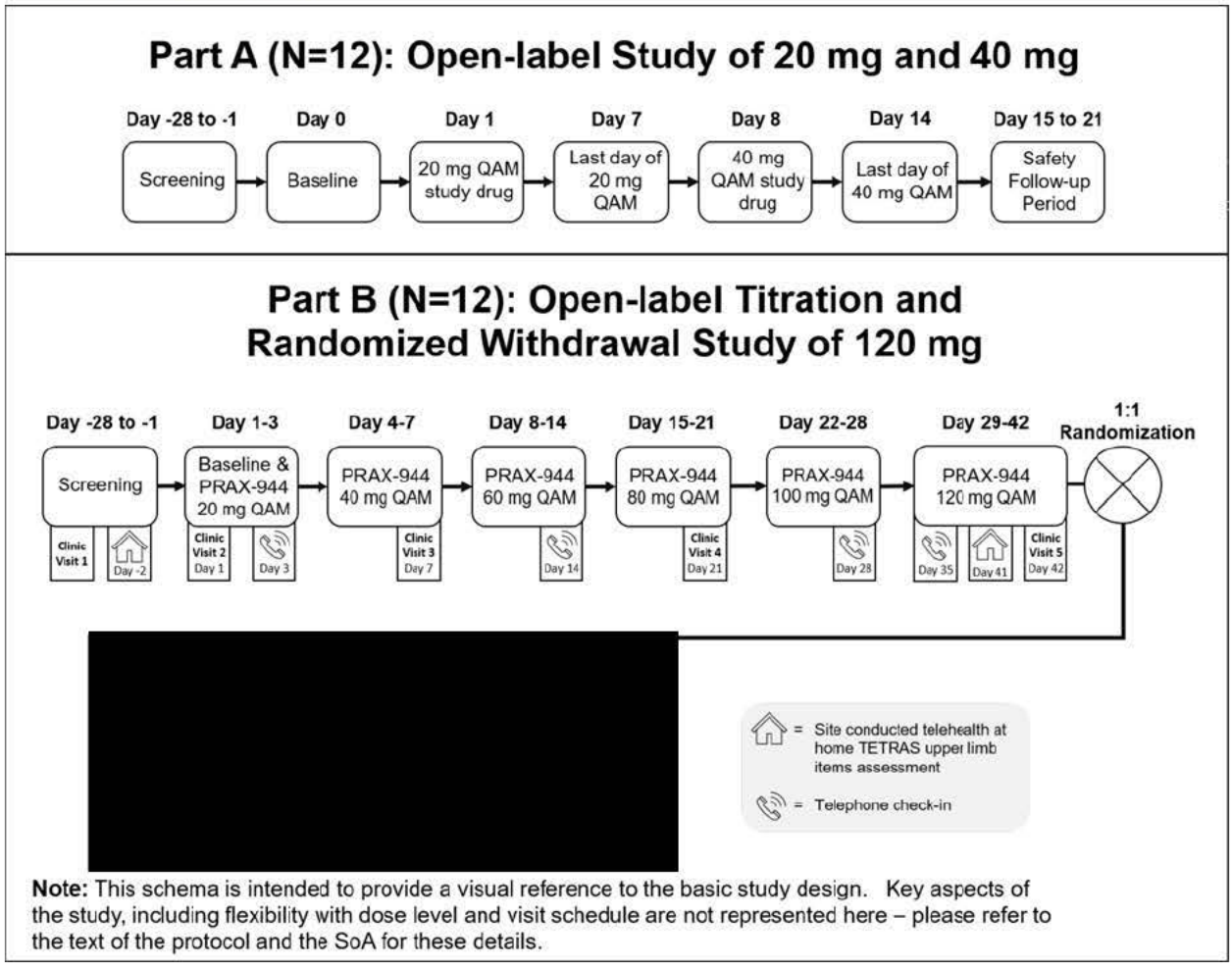
Adverse event data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants experiencing any treatment-emergent AE (TEAE) will be summarized by system organ class (SOC) and preferred term (PT). In addition, TEAEs will be summarized similarly by maximum severity and maximum relationship to PRAX-944. Serious AEs (SAEs) and TEAEs leading to discontinuation of PRAX-944 will be listed. Reported values and change from Baseline values in vital signs, ECG parameters, and hematology and clinical chemistry laboratory parameters will be summarized by time point.

For the C-SSRS, the number and percentage of participants with suicidal ideation or behavior events will be tabulated.

For Part A, standard PK parameters will be estimated using noncompartmental methods based on the concentration-time data. These parameters will include, where possible, C_{max}, T_{max}, $t_{1/2}$, $AUC_{0\text{-}tau}$, CL/F and Vd/F. Part B, concentration-time data will be summarized. Exploratory analyses examining the relationship between PK and efficacy parameters may be performed for the PK Analysis Set.

1.2. Study Schema

Figure 1: Study Schema



Note: This schema is intended to provide a visual reference to the basic study design. Key aspects of the study, including flexibility with dose level and visit schedule are not represented here – please refer to the text of the protocol and the SoA for these details.

1.3. Schedule of Activities

The schedule of clinical trial activities for Part A is presented in Table 2. The schedule of clinical trial activities for Part B is presented in Table 3.

Table 2: Schedule of Activities (SoA) – 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

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
TETRAS Video Recording [f]	X	X	X	X	X	X
TETRAS Performance Upper Limb Items with Accelerometer [g]		X	X	X	X	X
[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]				[redacted]	[redacted]	
[redacted]				[redacted]	[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.

* Day 0 (Baseline) activities may be combined with Day 1 activities, provided that Baseline activities are completed before dosing in the morning. Baseline testing of TETRAS Performance, TETRAS Video Recording, and TETRAS Performance Upper Limb Items with Accelerometer should all be done on the same day and can occur on Day 0 or Day 1 pre-dose, but not both.

[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 (if not done on Day 0) and 6 (±2) hours post-dose; Day 7 and Day 14, 6 (±2) hours post-dose.

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

[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 of the two accelerometer assessments should be completed immediately after the 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); Day 1, 7 and 14; 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).

Table 3: Schedule of Activities (SoA) – Part B

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)										
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	
Physical Examination	X		X*									
Clinical Laboratory Tests [c]	X		X*		X		X				X	
12-lead ECG [d]	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)										
C-SSRS (Baseline/Screening)	X											
C-SSRS (Since Last Visit)			X*		X		X				X	
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	
TETRAS Video Recording [f]	X		X		X		X				X	
TETRAS Performance Upper Limb Items with Accelerometer [g]	X		X		X		X				X	
Telehealth TETRAS Upper Limb Items Assessment		X								X		

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**		
TETRAS ADL[h]	X		X		X		X				X		
[redacted]													
[redacted]													
[redacted]													
QUEST			X		X		X				X		
[redacted]													
[redacted]													
PHARMACOKINETICS													
Blood Collection for Study Drug Concentration [i]			X		X		X				X		
STUDY DRUG													
Randomization [j]											X		
Study Drug Dispensing			X		X		X				X		
Study Drug Administration [k]			X *(open label)*										

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)										

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.

[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

Study Phase	Screening			Open-label Titration								Double-Blind Randomized Withdrawal	Safety Follow-up
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 56	Day 70/ET (End of Clinical Trial)
		Day -2 (-2)											

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.

2. INTRODUCTION

2.1. Background and Clinical Trial Rationale

Essential Tremor (ET) is one of the most common neurological disorders with a prevalence of nearly 1% (Louis 2010). It is characterized by a 6 to 12 Hz postural and kinetic tremor. Tremor typically occurs in the hands, arms, head, and voice, and is less common in the face, legs, and trunk. ET, by definition, is not associated with other neurological signs, although a resting tremor and impairments in balance, particularly tandem gait, have been described (Deuschl 2011). The diagnosis of ET is based on medical history and neurological exam as described in The International Parkinson and Movement Disorders Society Consensus Statement on the Classification of Tremors (Bhatia 2018).

There is a range in the severity of ET; some patients require no treatment, whereas others have severe disability with impairment in activities of daily living (ADLs) such as dressing and eating. Treatments for ET include pharmacological therapies, regional injection of botulinum toxin (off-label usage), and surgical therapies for those with severe disability. The most effective pharmacological therapies are propranolol and primidone. They have limited efficacy, with about 50% of patients having a durable yet incomplete response. Dose-limiting side effects are common and include bradycardia for propranolol and sedation and dizziness for primidone (Deuschl 2011). Surgical therapies, including deep brain stimulation and ablation of the nucleus ventralis intermedius of the thalamus, are effective but they are reserved for medically refractory patients due to the risks associated with brain surgery. Many patients who are eligible for surgical therapies do not elect to have these procedures (Elias 2016). Thus, there is a high unmet need for efficacious and well-tolerated pharmacological therapies for ET.

While the genetics and pathophysiology of ET is not fully understood, it is thought to involve abnormal activity of cerebellar afferent and efferent pathways. This network consists of input from the inferior olive to the cerebellar cortex, and outflow through deep cerebellar nuclei to the ventral thalamus and cortex (Park 2013). Low voltage, T-type calcium (Ca^{2+})-channels in the inferior olive and thalamus may play a role in the pathogenesis and treatment of ET. The T-type Ca^{2+}-channel family is comprised of 3 different isoforms: $Ca_V3.1$, $Ca_V3.2$, and $Ca_V3.3$. These channels are involved in generation of physiological and pathophysiological rhythms in the brain. In the harmaline rodent model of ET, synchronous neuronal discharges which are associated with T-type Ca^{2+}-channels are increased. The abnormal discharges were attenuated in mice lacking the gene that encodes for $Ca_V3.1$, and in wildtype mice, selective knockdown of $Ca_V3.1$ in the inferior olive by shRNA suppressed the harmaline-induced tremor (Park 2010). The non-selective Ca^{2+}-channel blocker ethosuximide was found to suppress tremor in the harmaline model and in a genetic model of ET, in a dose-dependent fashion (Handforth 2010).

In a human (electroencephalogram) EEG/polysomnography clinical trial, PRAX-944 showed robust suppression of the sigma frequency band during non-rapid eye movement (NREM) sleep, a marker of sleep spindle activity, at the 20 mg, 40 mg, and 60 mg dose levels. Sleep spindles are prominent oscillations of 11 to 15 Hz observed in the human scalp EEG during NREM sleep that are mediated by activation of T-type Ca^{2+}-channels in the thalamus. Thus, these data suggest that PRAX-944 blocks T-type Ca^{2+}-channels in the central nervous system (CNS) at well-tolerated doses.

The aim of this development program is to evaluate whether oral administration of PRAX-944 can provide therapeutic benefit to patients with ET. The study is divided into 2 parts: Part A is designed to study the dose titration from 20 to 40 mg every morning (QAM) (ie, 2 weeks with 7 days at each dose level) and Part B is designed to study the dose titration from 20 to up to 120 mg QAM with at least 14 days of dosing at the highest tolerated dose for each participant.

2.2. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PRAX-944 may be found in the Investigator's Brochure (IB).

2.3. Known Potential Benefits

Since PRAX-944 has not yet been studied in the ET population, there are no known benefits.

2.4. Known Potential Risks

In the Z944-104 study, administration of 20 and 40 mg doses of PRAX-944 [redacted] on Day 1 of dosing was well tolerated, but a 60 mg single dose led to nausea and vomiting. In addition, a 20 mg daily dose and a 40 mg daily dose, each administered for 8 days, were determined to be safe and tolerable in healthy volunteers. More recently, in the completed PRAX-944-105 study, daily doses up to 120 mg were determined to be safe and well tolerated in healthy volunteers following a titration schedule nearly identical to the schedule planned for this clinical trial.

The more common (5 or more in 100) or medically relevant AEs that have occurred with PRAX-944 are as follows: feeling abnormal or dizzy, headache, nausea, elevated mood, visual hallucinations, drowsiness, difficulty concentrating, skin tingling, fatigue, numbness, tremor, poor sleep, feeling anxious, spinning sensation, vomiting, and strange dreams (see IB Section 6 for additional information). Most of these side effects were short-lived, and all symptoms resolved.

No serious AEs (SAE)s have been reported with PRAX-944.

[redacted]

3. OBJECTIVES AND ENDPOINTS

To evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of PRAX-944 in adults with ET.

3.1. 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: o TETRAS Performance subscale total score o Accelerometer-based upper limb score (bilateral sum of items 4a, 4b, and 4c) o 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]

Objective	Endpoint
[redacted]	

3.2. 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: o TETRAS Performance subscale total score o Accelerometer-based upper limb score (bilateral sum of items 4a, 4b, and 4c) o TETRAS Performance individual item scores

Objective	Endpoint
• 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: o TETRAS ADL subscale score o Quality of Life in Essential Tremor Questionnaire (QUEST) total and subscale scores
Exploratory	
[redacted]	

Objective	Endpoint
[redacted]	[redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall 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 an onset before age 65.

The clinical trial will be conducted in 2 parts (Part A and Part B). Both parts will consist of 3 periods: Screening/Baseline, Intervention, and Safety Follow-up.

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.

Participants who received study drug in Part A are not eligible for Part B (see Exclusion Criterion #19).

4.1.1. 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 procedures, participants will provide written informed consent to participate in the clinical trial. Key Screening assessments will include medical history, demographics, physical examination, drug screen, clinical laboratory evaluations and serum pregnancy for women of childbearing potential, 12-lead ECG, vital signs, C-SSRS, assessment of ET severity using the TETRAS Performance subscale (including a video for independent review of eligibility), and a review of concomitant medications. To be eligible, potential participants who are taking prohibited medications will need to successfully discontinue these medications for at least 5 half-lives or 14 days prior (whichever is the longer period of time) before the first dose of study drug.

For those participants requiring the 14 additional days in the Screening period to discontinue primidone, all or some of the Screening assessments may need to be repeated, pending approval by the Sponsor's Medical Monitor.

For participants in **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. In addition, Baseline efficacy assessments should either be conducted on Day 0 or Day 1 pre-dose, but not both to avoid learning effects.

For participants in **Part B**, [redacted] will also be completed with accelerometry at Screening and via telehealth on Day -2 of the Screening period. The Screening telehealth visit is needed to ensure participants can complete the [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 Table 3) may be completed on Day -1.

4.1.2. Intervention Period

4.1.2.1. 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 again 6 hours post-dose. After the first dose, participants will continue QAM dosing at home after breakfast through Day 7. Participants will return to the clinic on Day 7 for efficacy testing at the 20 mg dose level. On Day 8, the dose will increase to 40 mg QAM after breakfast through Day 14 for efficacy testing at the 40 mg dose level. Participants will return to the clinic on Day 14 for efficacy testing at the 40 mg dose level. Participants who agree to optional additional PK sampling will remain overnight in the clinic on Day 1, Day 7, and Day 14.

Key safety measures will include clinical laboratory evaluations, 12-lead ECG, C-SSRS, and vital signs (Table 2). Key efficacy assessments will include the TETRAS Performance subscale, [redacted] (Table 2). Blood samples will be obtained for the determination of PRAX-944 plasma concentrations using a validated bioanalytical method and may also be used for exploratory method development and/or metabolite characterization.

AEs and concomitant medication use and procedures will be monitored from the time of informed consent to Day 21 (±1 day). At that time, participants will have completed the clinical trial. Participants who received study drug in Part A are not eligible for Part B (see Exclusion Criterion #19).

4.1.2.2. Part B

4.1.2.2.1. Open-label Titration Phase

On Day 1, participants will receive a 20 mg dose of PRAX-944 on an empty stomach (at least 1 hour before breakfast). 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 least 1 hour before breakfast at home.

Participants will continue taking PRAX-944 20 mg QAM at home through Day 3.

On Day 3, participants will receive a telephone call from site staff to inquire about AEs and concomitant medications, confirm dose escalation, and remind the participant about the number of study drug tablets to take on Day 4 through Day 7.

On Day 4, participants will escalate to 40 mg QAM through Day 7, when they will return to the clinic for safety assessments and efficacy testing. On Day 8, participants should escalate to 60 mg QAM through Day 14.

On Day 14, participants will receive a telephone call from site staff to inquire about AEs and concomitant medications, confirm dose escalation, and remind the participant about the number of study drug tablets to take on Day 15 through Day 21.

On Day 15, participants should escalate to 80 mg QAM through Day 21, when they will return to the clinic for safety assessments and efficacy testing. On Day 22, participants should escalate to 100 mg QAM through Day 28.

On Day 28, participants will receive a telephone call from site staff to inquire about AEs and concomitant medications, confirm dose escalation, and remind the participant about the number of study drug tablets to take on Day 29 through Day 42.

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. The dose on Day 42 will be taken in the clinic (see Section 4.1.2.2.2 below).

On Day 35, participants will receive a telephone call from site staff to inquire about AEs and concomitant medications.

On Day 41, participants will complete a TETRAS Performance Upper Limb assessment via a telehealth visit.

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. The Investigator should discuss the decision to continue at a lower dose level with the Sponsor and Medical Monitor. Participants can only change to a lower dose level once, and no dose changes may occur after Day 36.

4.1.2.2.2. Double-blind Randomized Withdrawal Phase

On Day 42, participants will complete the final clinic visit of the open-label titration phase. Participants will receive their dose of PRAX-944 administered in the clinic on an empty stomach (at least 1 hour before breakfast). 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.

After Day 42, participants will 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.

4.1.3. Safety Follow-up Period

4.1.3.1. 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 (±1 day) for the final clinical trial assessments (Table 2).

[redacted]

4.1.4. Clinical Trial Duration

Participants will be part of the clinical trial for the following time intervals:

4.1.4.1. Part A

Screening/Baseline Period	Up to 28 days (+14 days if on primidone)
Intervention Period	14 days
Safety Follow-up Period	7 days
Total Participation	Up to 49 days (63 days if on primidone)

4.1.4.2. Part B

Screening/Baseline Period	Up to 28 days (+14 days if on primidone)
[redacted]	
Safety Follow-up Period	14 days
Total Participation	Up to 98 days (112 days if on primidone)

4.2. Scientific Rationale for Clinical Trial Design

This is the first trial of PRAX-944 in ET.

4.3. Justification for Dose

The dose range of up to 120 mg QAM is based on the observed safety, tolerability and pharmacodynamic biomarker data in healthy volunteers. The [redacted] was well tolerated at doses of up to 40 mg/day over 8 days in the z944-104 study and 120 mg/day over 4 days following a 27-day titration in the PRAX-944-105 clinical trial. The titration completed in PRAX-944-105 is nearly identical to the titration schedule used in this clinical trial.

[redacted]

[redacted]

4.4. Clinical Trial Committees

The Sponsor will review ongoing safety data. The clinical trial may be stopped, or clinical trial enrollment suspended if:

- The Sponsor, in consultation with the Principal Investigators, consider that the number and/or severity of AEs justify discontinuation of the clinical trial
- The Sponsor makes a decision to do so

4.5. End of Clinical Trial Definition

A participant is considered to have completed the clinical trial if he/she has completed the clinical trial intervention period including the last visit as shown in the Schedule of Activities (SoA).

The end of the clinical trial is defined as the date of the last visit of the last participant in the clinical trial.

5. POPULATION

The intended population is participants with signs and symptoms of ET for at least 3 years who meet all eligibility criteria. If a participant's signs and symptoms are judged by the investigator to be due to the diagnosis of ET, it is acceptable for them to also have one or more of the following ET plus signs:

- Mild dystonic posturing
- Mild rest tremor in the setting of advanced ET and in the absence of other features of Parkinsonism
- Intention tremor
- Mild increase in tandem gait difficulty

The severity of these additional signs and the primary diagnosis of ET must be agreed upon by the central video reviewer.

Source documentation should capture both the unlikely alternate diagnoses and the additional ET plus signs.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Number of Participants

5.1.1. Part A

Up to 12 participants are planned to be administered PRAX-944.

5.1.2. Part B

Approximately 12 participants are planned to be administered PRAX-944 for the first 42 days followed by randomization (1:1) to 2 additional weeks on the highest tolerated dose of PRAX-944 or placebo. Up to 12 additional participants may be enrolled at the discretion of the Sponsor to ensure inclusion of a broad range of tremor severity.

5.1.3. Participant Replacement

Participants who withdraw from either Part A or Part B prior to completion of the clinical trial may be replaced at the discretion of the Sponsor. No more than 6 participants in either part of the study will be replaced.

5.2. Inclusion Criteria

A participant must meet the following criteria at Screening and Baseline (unless otherwise specified) to be eligible to participate in this clinical trial:

I 1. Male or non-pregnant, non-lactating female aged 18 years or older.

I 2. Willing and able to understand and sign an informed consent document indicating that he/she understands the clinical trial purpose, the clinical trial procedures, and that he/she is willing to participate in the clinical trial and comply with the protocol.

I 3. Body mass index (BMI) at Screening between 18 and 40 kg/m^2, inclusive.

I 4. Clinical diagnosis of ET consistent with Movement Disorders Society Criteria, a duration of ET of at least 3 years and with onset before the age of 65.

I 5. Moderate to severe ET as defined by the following:

a. A combined bilateral score of ≥10 on the TETRAS Upper Limb items 4 a, b, c. (UL tremor severity at Screening will be confirmed by central video review, for eligibility)

OR

b. A score of ≥2 on 2 or more of the following TETRAS activities of daily living (ADL) subscale items: (2) Feeding with a spoon, (3) Drinking from a glass, (5) Dressing, (6) Pouring, (9) Writing

OR

c. A score of ≥2 on 1 of the following TETRAS ADL subscale items: (2) Feeding with a spoon, (3) Drinking from a glass, (5) Dressing, (6) Pouring, or (9) Writing AND a score of ≥2 on both of the following TETRAS ADL subscale items: (10) Working and (12) Social Impact

Note: ET severity at Baseline will be confirmed by the Investigator at the clinical trial site.

I 6. Those currently receiving any medication for their ET must be willing and able to discontinue all but 1 tremor medication and be on a stable dose for at least 28 days.

I 7. Willing to comply with medically acceptable method of contraception as defined in Section 5.4.3.

5.3. Exclusion Criteria

A participant who meets any of the following criteria at Screening or Baseline (unless otherwise specified) will be excluded from this clinical trial:

E 1. Known hypersensitivity to any component of the formulation of PRAX-944.

E 2. Unwilling or unable to refrain from episodic use of medication(s)/substance(s) that might interfere with the evaluation of tremor during the trial. Stable use of medication(s)/substance(s) that might impact tremor, including beta-agonist bronchodilators, is allowed so long as the tremor is judged by the investigator to be primarily due to the participant's ET diagnosis.

E 3. Trauma to the nervous system within 3 months preceding the onset of tremor.

E 4. Clinical evidence of psychogenic tremor as ascertained by the Investigator.

E 5. History of other medical, neurological or psychiatric condition that may explain or cause tremor, including but not limited to Parkinson's disease, dystonia, cerebellar disease, family history of Fragile X syndrome, traumatic brain injury, alcohol abuse or withdrawal, benzodiazepine abuse or withdrawal, multiple sclerosis, polyneuropathy and endocrine states such as hyperthyroidism.

E 6. Prior magnetic resonance-guided focused ultrasound or surgical intervention for ET such as deep brain stimulation or thalamotomy.

E 7. Botulinum toxin injection for ET in the 6 months prior to Screening.

E 8. Unwilling or unable to discontinue primidone.

E 9. Unwilling or unable to refrain from alcohol 24 hours before and during clinical trial visits. Or regular use of alcohol that would preclude abstinence from alcohol in this period, in the judgement of the Investigator.

E 10. Substance use disorder in the judgement of the Investigator

E 11. Sporadic use of a benzodiazepine, sleep medication or anxiolytic, that in the judgement of the Investigator or Sponsor would confound the assessment of tremor. Stable use at a consistent dose not exceeding the equivalent of 2 mg/day of lorazepam (see Section 6.5.2) is allowed as long as tremor persists against the background of regular medication use.

E 12. Use of prescription or non-prescription products and food known to be strong inhibitors or inducers of CYP3A4 or known to be a P-gp substrate (see Section 6.5.1) which cannot be discontinued at least 5 half-lives or 14 days prior (whichever is the longer period of time) and withheld throughout the clinical trial, including primidone.

E 13. The participant has any of the following at the Screening visit: a serum total bilirubin value >1.5×ULN; a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2×ULN. As an exception, participants that present with elevated bilirubin in the absence of elevations in ALT or AST that fits the pattern of Gilbert's syndrome may be enrolled after discussion with the medical monitor if their conjugated bilirubin is within the ULN.

E 14. Criterion removed from protocol in Version 5.0.

E 15. History of any suicide attempt within the past 2 years.

E 16. History of structural heart disease (eg, congestive heart failure, depressed ejection fraction or left ventricular hypertrophy) or clinically significant cardiac arrhythmias (eg ventricular tachycardia) excluding sinus arrhythmia.

E 17. History of cancer treated with chemotherapy

E 18. Any other significant disease, disorder, lab abnormalities, or environmental factor that, in the opinion of the Investigator or Sponsor, may either put the participant at risk due to participation in the clinical trial, may influence or confound the result of the clinical trial, or affect the participant's ability to participate in the clinical trial.

E 19. Has previously received treatment with PRAX-944 in any clinical trial (including Part A of the current trial for participants enrolling in Part B)

5.4. Lifestyle Considerations

Participants must refrain from donating plasma, blood, or blood products (other than for this clinical trial) from Day -1 until 93 days following last dose of study drug. Participants must refrain from adopting any new exercise programs during the trial.

5.4.1. Meals and Dietary Restrictions

Grapefruits and grapefruit juice must be avoided during participation in the clinical trial.

Participants should be instructed to refrain from alcohol 24 hours before and during clinical trial visits.

For Part B on Day 1 and Day 42, PRAX-944 is to be administered in the clinic on an empty stomach (at least 1 hour before breakfast). Only water and allowable concomitant medications are permitted prior to breakfast on Day 1 and Day 42. For dosing on other days, participants should be instructed to dose QAM at least 1 hour before breakfast.

5.4.2. Activity Restrictions

Because PRAX-944 may cause sedation and dizziness, caution must be used in activities requiring mental alertness such as driving a car or operating heavy machinery. This impairment may be made worse by other medications that also cause sedation or reduce alertness.

5.4.3. Contraception

The effects of PRAX-944 on fetal development have not been ascertained. As such, all participants must agree to an approved form, or forms, of contraception. Participants will be provided information on acceptable methods of contraception as part of the informed consent process and will sign an informed consent form (ICF) stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during and after the course of this clinical trial. The approved options are listed below. Every participant must agree to 1 of the 3 main options (1, 2 or 3):

1. Male or female participants may agree to total (true) abstinence (when this is in line with their preferred and usual lifestyle). Total (true) abstinence is defined as the strict avoidance of all forms of sexual activity. In males, this must extend from Day -1 through 90 days + 5 half-lives (ie, total of 93 days) after the last dose of study drug. In females, this must extend from Day -1 through 30 days + 5 half-lives (ie, total of 33 days) after the last dose of study drug. Periodic abstinence (eg, calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods.
2. Participants do not need to use contraception if either they or their partner are sterile. Sterility is defined as follows:
    a. A female is considered to be surgically sterile if she has had 1 of the following procedures: tubal ligation, tubal occlusion, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
    b. A female is considered to be postmenopausal and sterile if it has been at least 2 years since last regular menses and follicle-stimulating hormone (FSH) >40 IU/L, or at least 5 years since last regular menses, confirmed before any study drug is administered.
    c. A male participant is considered sterile if he is at least 1-year post vasectomy and has obtained documentation of the absence of sperm in their ejaculate.
3. If neither option 1 nor option 2 criteria are met, then the participant must agree to using a combination of 2 of the highly effective methods listed below (a+a, a+b or a+c or b+c):
    a. Barrier contraception with or without spermicide, eg, male condom or female diaphragm with or without spermicide (foam, gel, film, cream, or suppository);

b. Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy;
c. Placement of an intrauterine device or intrauterine system.

Note:

- A participant can agree to using 2 methods, 1 of which is primarily dependent on their partner. For example, a male participant can agree to a barrier with spermicide and for his female partner to use oral hormonal contraception. Similarly, a female participant can agree to using oral hormonal contraception and for her male partner to use a barrier with spermicide.
- Male participants must use 2 highly effective methods from Day -1 through 90 days + 5 half-lives (3 days) after the last dose of study drug (ie, 93 days).
- Female participants must use 2 highly effective methods from Day -1 through 30 days + 5 half-lives (3 days) after the last dose of study drug (ie, 33 days).

5.4.4. Sperm and Ova Donation

- Male participants must refrain from sperm donation from Day -1 through 90 days + 5 half-lives (+3 days) after the last dose of study drug.
- Female participants must refrain from ova donation from Day -1 through 30 days + 5 half-lives (+3 days) after the last dose of study drug.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the clinical trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this clinical trial (screen failure) may be rescreened after consultation with the Sponsor and Medical Monitor.

6. CLINICAL TRIAL INTERVENTION

Clinical trial intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a clinical trial participant according to the clinical trial protocol.

6.1. Study Drug(s) Administered

20 mg PRAX-944 [redacted] or matching placebo will be administered orally and provided in pre-packaged containers to the participants.

6.1.1. Part A

All participants will receive PRAX-944 orally, 20 mg QAM for 7 days and 40 mg QAM for 7 days.

6.1.2. Part B

6.1.2.1. Open-label Titration

The planned titration schedule for PRAX-944 is as follows:

- 20 mg QAM for 3 days
- 40 mg QAM for 4 days
- 60 mg QAM for 7 days
- 80 mg QAM for 7 days
- 100 mg QAM for 7 days
- 120 mg QAM for 14 days

[redacted]

Table 4: Study Drug Information

ARM Name	Open-Label Part A	Open-label Part B	Double-blind PRAX-944	Double-blind Placebo
Intervention Name	PRAX-944			Placebo
Type	Drug			Placebo
Dose Formulation	Modified-release tablet			Tablet
Unit Dose Strength(s)	20 mg			Placebo
Dosage Level(s)	• 20 mg QAM Day 1 through Day 7 • 40 mg QAM Day 8 through Day 14	• 20 mg QAM Day 1 through Day 3 • 40 mg QAM Day 4 through Day 7 • 60 mg QAM Day 8 through Day 14 • 80 mg QAM Day 15 through Day 21 • 100 mg QAM Day 22 through Day 28 • 120 mg QAM Day 29 through Day 42	• 120 mg or highest tolerated dose QAM Day 43 through Day 56	• Placebo QAM Day 43 through Day 56
Route of Administration	Oral			
[redacted]				None
Sourcing	Provided centrally by the Sponsor			
Packaging and Labeling	Study drug will be provided in pre-packaged containers. Each container will be labeled as required per country requirements.			

6.2. Preparation/Handling/Storage/Accountability

The following requirements for handling, storing, and accounting for study drug must be followed:

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only participants enrolled in the clinical trial may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information, including for the final disposition of unused study drugs are provided in the Pharmacy Manual.

6.3. Randomization and Blinding

This trial includes both open-label (unblinded) and double-blind phases.

Study drug will be dispensed at the clinical trial visits as summarized in the SoA (Table 2 and Table 3). Returned study drug must not be re-dispensed.

[redacted]

Randomization in a 1:1 fashion to one of these groups may be completed at any time on Day 37 through 42. The assignments will be blinded to all participants, Investigators, site personnel, and Sponsor personnel.

Replacement randomization numbers will be used as needed for any participant that is replaced in Part B.

6.3.1. Breaking the Blind

In the event of a medical emergency, where knowledge of the study drug assignment is needed to medically treat the participant, the treatment assignment of an individual participant can be obtained via code break envelopes. Whenever possible, the Principal Investigator should consult with the Medical Monitor or the Sponsor Medical Director prior to unblinding a participant. If that is not possible, the Investigator may unblind to treat a medical emergency without consultation. Code breaks must be promptly communicated to the Medical Monitor and Sponsor Medical Director and detailed in the source documentation.

6.4. Study Drug Compliance

Participant compliance with study drug will be assessed at each visit. Compliance will be assessed throughout the clinical trial by participant reporting, measuring plasma exposure, and return of used and unused PRAX-944 containers. This clinical trial will also employ a medication adherence monitoring platform (“Platform”). The Platform uses artificial intelligence

on smartphones to confirm medication ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions.

Deviation(s) from the prescribed dosage regimen should be documented.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving from 30 days prior to Screening or receives during the clinical trial must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency of administration

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

[redacted]

6.5.2. Permitted Medications

Participants may take only 1 concomitant medication for their ET and must be on stable doses of that 1 medication for at least 28 days prior to Screening in the clinical trial. Stable use at a consistent dose not exceeding the equivalent of 2 mg/day of lorazepam is allowed as long as tremor persists against the background of regular medication use (sporadic use of a benzodiazepine, sleep medication or anxiolytic, that in the judgement of the Investigator or Sponsor would confound the assessment of tremor, is not allowed). Concomitant use of allowable benzodiazepines must be limited to a daily dosage equivalent of 2 mg of lorazepam (refer to Appendix 3).

6.6. Dose Modification

No dose modifications are permitted in Part A or the Part B double-blind randomized withdrawal phase.

In the Part B open-label titration phase, participants may return to a lower dose of PRAX-944 after escalating due to tolerability or safety concerns. The Investigator should discuss the decision to continue at a lower dose level with the Sponsor and Medical Monitor. Participants can only change to a lower dose level once. No dose changes are permitted after Day 36.

The Sponsor may discontinue any dose of PRAX-944 based on ongoing monitoring of safety and tolerability.

6.7. Intervention After the End of the Clinical Trial

There is no intervention following the end of the clinical trial. Participants will continue to receive standard of care for what is normally expected for their condition.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue study drug. If study drug is permanently discontinued, the participant will remain in the clinical trial to be evaluated for safety and efficacy. See the SoA for data to be collected at the time of early termination for each part, if applicable.

7.1.1. Temporary Discontinuation

Temporary discontinuations of study drug is allowed on a case-by-case basis, pending approval from the Sponsor.

7.1.2. Rechallenge

Rechallenges of study drug are allowed on a case-by-case basis in Part A, pending approval from the Sponsor.

One dose reduction is permitted in Part B but thereafter rechallenge is not allowed. No dose changes after Day 36 are allowed.

7.2. Participant Discontinuation/Withdrawal from the Clinical Trial

A participant may withdraw from the clinical trial at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the clinical trial, if possible, an early termination visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of clinical trial discontinuation and follow-up and for any further evaluations that need to be completed for each part.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the clinical trial, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site clinical trial records.

Participants who do not complete 14 days of study drug in Part A or 56 days of study drug in Part B or do not complete their scheduled safety, efficacy, or PK assessments may be replaced to ensure a sufficient number of participants are evaluable. No more than 6 participants in either part of the study will be replaced.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical trial site.

The following actions must be taken if a participant fails to return to the clinic for a required clinical trial visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the clinical trial.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the clinical trial.

8. CLINICAL TRIAL ASSESSMENTS AND PROCEDURES

Clinical trial procedures and their timing are summarized in the SoA (Table 2 and Table 3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug. If this discussion is not possible and the concern is urgent, the Investigator may discontinue study drug without consultation, but these situations are expected to be rare.

Adherence to the clinical trial design requirements, including those specified in the SoA, is essential and required for clinical trial conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screen failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 2 and Table 3).

For Part A, the amount of blood collected from each participant over the duration of the clinical trial, including any extra assessments that may be required, will be approximately 50 mL with sparse sampling for PK or 180 mL with serial sampling for PK. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For Part B, the amount of blood collected from each participant over the duration of the clinical trial, including any extra assessments that may be required, will be approximately 115 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

A suggested order of assessments for Part B is provided in the Assessment Manual.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Table 2 and Table 3). Efficacy will be measured using the following instruments:

8.1.1. TETRAS

The TETRAS was developed by the Tremor Research Group (TRG; www.tremorresearchgroup.org) to quantify ET severity and its impact on ADLs. This scale requires only pen and paper and can be completed in about 10 minutes. The full scale has 2 sections, 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. The TETRAS scale demonstrated face validity, inter- and intra-rater reliability, and sensitivity to change (Elble 2016).

For Part B, 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

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.

8.1.1.1. Performance Subscale

There are 9 items covering different body regions in the Performance subscale. Each Performance subscale item is rated on a scale of 0 to 4, with higher scores indicating higher tremor severity. 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 Performance subscale score is calculated as the sum of all 9 items and ranges from 0 to 64. Toward interpreting certain items (eg, Archimedes Spirals, handwriting and dot approximation), it is important to note whether the participant's dominant hand is their left or their right.

8.1.1.2. Upper Limb Item

Item 4 of the Performance subscale is the upper limb item. For this item, 3 tasks are performed on each side of the body: 4a) postural tremor with upper limbs held forward and horizontally, 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, with higher scores indicating higher tremor amplitude of the upper limb. The upper limb total score is the sum of these 6 sub-items and ranges from 0 to 24.

The upper limb item will be assessed via clinician, Kinesia ONE (accelerometer), and video rating by an independent rater. The initial assessment of the upper limb item will be performed by the clinician with each task being performed for each side. The participant will then perform the same tasks while wearing an accelerometer. The accelerometer will record rotations and accelerations in the 3D space over time. As with the clinician assessment, each task will be performed for each side first for the right arm and then for the left. For the purposes of confirming eligibility, an independent central rater will score a video of the initial assessment described above.

For Part B, 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). Kinesia ONE assessments should be completed twice at each timepoint with the 2 assessments separated by at least 30 minutes.

[redacted]

8.1.1.4. TETRAS Telehealth 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 purpose of this assessment is to compare upper limb item scores obtained via a telehealth visit to scores obtained in the clinic to assess the reliability of telehealth assessments.

8.1.1.5. TETRAS Activities of Daily Living (ADL)

The TETRAS ADL subscale is a 12-item assessment of typical daily activities that are impacted by tremor. 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.

[redacted]

8.1.4. Quality of Life in Essential Tremor Questionnaire (QUEST; Part B Only)

The QUEST is a brief, 30-item, patient-reported ET-specific quality of life scale. 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. Respondents are also asked to indicate which tremor was perceived to impact a function or be associated with the feeling or attitude in question. The QUEST total and subscale scores are calculated as the sum of all applicable items divided by the number of applicable items times 100.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 2 and Table 3). AEs will be evaluated and reported (Section 8.4). Safety will be assessed as described below.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded (at Screening only).

8.2.2. Vital Sign Measurements

This assessment will measure changes in vital sign measurements, specifically of the following:

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure (systolic and diastolic) and pulse measurements will be preceded by at least 5 minutes of rest, in a quiet setting without distractions (eg, tablets, television,

mobile phones). These measurements will be assessed after the participant has been supine for at least 5 minutes, and standing for at least 2 minutes.

8.2.3. Electrocardiograms

This assessment will measure changes in ECG parameters, specifically:

- ECGs will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECGs will be read centrally.
- Triplicate measurement will be taken at Screening only; for all other timepoints, single measurement is acceptable. When triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.2.4. Clinical Safety Laboratory Assessments

This assessment will measure changes in laboratory values, specifically:

- The Investigator must review the laboratory report, document this review, and record laboratory values. Any clinically significant, adverse changes occurring during the clinical trial should be documented as AEs. Laboratory-assessment related AEs should be documented and follow as with other AEs.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
- Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- See Appendix 1 for the list of clinical laboratory tests to be performed and to the SoA (see Table 2 and Table 3) for the timing and frequency.

Refer to the Laboratory Manual for additional details on sample handling and processing.

8.2.4.1. Monitoring for Safety Laboratory Assessments of Special Interest

Renal function monitoring will be based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines and criteria for acute kidney injury (AKI)(Kellum 2012). According to the KDIGO guidelines, AKI is defined as any of the following:

- Increase in SCr by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; or
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days

If a participant’s laboratory values exceed these thresholds, dosing of that participant will be stopped and the laboratory tests will be repeated. Pending the results of these tests, a discussion will occur to determine pausing, stopping or continuing dosing the specific participant and/or the remainder of the participants in the study. Throughout the duration of the clinical trial,

participants should immediately notify the study team if there are any significant changes in their urine frequency or volume.

8.2.5. Columbia-Suicide Severity Rating Scale (C-SSRS) Measurements

The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in participants during participation in a clinical trial of centrally-acting drugs (Posner 2011). The C-SSRS is composed of 5 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with sub-questions assessing the severity. Two versions of the C-SSRS will be used in this clinical trial: the Baseline/Screening Version (at the Screening visit) and the Since Last Visit Version (at all other visits). It takes approximately 5 to 10 minutes to administer the C-SSRS. The tool should be administered via interview with the participant (by a trained operator/interviewer).

8.3. Pharmacokinetic Assessments

Blood samples will be collected for measurement of blood concentrations of PRAX-944 as specified in the SoA (Table 2 and Table 3). Samples collected may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the clinical trial. PRAX-944 plasma samples may also be used for additional exploratory method development and/or metabolite characterization purposes.

Refer to the Laboratory Manual for additional details on sample handling and processing.

8.4. Adverse and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or clinical trial procedures, or that caused the participant to discontinue the clinical trial.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AE and SAE information will be collected from the signing of the ICF until the end of the clinical trial at the time points specified in the SoA.

All SAEs and AEs of special interest will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Appendix 2.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. AEs of Special Interest

Any event of seizure, seizure-like phenomena, loss of consciousness, altered state of consciousness, tardive dyskinesia, acute dystonic reactions, akathisia, or acute Parkinsonian symptoms (eg, bradykinesia, tremor, cogwheel rigidity, mask-like faces) will be regarded as an adverse event of special interest in this trial and must be reported to the Sponsor within 24 hours.

8.4.6. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study drug through completion of the pregnancy.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Male participants will be instructed via the ICF to immediately inform the Investigator if their female partner becomes pregnant

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Fluctuations of individual items on the efficacy assessments that are consistent with the typical course of ET should not be interpreted as worsening or improvements of the overall condition. Changes in disease severity should be determined by the Investigator based on an assessment of the participant's overall condition.

[redacted]

8.6. Treatment of Overdose

The Sponsor does not recommend specific treatment for an overdose and care should be supportive in keeping with local institutional practices.

In the event of a documented or suspected overdose, the Investigator/treating physician should:

- Ensure the participant receives necessary medical care
- Contact the Medical Monitor immediately
- Closely monitor the participant for any AE/SAE, including laboratory abnormalities

The effects of overdose of PRAX-944 are unknown. As such, no specific antidote for PRAX-944 overdose is known. Although it is not expected that overdose will occur in this clinical trial, participants should be managed with appropriate supportive care should overdose with PRAX-944 inadvertently occur. Please also see the mitigation of overdose risk Section 6.10 in the IB.

Risks unrelated to PRAX-944 include those from collection of blood samples, including bruising, pain at the site, swelling, redness, bleeding, or infection.

8.7. Genetics

Genetics are not evaluated in this clinical trial.

8.8. Health Economics/Medical Resource Utilization and Health Economics

Health Economics/Medical Recourse Utilization and Health Economics parameters are not evaluated in this clinical trial.

9. STATISTICAL CONSIDERATIONS

This section outlines the general statistical methods contributing to the clinical trial design and planned analysis of clinical trial data. A comprehensive statistical analysis plan (SAP) will be developed and finalized prior to database lock and will provide a more detailed description of analysis sets, endpoint derivations (including any procedures for missing data), and analysis methods (including mock tables and listings).

9.1. Sample Size Determination

The sample size of each part (up to 12 participants) 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. Part B sample size may be increased to up to 24 participants to ensure inclusion of a broad range of tremor severity. 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.

9.2. Populations for Analyses

All data analyses will be performed using at least 1 of the following analysis sets.

Analysis Set	Description
Enrolled Analysis Set	All participants who sign an ICF and are provided with an enrollment number. The Enrolled Analysis Set will be used for all participant disposition analyses.
Safety Analysis Set	All participants who received at least 1 dose of study drug. Participants will be classified according to actual intervention received. The Safety Analysis Set will be used for all demographic, baseline characteristics, prior/concomitant medication, study drug exposure, and safety analyses.
Full Analysis Set	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.
PK Analysis Set	The PK Analysis Set includes all participants who received at least 1 dose of study drug and have at least 1 evaluable plasma concentration. The PK Analysis Set will be used for the analysis of plasma concentrations and PK parameters.

9.3. Statistical Analyses

The SAP will be developed and finalized prior to database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. For all data displays, separate summaries will be generated for each part of the clinical trial. For the randomized portion of Part B, data will be summarized by the randomized

continuation treatment. Safety, tolerability, PK and efficacy variables will be summarized using descriptive statistics. Descriptive summaries for categorical variables will include counts and percentage. Descriptive summaries for continuous variables will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Where appropriate, 95% confidence intervals (CIs) may be reported. Summaries will be presented by time point, where appropriate.

Unless specified otherwise, all data recorded will be listed by participant.

9.3.1. Efficacy Analyses

Reported values and change from baseline values in TETRAS Upper Limb score, TETRAS Performance subscale total and individual scores, TETRAS Upper Limb accelerometer score, TETRAS Upper Limb telehealth score, TETRAS ADL Subscale score, [redacted], QUEST total and subscale scores, [redacted] will be summarized by time point. In addition, change from baseline scores will also be analyzed using paired t-tests or similar methods. For [redacted], reported values will be summarized by time point.

9.3.2. Safety Analyses

Adverse event data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants experiencing any treatment-emergent AE (TEAE) will be summarized by system organ class (SOC) and preferred term (PT). In addition, TEAEs will be summarized similarly by maximum severity and maximum relationship to PRAX-944. SAEs and TEAEs leading to discontinuation of PRAX-944 will be listed. Reported values and change from baseline values in vital signs, ECG parameters, and hematology and clinical chemistry laboratory parameters will be summarized by time point.

For the C-SSRS, the incidence of suicidal ideation/behavior at any time will be summarized for each C-SSRS ideation, behavior, and ideation/behavior indicator.

9.3.3. Pharmacokinetic Analyses

For Part A, standard PK parameters will be estimated using noncompartmental methods based on the concentration-time data. These parameters will include, where possible, C_{max}, T_{max}, $t_{1/2}$, $AUC_{0\text{-}tau}$, CL/F, and Vd/F. Exploratory analyses examining the relationship between PK and efficacy parameters may be performed for the PK Analysis Set.

The PK parameters described are those normally calculated for this type of clinical trial; however, the actual parameters calculated may vary depending on the availability and viability of the data obtained. Other parameters may be added as appropriate. Final PK parameters to be reported will be detailed in the SAP or a separate PK analysis plan.

9.3.4. Other Analyses

PK and selected efficacy data may be utilized in a population PK analysis, which will be presented separately from the main clinical study report (CSR).

9.3.5. Interim Analyses

No formal interim analysis is planned for this clinical trial. Clinical trial data from Part A and open-label data from Part B will be reviewed on an ongoing basis.

10. REGULATORY, ETHICAL, AND CLINICAL TRIAL OVERSIGHT CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

This clinical trial will be conducted in accordance with this protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the clinical trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the clinical trial design, except for changes necessary to eliminate an immediate hazard to clinical trial participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the clinical trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the clinical trial at the site and adhering to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the clinical trial and for 1 year after completion of the clinical trial.

10.3. Informed Consent Process

The Investigator or his/her representative will explain the nature of the clinical trial to the participant or his/her legally authorized representative and answer all questions regarding the clinical trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/IEC or clinical trial center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the clinical trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the clinical trial.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.4. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal clinical trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5. Data Quality Assurance

All participant data relating to the clinical trial will be recorded on printed or electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit clinical trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this clinical trial including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Clinical trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the clinical trial is being conducted in accordance with the currently approved protocol and any other clinical trial agreements, ICH GCP, and all applicable regulatory requirements.

10.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the clinical trial.

The required source data should include sequential notes containing at least the following information for each participant:

- participant identification (name, date of birth, sex)
- documentation that participant meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- participation in trial (including trial number)
- trial discussed and date of informed consent
- dates of all visits
- documentation that protocol-specific procedures were performed
- results of efficacy parameters, as required by the protocol
- start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well)
- record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity)
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated)
- date of trial completion and reason for early discontinuation, if applicable

10.7. Clinical Trial Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the clinical trial to be fully documented and the clinical trial data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) Investigator's clinical trial file, and (2) participant clinical source documents.

The Investigator's clinical trial file will contain the protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

All clinical trial documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be

required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Investigator must notify the Sponsor before destroying any clinical trial records.

Should the Investigator wish to assign the clinical trial records to another party or move them to another location, the Sponsor must be notified in advance. If the Investigator cannot guarantee this archiving requirement at the clinical trial site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit.

10.8. Clinical Trial and Site Closure

The Sponsor reserves the right to close the clinical trial site or terminate the clinical trial at any time for any reason at the sole discretion of the Sponsor. Clinical trial sites will be closed upon clinical trial completion. A clinical trial site is considered closed when all required documents and clinical trial supplies have been collected and a clinical trial site closure visit has been performed.

The Investigator may initiate clinical trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a clinical trial site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study drug development

10.9. Clinical Study Report

A CSR will be prepared and provided to the regulatory agency(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared as applicable.

10.10. Publication Policy

The results of this clinical trial may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of clinical trial results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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12. APPENDICES

APPENDIX 1. CLINICAL LABORATORY EVALUATIONS

The tests detailed in Appendix Table 1 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.

Appendix Table 1: Protocol-Required Laboratory Assessments

Clinical Chemistry	**Hematology**	**Urinalysis**
Alanine aminotransferase (ALT) Alkaline phosphatase Aspartate aminotransferase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride 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 virus (HCV) antibody and HIV antibody/antigen Urinary albumin Urinary creatinine (Part A only) [redacted]

APPENDIX 2. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of Adverse Events

AE Definition
• An 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. • NOTE: 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.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the clinical trial. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • For efficacy studies: "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the clinical trial that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important Medical Event: • Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the clinical trial and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the study drug, as related or not related, based on clinical judgement and using all available information, and may include consideration of the following factors:
  - Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
  - The temporal association between study drug exposure and onset of the AE.
  - Whether the manifestations of the AE are consistent with known actions or toxicity of the study drug.
  - The AE resolved or improved with decreasing the dose or stopping use of the study drug (dechallenge). Judgement should be used if multiple products are discontinued at the same time.
- The causal relationship between the study drug and the AE will be assessed using one of the following categories:
  - Not Related: Factors consistent with an assessment of Not Related include:
    - Temporal relationship is lacking (eg, the event did not occur within a reasonable time frame following administration of the study drug); or
    - Other causative factors more likely explain the event (eg, a pre-existing condition, other concomitant treatments).
  - Related: Factors consistent with an assessment of Related include:
    - There is a positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of study drug); or
    - The AE is more likely explained by the investigational product than by another cause (ie, the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the study drug).

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting

- Email transmission of the SAE form is the preferred method to transmit this information.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE form within the designated reporting time frames.
- Contact Information for SAE reporting: Safety@novotech-cro.com

APPENDIX 3. ACCEPTABLE BENZODIAZEPINES FOR CONCOMITANT USE

Benzodiazepine Equivalency

	Approximately Equivalent Oral Dose, mg	Time to Peak Level, hours	Half-life, hours
Alprazolam (Xanax)	≤1	1-2	12
Bromazepam (Lexotan)	≤6	1-4	20
Chlordiazepoxide (Librium)	≤25	1-4	100
Clonazepam (Klonopin)	≤0.5	1-4	34
Clorazepate (Tranxene)	≤15	0.5-2	100
Diazepam (Valium)	≤10	1-2	100
Flurazepam (Dalmane)	≤30	0.5-1	100
Lorazepam (Ativan)	≤2	1-4	15
Nitrazepam (Mogadon)	≤10	0.5-2	30
Oxazepam (Serax)	≤30	1-4	8
Quazepam (Doral)	≤20	1.5	25-41
Temazepam (Restoril)	≤20	2-3	11
Triazolam (Halcion)	≤0.5	1-2	2

Adapted from: Farinde A. Benzodiazepine Equivalency Table 2018 [cited 2018 December 20]. Available from: https://emedicine.medscape.com/article/2172250-overview (Farinde 2018)