TITLE PAGE

Protocol Title: A Phase 2b, 12-week, Double-blind, Placebo-controlled, Randomized, Parallel-group, Multicenter Study of the Safety and Efficacy of JZP385 in the Treatment of Adults with Moderate to Severe Essential Tremor

Study Number: JZP385-201

Protocol Number: JZP385-201-04

Amendment Number: Amendment 04

Compound: JZP385

Brief Title: A Study of JZP385 in Adults with Moderate to Severe Essential Tremor

Study Phase: Phase 2b

Sponsor Name: Cavion, Inc., a subsidiary of Jazz Pharmaceuticals, Inc.

Legal Registered Address: 3170 Porter Drive, Palo Alto, CA, USA 94304

Regulatory Agency Identifier Number(s): IND: 130296
EudraCT Number: 2020-002463-61

Refer to the final page of this protocol for electronic signature and date of approval.

Sponsor Signatory:

{Please see appended electronic signature page.}

[redacted] **MD**
[redacted]
Clinical Development,
Neuroscience
Jazz Pharmaceuticals, Inc.

Date

Investigator Signatory:

[Name]
[Title]

Date

medical monitor name and contact information can be found in the Trial Site Binder (or equivalent).

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 04	Please see appended electronic signature page for the date.
Amendment 03	07 October 2022
Amendment 02	15 November 2021
Amendment 01	19 May 2021
Original Protocol	26 January 2021

Amendment 04

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for this amendment is to facilitate participant enrollment by allowing participants to enter the study without having to discontinue concomitant antitremor medications, unless these medications (eg, primidone) are prohibited in accordance with other exclusion criteria.

Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis (Table 1) 3 Objectives, Estimands and Endpoints 9.4.1.2 Intercurrent Event Strategies 9.4.2 Primary Estimand 9.4.3.1 Secondary Estimand	A new type of intercurrent event was added to account for any changes in concomitant medications after initiation of study intervention.	To align with the allowance of concomitant use of antitremor medication.
1.3 Schedule of Assessments 5.1 Inclusion Criteria 8.2.2 Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale (Table 5)	Clarification was added that the TETRAS-ADL subscale and the CGI-S scale are to be performed at Screening Visit 1 only for participants who do not need to washout from medications that impact tremor; otherwise, these assessments should be performed at Screening Visit 2.	To align with the allowance of concomitant use of antitremor medication.

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment 2.3.3 Overall Benefit: Risk Summary	Clarification was added that the potential risks associated with discontinuation of prior medications are relative to protocol-prohibited medications.	To ensure potential risks regarding discontinuation of any prior medications are clearly understood.
	The statement relative to the potential risk of untreated symptoms of ET for those who are randomized to placebo was modified to specify the risk applies only to those who discontinue protocol-prohibited antitremor medication (eg, primidone) in order to participate in the study.	To align with the allowance of concomitant use of anti-tremor medication.
1.1 Synopsis (Table 3) 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 9.4.2 Primary Estimand 9.4.3 Secondary Estimand	Stratification at randomization will include a stratum relative to whether the participant is taking antitremor medication at the Baseline Visit.	Concomitant use of antitremor medication(s) may impact response to treatment with JZP385.
5.1 Inclusion Criteria	A note was modified in Inclusion Criterion #3a relative to medication washout and screening for study entry.	Clarification.
	Inclusion Criterion #4 was updated to clarify that male partners of WOCBP are required to use barrier protection from the first dose of study intervention until 30 days after the last dose of study intervention.	Clarification

Section # and Name	Description of Change	Brief Rationale
	Inclusion Criterion #7 was added to require that, for participants who are being treated with antitremor medication, the dosage of medication must be stable for at least 6 weeks prior to their Screening Visit, and they do not anticipate any changes during the study. For participants not taking antitremor medication upon entering the study, they must have refrained from taking any antitremor medication within 6 weeks prior to their Screening Visit and not anticipate taking concomitant antitremor medication during participation in the study.	To clarify restrictions surrounding stability of dosage for concomitant antitremor medications (or lack of use of antitremor medications).
5.2 Exclusion Criteria	Exclusion Criterion #6 was updated to indicate that participants with a history of Gilbert's syndrome may be eligible for the study.	To allow inclusion of participants with Gilbert's syndrome as UGT1A1 is not involved in JZP385 metabolism.
	Exclusion Criterion #13 was modified to remove the exclusion of antitremor medications.	To align with the allowance of concomitant use of antitremor medication.
	Information on timing of discontinuation of primidone relative to study intervention was moved from Exclusion Criterion #13 to #14.	Modification of an exclusion criterion resulted in moving information as appropriate.
	Exclusion Criterion #17 was modified to clarify that participants should refrain from using medication(s)/substance(s) that might produce tremor or interfere with the evaluation of tremor prior to discharge on study visit days.	Clarification

Section # and Name	Description of Change	Brief Rationale
	Exclusion Criterion #21 was updated to indicate that screening laboratory tests may be repeated as needed.	To allow repeat screening laboratory tests to be performed more than once in circumstances in which these additional tests are needed to confirm eligibility.
	Information about the exclusion of medical and recreational use of cannabinoids (including CBD) was moved from Exclusion Criterion #13a to #22.	Modification of an exclusion criterion resulted in moving information as appropriate.
1.3 Schedule of Assessments 5.4 Screen Failures 8 Study Assessments and Procedures 8.2.2 Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale (Table 5)	Rescreened participants, who had previously met the inclusion criterion relative to ET diagnosis confirmed by EAC (Inclusion Criterion #2), will not be assessed again for that criterion when rescreened and will not complete the TETRAS-PS at screening.	This procedure lessens the burden on potential participants permitted to be rescreened for entry into the study without impacting the study's integrity, as an ET diagnosis is not anticipated to change.
8.1.1 Informed Consent	Clarified that no study procedures, including washout of prior medications, may be undertaken before signing the ICF.	Clarification
8.1.4. Medication Review (Prior or Concomitant Medications)	Medication(s) taken for ET should be reviewed within the prior 6 weeks (as opposed to prior 30 days) for all other medications.	To ensure complete information on ET medication history is collected to align and confirm with new eligibility criteria specifications.
Appendix 1: Abbreviations and Definitions	The abbreviations CBD (for cannabidiol) and PRN were added.	CBD and PRN are used in the body of the protocol.
General/Throughout	Amendment 03 Summary of Changes was moved to Appendix 8: Protocol Amendment History	Formatting standard

Section # and Name	Description of Change	Brief Rationale
	The sponsor's signatory for the protocol was changed.	Organizational change
	Where appropriate, the term "treatment" was changed to "study intervention." The term TETRAS composite outcome score was made consistent.	For consistency of terms throughout the protocol
	Stratification at baseline regarding the Baseline TETRAS composite outcome score was corrected from "≤ 17 and > 17" to "≤ 17 or > 17."	Correction
	JZP385 (as opposed to suvecaltamide) is used consistently throughout the protocol.	Editorial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2b, 12-week, Double-blind, Placebo-controlled, Randomized, Parallel-group, Multicenter Study of the Safety and Efficacy of JZP385 in the Treatment of Adults with Moderate to Severe Essential Tremor

Brief Title: A Study of JZP385 in Adults with Moderate to Severe Essential Tremor (ET)

Rationale:

This is a 12-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP385 (also known as CX-8998, suvecaltamide, and MK-8998) in the treatment of adult participants with ET, as defined by the Movement Disorder Society (MDS) Consensus Statement on the Classification of Tremors from the Task Force on Tremor of the International Parkinson's and MDS. This study was designed to be consistent with the United States (US) Food and Drug Administration (FDA) Guidance for Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, the International Conference on Harmonisation (ICH) E1A and E8 Guidance, and with the ethical principles in these guidances that originate from the Declaration of Helsinki. A phase 2a study, CX-8998-CLN2-001 (T-CALM), provided proof-of-concept and informed the design of this study.

The target patient population is participants with moderate to severe ET, which was selected to reflect the patient population within clinical practice for whom a therapeutic intervention for ET would be considered. Patients with mild ET are typically not treated with medication, as the tremor is not usually associated with significant functional disability. Essential tremor severity level in this study will be defined by eligibility criteria on the patient-rated (Tremor Research Group Essential Tremor Rating Assessment Scale [TETRAS] – Activities of Daily Living [TETRAS-ADL]) and clinician-rated (Clinical Global Impression of Severity [CGI-S]) measures of disability. The inclusion of a placebo control group in this study is necessary to determine the efficacy and safety of JZP385.

The primary endpoint for the study is a composite of the sum of modified items 1 to 11 of the TETRAS-ADL subscale and modified items 6 and 7 of the TETRAS-PS (ie, TETRAS composite outcome score). The TETRAS-ADL subscale is a patient-rated scale of the impact of tremor on day-to-day functioning administered by a trained interviewer. The TETRAS-ADL subscale directly measures how a patient functions by assessing activities impacted by tremor, such as eating and drinking, dressing and personal hygiene, carrying items, and fine motor skills. The TETRAS-ADL demonstrated sensitivity to change with JZP385 in the T-CALM study (see the JZP385 Investigator's Brochure [IB] for full results). The TETRAS-PS is a valid and reliable clinical rating scale that has demonstrated sensitivity to change with treatment and is recommended by the MDS Task Force to assess tremor severity. Items 6 (drawing an Archimedes spiral) and 7 (handwriting) of the TETRAS-PS evaluate the impact of upper limb tremor on performance, and thus represent an objective measure of the impact of upper limb tremor on functional tasks. Together, the items from the TETRAS-ADL subscale and

TETRAS-PS that comprise the primary endpoint represent both patient-rated and objective measures of the functional impact of tremor.

The key secondary endpoint is the CGI-S. The CGI-S will specifically evaluate the severity of participants' ET with respect to functional impairment and will adequately complement the primary endpoint. In the T-CALM study, a numerically higher percentage of participants reported improvement on the Clinical Global Impression of Change (CGI-C) when treated with JZP385 at 16 and 20 mg daily doses (administered as 8 mg and 10 mg twice daily [BID], respectively) compared to placebo. Given that the CGI-C score generally correlates with the CGI-S such that improvement in one follows the other, these data provide preliminary support that CGI-S will be sensitive to improvement with JZP385.

Table 1: Primary and Key Secondary Objectives and Estimands

Objectives	**Estimand and Attributes**
Primary	
To evaluate the efficacy of JZP385 to improve functional and performance-based impairment due to tremor when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.	• Treatment: 10, 20, and 30 mg/day JZP385 and placebo. • Population: Adults with moderate to severe ET. • Variable: Change from Baseline to Week 12 on the TETRAS composite outcome score.[a] • Intercurrent events: – Discontinuation of study intervention due to an AE, for lack of efficacy, or any other reason. Participants who experience this type of intercurrent event will be addressed by hypothetical strategy. – Any change to concomitant antitremor medication use after the initiation of study intervention. Participants who experience this type of intercurrent event will be addressed by treatment policy. • Summary: Difference in the mean TETRAS composite outcome score[a] from Baseline to Week 12 between each dose of JZP385 and placebo.
Key Secondary	
To evaluate the efficacy of JZP385 to improve functional impairment due to tremor when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.	• Treatment: 10, 20, and 30 mg/day JZP385 and placebo. • Population: Adults with moderate to severe ET. • Variable: Proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 12 on the CGI-S. • Intercurrent events: – Discontinuation of study intervention due to an AE, for lack of efficacy, or any other reason. Participants who experience this type of intercurrent event will be addressed by hypothetical strategy. – Any change to concomitant antitremor medication use after the initiation of study intervention. Participants who experience this type of intercurrent event will be addressed by treatment policy.

Objectives	Estimand and Attributes
	• Summary: Difference in the proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 12 on the CGI-S between each dose of JZP385 and placebo.

Abbreviations: AE = adverse event; ET = essential tremor; CGI-S = Clinical Global Impression of Severity; TEAE = treatment-emergent adverse event; TETRAS-ADL = Tremor Research Group Essential Tremor Rating Assessment Scale – Activities of Daily Living; TETRAS-PS = Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale.
[a] The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL subscale and modified items 6 and 7 of the TETRAS-PS. For TETRAS-ADL, each item is modified from 5 response items to 4 response items by collapsing options 0 and 1 together and for TETRAS-PS, each item is modified from 9 response items (due to 0.5 scoring increments) to 4 response items.

Table 2: Secondary and Exploratory Objectives and Endpoints

Objectives	Endpoints
Secondary	
• To evaluate the efficacy of JZP385 to improve overall ET when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.	• Proportion of participants reported as much improved on the CGI-C at Week 12. • Proportion of participants reported as much improved on the Patient Global Impression of Change (PGI-C) at Week 12. • Change from Baseline to Week 12 on the TETRAS-ADL subscale as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the TETRAS-PS as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the upper limb score (item 4) of the TETRAS-PS as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the TETRAS total score, as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the Quality of life in Essential Tremor Questionnaire (QUEST) as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the Essential Tremor Embarrassment Assessment (ETEA) as summarized by each dose of JZP385 and placebo.
• To evaluate the safety and tolerability of JZP385 administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day in the treatment of adult participants with ET.	• Incidence and severity of TEAEs, evaluation of safety laboratory assessments, vital signs, ECG results, Columbia Suicide Severity Rating Scale (C-SSRS) results, and physical examination findings.

Objectives	Endpoints
Exploratory	
• To characterize the PK and exposure-response of JZP385 in adult participants with ET using sparse PK sampling.	• Plasma concentrations of JZP385 and its metabolites, if applicable, will be listed and summarized. • PK parameters (eg, C_{max}, T_{max}, $t_{½}$, C_{tau}, AUC) of JZP385 and its metabolites, if applicable, will be estimated using a population PK model and will be presented separately from the study data. • Population exposure-response analysis for JZP385 and its metabolites, if applicable, will be performed and will be presented separately from the study data.
• To evaluate the efficacy of JZP385 to improve overall ET when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.	• Change from Baseline to Week 12 on the sum of modified items 6 and 7[a] of the TETRAS-PS as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the sum of modified items 1 to 11[a] of the TETRAS-ADL subscale as summarized by each dose of JZP385 and placebo. • Proportion of participants who improved (≥ 1-point improvement) from Baseline to Weeks 4 and 8 on the CGI-S. • Change from Baseline to Weeks 4 and 8 on the TETRAS composite outcome score[a], TETRAS-ADL, TETRAS-PS, TETRAS upper limb score (item 4), and TETRAS total score. • Proportion of participants reported as much improved on the PGI-C and CGI-C at Weeks 4 and 8. • Change from Baseline to Week 12 on the 36-item Short Form Health Survey (SF-36) as summarized by each dose of JZP385 and placebo. • Time course analysis on the sum of modified items 6 and 7[a] of the TETRAS-PS as summarized by each dose of JZP385 and placebo.

Abbreviations: AUC = area under the plasma concentration-time curve; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C_{max} = maximum plasma concentration; C-SSRS = Columbia Suicide Severity Rating Scale; C_{tau} = concentration at trough; ECG = electrocardiogram; ET = essential tremor; ETEA = Essential Tremor Embarrassment Assessment; PGI-C = Patient Global Impression of Change; PK = pharmacokinetics; QUEST = Quality of life in Essential Tremor Questionnaire; SF-36 = 36-item Short Form Health Survey; $t_{½}$ = terminal half-life; TEAE = treatment-emergent adverse event; TETRAS-ADL = Tremor Research Group Essential Tremor Rating Assessment Scale – Activities of Daily Living; TETRAS-PS = Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale; T_{max} = time to maximum concentration.

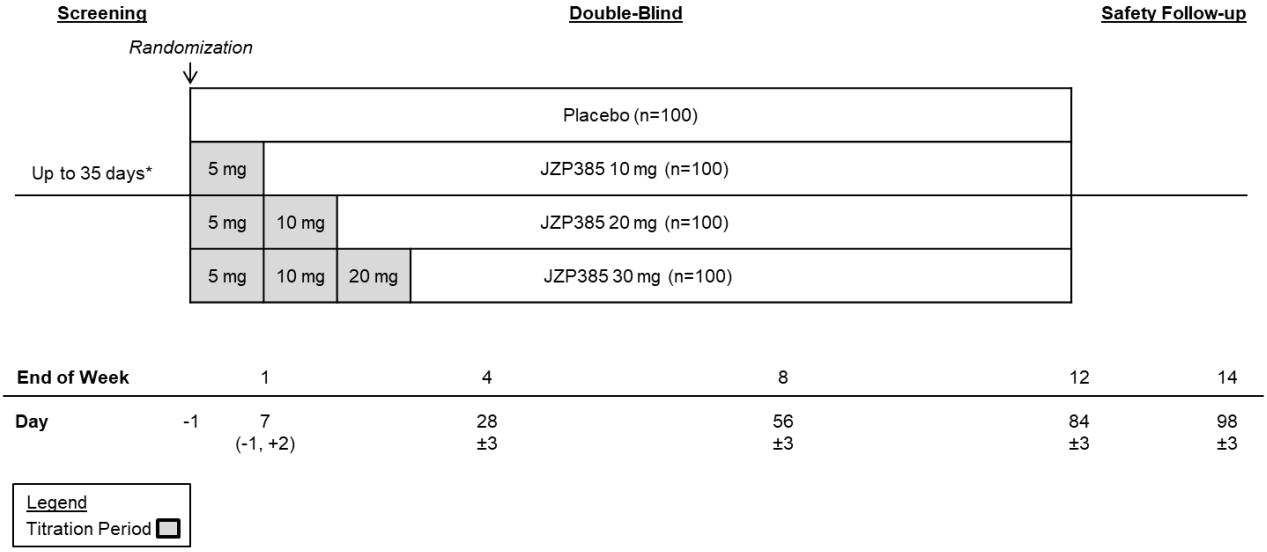
[a] The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL subscale and modified items 6 and 7 of the TETRAS-PS. For TETRAS-ADL, each item is modified from 5 response items to 4 response items by collapsing options 0 and 1 together and for TETRAS-PS, each item is modified from 9 response items (due to 0.5 scoring increments) to 4 response items.

Table 3: Overall Study Design

Overall Design	
Study Phase	Phase 2b
Clinical Indication	Essential Tremor
Study Type	Interventional
Type of Design	Randomized, parallel-group, 4-arm, multicenter Randomization will be stratified by the following: • The select modified items from the TETRAS-ADL subscale and TETRAS-PS (ie, TETRAS composite outcome score)[a] (≤ 17 or > 17), as assessed at the Baseline Visit • The use of concomitant antitremor medication (Yes or No)
Type of Control	Placebo Control
Study Blinding	Double-blind (Interactive response technology [IRT])
Population	Participants with moderate to severe ET
Number of Participants	Approximately 400 participants will be randomized, with approximately 100 participants randomized to each treatment arm and 80 evaluable participants in each treatment arm of the study.
Duration of Participation	The study starts from the time participants sign the informed consent form (ICF) through the end of the study procedures/contact. The study comprises 3 periods: up to 35 days Screening Period (an additional 28 days are permitted for participants who require washout of primidone) including Baseline, followed by a 12-week Double-blind Treatment Period, and a 2-week Safety Follow-up Period. Each participant will be enrolled for approximately 19 weeks.
Number of Treatment Arms	4
Treatment Groups	10, 20, or 30 mg/day JZP385, or placebo
Data Monitoring Committee	Not applicable

[a] The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL subscale and modified items 6 and 7 of the TETRAS-PS. For TETRAS-ADL, each item is modified from 5 response items to 4 response items by collapsing options 0 and 1 together and for TETRAS-PS, each item is modified from 9 response items (due to 0.5 scoring increments) to 4 response items.

1.2. Schema



*An additional 28 days during the Screening Period are permitted for participants who require washout of primidone.
Note: All JZP385 doses will be administered once daily on a mg/day basis.

1.3. Schedule of Activities (SoA)

	Screening (up to 35 days[a])			Double-blind Treatment Period (12 weeks)							E/D Visit	Safety Follow-up Period (2 weeks)	Comments
	SV1	SV2[b]	Baseline Visit	W1	W2, W3	W4	W5, W6, W7	W8	W9, W10, W11	W12		EoS Visit / Safety FU[c]	
Days (Window)	-35[a] to -2		-1	7 (-1, +2)	14 (-1, +2); 21±3	28±3	35±3; 42±3; 49±3	56± 3	63±3; 70±3; 77±3	84± 3		98[d] ±3	
Clinic Visit	X	X	X	X[e]		X[e]		X[e]		X	X[e]	X[e]	
Phone Contact					X[f]		X[f]		X[f]				
Activity													
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X	X										
Demographics	X												
Medical History	X	X	X										Confirm medical history at SV2 (if applicable) and Baseline Visit
Physical Exam	X									X	X	X	Full examination of body systems (except genitourinary)
Height	X												Height should be assessed in ordinary indoor clothes without shoes
Weight	X		X	X		X		X		X	X	X	Weight should be assessed in ordinary indoor clothes without shoes
MoCA	X												
Serum Pregnancy Test	X												Only for WOCBP. Serum pregnancy tests can be conducted at additional visits to

	Screening (up to 35 days[a])			Double-blind Treatment Period (12 weeks)							E/D Visit	Safety Follow-up Period (2 weeks)	Comments
	SV1	SV2[b]	Baseline Visit	W1	W2, W3	W4	W5, W6, W7	W8	W9, W10, W11	W12		EoS Visit / Safety FU[c]	
Days (Window)	-35[a] to -2		-1	7 (-1, +2)	14 (-1, +2); 21±3	28±3	35±3; 42±3; 49±3	56± 3	63±3; 70±3; 77±3	84± 3		98[d] ±3	
Clinic Visit	X	X	X	X[e]		X[e]		X[e]		X	X[e]	X[e]	
Phone Contact					X[f]		X[f]		X[f]				
Activity													
													confirm positive urine test and/or if required by local regulatory or IRB/IEC.
Urine pregnancy test		X	X	X		X		X		X	X	X	Only for WOCBP. If positive, conduct confirmatory serum pregnancy test.
Urine drug screen	X	X	X							X	X		Additional urine drug screens can be obtained at any other clinic visits per the investigator's judgment.
Breath alcohol test	X	X	X			X		X		X	X		Additional breath alcohol tests can be obtained at any other clinic visits per the investigator's judgment.
Laboratory assessments (Chemistry, Hematology)	X		X	X		X		X		X	X		Laboratory assessments should be conducted under fasting conditions. Repeat laboratory assessments at the Baseline Visit only if the visit occurs > 35 days after screening.

	Screening (up to 35 days[a])			Double-blind Treatment Period (12 weeks)							E/D Visit	Safety Follow-up Period (2 weeks)	Comments
	SV1	SV2[b]	Baseline Visit	W1	W2, W3	W4	W5, W6, W7	W8	W9, W10, W11	W12		EoS Visit / Safety FU[c]	
Days (Window)	-35[a] to -2		-1	7 (-1, +2)	14 (-1, +2); 21±3	28±3	35±3; 42±3; 49±3	56± 3	63±3; 70±3; 77±3	84± 3		98[d] ±3	
Clinic Visit	X	X	X	X[e]		X[e]		X[e]		X	X[e]	X[e]	
Phone Contact					X[f]		X[f]		X[f]				
Activity													
Urinalysis	X		X	X		X		X		X	X		Repeat urinalysis at the Baseline Visit only if the visit occurs > 35 days after screening.
Blood sample for genetic testing				X									The sample is optional and should be collected at the same time as the predose PK sample.
Supine and standing blood pressure and pulse	X	X	X	X		X		X		X	X	X	SV1, SV2 (if applicable), and Baseline: Triplicate measurements at 15- to 30-minute intervals. All other visits: 1 measurement postdose.
Temperature and respiratory rate	X	X	X	X		X		X		X	X	X	
12-lead ECG	X		X	X		X		X		X	X	X	At each time point, ECGs will be taken in triplicate at approximately 2-minute intervals. Additional ECGs may be obtained at any time per the investigator's judgment.

	Screening (up to 35 days[a])			Double-blind Treatment Period (12 weeks)							E/D Visit	Safety Follow-up Period (2 weeks)	Comments
	SV1	SV2[b]	Baseline Visit	W1	W2, W3	W4	W5, W6, W7	W8	W9, W10, W11	W12		EoS Visit / Safety FU[c]	
Days (Window)	-35[a] to -2		-1	7 (-1, +2)	14 (-1, +2); 21±3	28±3	35±3; 42±3; 49±3	56± 3	63±3; 70±3; 77±3	84± 3		98[d] ±3	
Clinic Visit	X	X	X	X[e]		X[e]		X[e]		X	X[e]	X[e]	
Phone Contact					X[f]		X[f]		X[f]				
Activity													
C-SSRS Screening/ Baseline Version	X												
C-SSRS Since Last Visit Version		X	X	X		X		X		X	X	X	
Instruction on medication washout	X	X											
TETRAS-ADL Subscale	X	X	X			X		X		X	X		At SV1, perform the TETRAS-ADL subscale only for participants who do not need to washout of medications that impact tremor (eg, primidone); otherwise, this assessment should be performed at SV2.
TETRAS-PS	X	X	X			X		X		X	X		The TETRAS-PS will be conducted as indicated in Table 5.
CGI-S	X	X	X			X		X		X	X		At SV1, perform the CGI-S only for participants who do not need to washout of medications that impact tremor (eg, primidone); otherwise, this assessment should be performed at SV2.

	Screening (up to 35 days[a])			Double-blind Treatment Period (12 weeks)							Safety Follow-up Period (2 weeks)	Comments
	SV1	SV2[b]	Baseline Visit	W1	W2, W3	W4	W5, W6, W7	W8	W9, W10, W11	W12	E/D Visit	EoS Visit / Safety FU[c]	
Days (Window)	-35[a] to -2		-1	7 (-1, +2)	14 (-1, +2); 21±3	28±3	35±3; 42±3; 49±3	56± 3	63±3; 70±3; 77±3	84± 3		98[d] ±3	
Clinic Visit	X	X	X	X[e]		X[e]		X[e]		X	X[e]	X[e]	
Phone Contact					X[f]		X[f]		X[f]				
Activity													
CGI-C						X		X		X	X		
PGI-C						X		X		X	X		
QUEST			X							X	X		
SF-36v2			X							X	X		
ETEA			X							X	X		
Light breakfast	X		X	X		X		X		X	X		
Light lunch			X					X					Only provided to participants who are doing optional serial items 6 and 7 TETRAS-PS assessments and 5- to 8-hour postdose PK sample.
Randomization			X										
Dispense study intervention			X	X		X		X					Participants should begin taking study intervention at home on Day 1 (the day following the Baseline Visit). *Note:* A phone visit can be converted to a site visit if country regulations restrict

	Screening (up to 35 days[a])			Double-blind Treatment Period (12 weeks)							Safety Follow-up Period (2 weeks)	Comments
	SV1	SV2[b]	Baseline Visit	W1	W2, W3	W4	W5, W6, W7	W8	W9, W10, W11	W12	E/D Visit	EoS Visit / Safety FU[c]	
Days (Window)	-35[a] to -2		-1	7 (-1, +2)	14 (-1, +2); 21±3	28±3	35±3; 42±3; 49±3	56± 3	63±3; 70±3; 77±3	84± 3		98[d] ±3	
Clinic Visit	X	X	X	X[e]		X[e]		X[e]		X	X[e]	X[e]	
Phone Contact					X[f]		X[f]		X[f]				
Activity													
													dispensation of study intervention to no more than a 28-day supply.
Collect study intervention/ assess compliance				X		X		X		X	X		If participants do not return study intervention at the W12 or E/D visit, they should be asked to return unused study intervention at the Safety Follow-up Visit.
Administer study intervention on site				X		X		X		X			Participants will be instructed to refrain from eating or drinking (except water) prior to the clinic visit such that study intervention is taken on an empty stomach in the clinic. Participants should also abstain from eating or drinking (except for water) for 60 minutes after taking study intervention.
Blood draws for PK				X		X		X		X			W1, W4, W8, and W12 visits: Predose and 1 sample anytime between 0.5 to 3 hours postdose.

	Screening (up to 35 days[a])			Double-blind Treatment Period (12 weeks)							E/D Visit	Safety Follow-up Period (2 weeks)	Comments
	SV1	SV2[b]	Baseline Visit	W1	W2, W3	W4	W5, W6, W7	W8	W9, W10, W11	W12		EoS Visit / Safety FU[c]	
Days (Window)	-35[a] to -2		-1	7 (-1, +2)	14 (-1, +2); 21±3	28±3	35±3; 42±3; 49±3	56± 3	63±3; 70±3; 77±3	84± 3		98[d] ±3	
Clinic Visit	X	X	X	X[e]		X[e]		X[e]		X	X[e]	X[e]	
Phone Contact					X[f]		X[f]		X[f]				
Activity													
													W8 visit: An additional sample anytime between 5 to 8 hours postdose [*Note:* this sample is optional].
AEs/SAEs			←	—	—	—	—	—	—	→			For medical occurrences that begin before the start of study intervention, but after obtaining informed consent, see Section 8.4.1.
Prior/ Concomitant Medications	←	—	—	—	—	—	—	—	—	→			
Schedule next visit and/or phone contact	X	X	X	X	X	X	X	X	X	X	X		Tentatively schedule all study visits during the Screening Period. Confirm visits at each subsequent visit.

Abbreviations: CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; COVID-19 = Coronavirus disease 2019; EAC = Eligibility Adjudication Committee; ECG = electrocardiogram; E/D = early discontinuation; EoS = end of study; ET = essential tremor; ETEA = Essential Tremor Embarrassment Assessment; FU = follow-up; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MoCA = Montreal Cognitive Assessment; PGI-C = Patient Global Impression of Change; PK = pharmacokinetics; QUEST = Quality of life in Essential Tremor Questionnaire; SAE = serious adverse event; SF-36v2 = 36-item Short Form Health Survey Version 2; SV1 = Screening Visit 1; SV2 = Screening Visit 2; TETRAS-ADL = Tremor Research Group Essential Tremor Rating Assessment Scale – Activities of Daily Living; TETRAS-PS = Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale; W = week; WOCBP = women of child bearing potential.

[a] An additional 28 days during the Screening Period is permitted for participants who require washout of primidone. Potential participants who do not meet the criteria for participation in this study (screen failure) may be rescreened once provided the rescreening is approved by the study medical monitor. Potential participants screened an additional time (rescreened) who had previously met the inclusion criteria relative to ET diagnosis confirmed by the EAC (Inclusion Criterion #2) will not be assessed again relative to that criterion as part of the rescreening process and will not have to complete the TETRAS-PS assessment at Screening Visit 1 or 2, as applicable.

[b] Screening Visit 2 is only for participants who need to washout of medications that impact tremor (eg, primidone) prior to Baseline.

[c] All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 8.4.3).

[d] If participant discontinues study intervention and requires an E/D Visit, the Safety FU should be 2 weeks after the E/D visit.

[e] Clinic visits at Week 1, Week 4, Week 8, E/D, and EoS/Safety FU may be conducted remotely, if required due to the COVID-19 pandemic, and with approval from the sponsor's medical monitor. The TETRAS-PS will not be performed at remote visits, and PK samples may not be collected.

[f] Phone contacts at Weeks 2 to 3, Weeks 5 to 7 and Weeks 9 to 11 may be converted to clinic visits if required due to local regulations or local requirements. If performed in-clinic, dispensing of study intervention may occur and urine pregnancy testing should be completed for WOCBP.

2. INTRODUCTION

Essential tremor (ET) is a serious, progressive, and chronically debilitating neurological disorder that can profoundly affect activities of daily living. Essential tremor is arguably the most common movement disorder among adults, but prevalence estimates vary. In a meta-analysis of 28 population-based studies from 19 countries, the estimated pooled prevalence across all ages was 0.9%. Prevalence of ET increases markedly with age; across studies, the estimated pooled prevalence in adults ≥ 65 years of age was 4.6%, with prevalence estimates in individual studies ranging from 0.8 to 20.5% (Louis and Ferreira, 2010). More recent meta-analyses have estimated the global prevalence of ET at 0.32% (Song, 2021) and 1.33% (Louis and McCreary, 2021). These meta-analyses similarly demonstrated an increased prevalence of ET with age; Song and colleagues estimate the prevalence of ET in adults aged ≥ 80 years at 2.87% and Louis and McCreary estimate the prevalence of ET in adults ≥ 65 years of age at 5.79%.

Essential tremor is characterized by an action tremor in the hands and arms that is bilateral and often slightly asymmetric. The tremor presents during voluntary movement (kinetic tremor) or while maintaining a fixed position against gravity (postural and orthostatic tremor). In patients with ET, tremor may also be present in the head, voice, and jaw, and less commonly the face or trunk (Louis, 2018). In the majority of individuals, tremor progresses slowly, starting on one side of the body and eventually affecting both sides, and further spreading to other regions of the body (National Institute of Neurological Disorders and Stroke [NINDS] 2019; NINDS 2020). In addition to motor features, there is increasing recognition that patients with ET exhibit significant non-motor symptoms including cognitive deficits, anxiety, social phobia, depression, and sleep disturbances (Louis, 2016; Musacchio, 2016; Sengul, 2015).

Study CX-8998-CLN2-001 was a phase 2, randomized, double-blind, multicenter, placebo-controlled, dose-titration study that assessed the efficacy and safety of immediate release (IR) JZP385 (also known as CX-8998, suvecaltamide, and MK-8998) in doses up to 20 mg/day (10 mg twice daily [BID]) for reducing the severity of tremor in participants with ET. This study demonstrated proof-of-concept, informed the design of the current phase 2b study, and provided preliminary evidence to support improvement in symptoms of ET with JZP385 treatment. Detailed results are available in the JZP385 Investigator's Brochure (IB).

2.1. Study Rationale

Based on the proof-of-concept findings in the T-CALM study, in which adult participants with ET were treated with JZP385, as well as the high unmet need for therapies that better treat the significant impact of tremor on patients' day-to-day functioning, Jazz Pharmaceuticals is conducting the present study with JZP385 to evaluate efficacy, safety, and PK information in this population. The dose-response at 3 doses of JZP385 will also be evaluated.

2.2. Background

Essential tremor has no cure, but symptomatic treatment of ET with drug therapies is considered when tremor interferes with a patient's day-to-day functioning. No marketed pharmacological therapy has been developed specifically for the treatment of ET. All currently available pharmacotherapies have limitations with respect to efficacy, safety, or limited evidence from randomized, controlled trials to support their widespread use (Haubenberger and Hallett, 2018). Propranolol (a β-blocker) is approved to treat patients with ET in the United States (US) and in the European Union (EU). Another option is primidone, an anticonvulsant used to treat ET (approved only in the United Kingdom and Hungary). However, up to half of patients with ET do not respond to either propranolol or primidone, and over 50% of patients reportedly discontinue one or both medications due to lack of efficacy and/or side effects (Diaz and Louis, 2010; Ferreira, 2019).

Other prescription medications are used off-label to treat ET, including topiramate, gabapentin, alprazolam, clonazepam, and other β-blockers. Many of these second- and third-line treatment options have limited data from randomized controlled trials in ET to support efficacy and the data do not suggest an efficacy profile that is any better than propranolol (Ferreira 2019; Hedera, 2013). Additionally, these medications are associated with dependency, abuse, withdrawal symptoms due to abrupt cessation, and other troublesome side effects (Hedera 2013). Neurosurgical procedures, such as deep brain stimulation targeting the central intermediate nucleus of the thalamus or magnetic resonance imaging-guided focused ultrasound thalamotomy, offer treatment options for patients whose ET is severely disabling and who are refractory to drug therapy (Zesiewicz, 2010). Thus, the challenges with current treatments for ET, coupled with the significant impact on patient quality of life, support the need for additional therapeutic options for this patient population.

Although the pathogenesis of ET has not been fully established, several studies have identified abnormal oscillations of neuronal activity in the cortico-bulbo-cerebello-thalamic pathways (Haubenberger and Hallett, 2018). T-type calcium channels (Ca_V3) are mediators of subthreshold oscillations and excessive rhythmicity in pathophysiologic states found in tremor (Llinás, 2003; Handforth, 2005; Llinás, 2007; Park, 2013). Numerous lines of pharmacological and genetic evidence suggest that the increased activation of Ca_V3 channels and excessive rhythmicity play a key role in neurological disorders such as ET (Park, 2010; Shipe, 2008; Handforth, 2010). For example, several pharmacological studies have demonstrated that drugs with antagonist activity at Ca_V3 reduce tremor in animal models (Shipe, 2008; Miwa, 2008; Handforth, 2010; Quesada, 2011). In clinical studies, zonisamide and topiramate, which are both thought to act, in part, through suppression of Ca_V3 activity, have shown some efficacy in patients with ET. However, their usefulness has been limited by poor tolerability and/or excessive premature discontinuations of treatment, potentially due to pharmacological activity on other types of ion channels (Morita, 2005; Ondo, 2007; Bermejo, 2008; Chang, 2015). Selective targeting of Ca_V3 channels may offer a more efficacious and better-tolerated treatment option for patients with chronic neurological conditions. The high selectivity of JZP385 as a Ca_V3 modulator, along with its lack of effects on other types of channels, make it a promising candidate for the treatment of ET.

JZP385 is formulated as an extended-release (ER) oral dosage form, containing immediate-release (IR) and delayed release (DR) pellets in a hard opaque capsule. The original

formulation of JZP385 was an IR formulation that required BID administration. To enable once-daily administration, a 2-component multi-particulate (pellet) dosage form was developed that contains an IR pellet to deliver the required initial plasma concentration for rapid onset of effect and a DR pellet to maintain plasma concentrations above the target therapeutic threshold. The current study will use the ER JZP385 product that has the identifier of "DR2" (see Table 4).

Preliminary evidence that JZP385 may provide a meaningful treatment option for ET was generated by Study CX-8998-CLN2-001 (T-CALM), a phase 2, randomized, double-blind, multicenter, placebo-controlled dose-titration study that assessed the efficacy and safety of the IR formulation of JZP385 in doses up to 20 mg/day (10 mg BID) for reducing the severity of tremor in participants with ET. Despite not meeting statistical significance on the primary endpoint (Tremor Research Group Essential Tremor Assessment Rating Scale [TETRAS] performance subscale [TETRAS-PS] as rated by independent video raters), numerical improvements, favoring JZP385, were observed on TETRAS-PS as rated by the investigators and the TETRAS activities of daily living (TETRAS-ADL) subscale. In addition, a numerically higher percentage of patients treated with JZP385 reported improvement in their overall condition as measured using the Clinical Global Impression of Change (CGI-C). JZP385, at doses up to 20 mg/day (10 mg BID) was well tolerated with the most commonly reported AEs in the System Organ Class (SOC) of Nervous System Disorders and Psychiatric Disorders. Most AEs were mild to moderate in severity.

Four phase 1 studies in healthy male and female participants have been completed with the IR formulation of JZP385 (PN001, PN002, PN003, and PN005). Two phase 1 studies (CX-8998-CLN2-005 and JZP385-101) evaluated the PK of JZP385 and its 2 active metabolites (M01 and M02) following single and multiple doses of various ER formulations administered once daily. Preliminary PK data from Study CX-8998-CLN2-005 suggest that both ER formulations tested achieved reduced JZP385 maximum plasma concentration (C_{max}) relative to the IR formulation, with limited impact on overall JZP385 plasma exposure as measured by area under the plasma concentration-time curve (AUC). Furthermore, a high-fat meal substantially delayed DR2 JZP385 time to maximum concentration (T_{max}) with minimal impact on C_{max} or overall AUC, indicating an impact of food on early (IR component of formulation) but not late (DR component of formulation) absorption. Study JZP385-101 characterized the PK of JZP385, M01, and M02, dose proportionality, and safety and tolerability following multiple doses of ER formulations (8, 16, 24, and 36 mg administered once daily). The study also explored the effect of food on both formulations. Preliminary data from this study suggest that both ER formulations had similar PK profiles and PK parameters following multiple daily doses of 8, 16, 24, and 36 mg. Both formulations result in approximately dose-proportional PK of JZP385 and its major metabolites (M01 and M02) in the dose range of 8 to 24 mg as assessed at steady state. This trend holds true through the 36 mg dose level considering that ~90% of JZP385 steady state is achieved following 4 days of 36 mg dosing. Doses up to 36 mg/day were well-tolerated and a similar safety profile was observed with the ER formulations compared to the IR formulation, with most commonly reported AEs in the SOCs of Nervous System Disorders and Psychiatric Disorders. Adverse events were primarily mild to moderate in severity, were reported during the first week of treatment (at the 8 mg/day dose) and were transient. The exploratory evaluation of the effect of a high-fat high-calorie meal on JZP385 ER formulations confirmed earlier findings of negligible impact of food on JZP385 C_{max} or AUC with a noteworthy delay in T_{max}.

A detailed description of the chemistry, pharmacology, efficacy, and safety of JZP385 is provided in the IB.

2.3. Benefit/Risk Assessment

A summary of the benefit-risk assessment for participation in Study JZP385-201 is provided in the subsections below.

2.3.1. Risk Assessment

Participants with ET who enroll in this study may encounter the following potential risks:

- For participants randomized to study intervention with JZP385, the risks are expected to be similar to those seen in previously conducted clinical studies. In general, AE profiles have been consistent across populations studied (eg, ET, schizophrenia, healthy volunteers). Analysis of TEAEs showed that JZP385 in the dose ranges from 1 mg to 24 mg (IR) and from 8 mg QD to 36 mg QD (ER formulations) was generally well tolerated by most participants. Generally, the most commonly reported AEs were in the SOC of Nervous System Disorders and Psychiatric Disorders; the most common AEs (≥ 5%) in participants with ET have included dizziness, headache, euphoric mood, and insomnia. Most AEs were mild or moderate in severity, were transient, and did not lead to study discontinuation. No clinically important trends in vital signs, safety laboratories, or ECG parameters have been observed in the completed clinical studies. The potential risks to participants will be managed and mitigated by the use of exclusion criteria which preclude subjects with an unstable or clinically significant medical condition, or who are at significant risk for cardiovascular complications, suicide or drug abuse from participating in the study. In addition, a titration schedule will be implemented such that subjects will start at a lower dose and titrate up to the final dose. Extensive monitoring of AEs, ECGs, orthostatic hypotension, and suicidal ideation and behavior will occur at frequent clinic visits throughout the study.
- For participants who are randomized to the placebo treatment arm and who discontinued antitremor medication(s) during the screening period, there may be risks associated with untreated symptoms of ET.
- Participants will be asked to discontinue protocol-prohibited medication(s) to enter the study. There may be risks associated with abrupt discontinuation of these medications, most notably, with primidone. To mitigate this risk, an extended screening period is implemented for participants who require washout of primidone to permit safe down-titration. Additionally, participants will not undergo discontinuation from prohibited antitremor medications and will be ineligible for the study if it is deemed unsafe by the investigator and medical monitor, as applicable.
- Study procedure-related risks, including risks and/or discomfort associated with blood collection, electrocardiograms (ECGs), physical examinations, and completion of questionnaires and other assessments.

2.3.2. Benefit Assessment

Participants with ET who enroll in this study may experience the following benefits:

- Receiving JZP385 for the study duration may alleviate the significant symptom burden associated with ET.
- Irrespective of which study intervention a participant receives in the study, all participants will contribute to the process of developing new therapies in ET.
- Participants will receive comprehensive clinical exams and clinical monitoring associated with the study.

2.3.3. Overall Benefit: Risk Summary

Benefits to participants include the potential to receive a therapy that may alleviate symptoms of ET and to contribute to the development of new therapeutics in ET, as well as receiving comprehensive physical examination and clinical monitoring.

Risks to participants include those related to JZP385 treatment, the potential need to discontinue protocol-prohibited medication, the potential that participants who discontinued or plan to discontinue antitremor medications to enter the study will be treated with placebo for the study duration, and risks related to the study procedures.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of JZP385 may be found in the IB.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Primary and Key Secondary Objectives and Estimands:

Objectives	Estimands and Attributes
Primary	
To evaluate the efficacy of JZP385 to improve functional and performance-based impairment due to tremor when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.	• Treatment: 10, 20, and 30 mg/day JZP385 and placebo. • Population: Adults with moderate to severe ET. • Variable: Change from Baseline to Week 12 on the TETRAS composite outcome score.[a] • Intercurrent events: – Discontinuation of study intervention due to an AE, for lack of efficacy, or any other reason. Participants who experience this type of intercurrent event will be addressed by hypothetical strategy. – Any change to concomitant antitremor medication use after the initiation of study intervention (refer to Section 9.4.1.2). Participants who experience this type of intercurrent event will be addressed by treatment policy. • Summary: Difference in the mean TETRAS composite outcome score[a] from Baseline to Week 12 between each dose of JZP385 and placebo.
Key Secondary	
To evaluate the efficacy of JZP385 to improve functional impairment due to tremor when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.	• Treatment: 10, 20, and 30 mg/day JZP385 and placebo. • Population: Adults with moderate to severe ET. • Variable: Proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 12 on the CGI-S. • Intercurrent events: – Discontinuation of study intervention due to an AE, for lack of efficacy, or any other reason. Participants who experience this type of intercurrent event will be addressed by hypothetical strategy. – Any change to concomitant antitremor medication use after the initiation of study intervention (refer to Section 9.4.1.2). Participants who experience this type of intercurrent event will be addressed by treatment policy. • Summary: Difference in the proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 12 on the CGI-S between each dose of JZP385 and placebo.

Abbreviations: AE = adverse event; ET = essential tremor; CGI-S = Clinical Global Impression of Severity; TEAE = treatment-emergent adverse event; TETRAS-ADL = Tremor Research Group Essential Tremor Rating Assessment Scale – Activities of Daily Living; TETRAS-PS = Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale.

[a] The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL subscale and modified items 6 and 7 of the TETRAS-PS. For TETRAS-ADL, each item is modified from 5 response items to 4 response items by collapsing options 0 and 1 together and for TETRAS-PS, each item is modified from 9 response items (due to 0.5 scoring increments) to 4 response items.

Secondary and Exploratory Objectives and Endpoints:

Objectives	Endpoints
Secondary	
• To evaluate the efficacy of JZP385to improve overall ET when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.	• Proportion of participants reported as much improved on the CGI-C at Week 12. • Proportion of participants reported as much improved on the PGI-C at Week 12. • Change from Baseline to Week 12 on the TETRAS-ADL subscale as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the TETRAS-PS as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the upper limb score (item 4) of the TETRAS-PS as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the TETRAS total score, as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the QUEST as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the ETEA as summarized by each dose of JZP385 and placebo.
• To evaluate the safety and tolerability of JZP385 administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day in the treatment of adult participants with ET.	• Incidence and severity of TEAEs, evaluation of safety laboratory assessments, vital signs, ECG results, C-SSRS results, and physical examination findings.
Exploratory	
• To characterize the PK and exposure-response of JZP385 in adult participants with ET using sparse PK sampling	• Plasma concentrations of JZP385 and its metabolites, if applicable, will be listed and summarized. • PK parameters (eg, C_{max}, T_{max}, $t_{½}$, C_{tau}, AUC) of JZP385 and its metabolites, if applicable, will be estimated using a population PK model and will be presented separately from the study data. • Population exposure-response analysis for JZP385 and its metabolites, if applicable, will be performed and will be presented separately from the study data.

• To evaluate the efficacy of JZP385 to improve overall ET when administered once daily for up to 12 weeks at fixed doses of 10, 20, and 30 mg/day.	• Change from Baseline to Week 12 on the sum of modified items 6 and 7[a] of the TETRAS-PS as summarized by each dose of JZP385 and placebo. • Change from Baseline to Week 12 on the sum of modified items 1 to 11[a] of the TETRAS-ADL subscale as summarized by each dose of JZP385 and placebo. • Proportion of participants who improved (≥ 1-point improvement) from Baseline to Weeks 4 and 8 on the CGI-S. • Change from Baseline to Weeks 4 and 8 on the TETRAS composite outcome score[a], TETRAS-ADL, TETRAS-PS, TETRAS upper limb score (item 4), and TETRAS total score. • Proportion of participants reported as much improved on the PGI-C and CGI-C at Weeks 4 and 8 • Change from Baseline to Week 12 on the 36-item Short Form Health Survey (SF-36) as summarized by each dose of JZP385 and placebo. • Time course analysis on the sum of modified items 6 and 7[a] of the TETRAS-PS as summarized by each dose of JZP385 and placebo.

Abbreviations: AUC = area under the plasma concentration-time curve; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C_{max} = maximum plasma concentration; C-SSRS = Columbia Suicide Severity Rating Scale; C_{tau} = concentration at trough; ECG = electrocardiogram; ET = essential tremor; ETEA = Essential Tremor Embarrassment Assessment; PGI-C = Patient Global Impression of Change; PK = pharmacokinetics; QUEST = Quality of life in Essential Tremor Questionnaire; SF-36 = 36-item Short Form Health Survey; $t_{½}$ = terminal half-life; TEAE = treatment-emergent adverse event; TETRAS-ADL = Tremor Research Group Essential Tremor Rating Assessment Scale – Activities of Daily Living; TETRAS-PS = Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale; T_{max} = time to maximum concentration.

[a] The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL subscale and modified items 6 and 7 of the TETRAS-PS. For TETRAS-ADL, each item is modified from 5 response items to 4 response items by collapsing options 0 and 1 together and for TETRAS-PS, each item is modified from 9 response items (due to 0.5 scoring increments) to 4 response items.

4. STUDY DESIGN

4.1. Overall Design

This is a 12-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP385 in the treatment of adult participants with moderate to severe ET.

The total duration of the study for each participant will be approximately 19 weeks. During the Screening Period, which will occur over a period of up to 35 days (an additional 28 days are permitted for participants who require washout of primidone), all participants will be evaluated for eligibility and will washout any prohibited medications. Participants may be allowed to rescreen once if the rescreening is approved by the medical monitor.

Participants eligible for the study will be randomized in a 1:1:1:1 ratio to receive once daily doses of 10, 20, or 30 mg JZP385 or placebo during a 12-week Double-blind Treatment Period. Randomization will be stratified by the TETRAS composite outcome score (≤ 17 or > 17) and the use of concomitant antitremor medication (Yes or No), as assessed at the Baseline Visit. JZP385 will be administered orally (PO) once daily in the morning on an empty stomach for 12 weeks. Dosing will be titrated as follows:

- Participants randomized to the 10 mg/day dose will initially receive 5 mg/day from Day 1 through Day 7, and 10 mg/day starting on Day 8.
- Participants randomized to the 20 mg/day dose will initially receive 5 mg/day from Day 1 through Day 7, 10 mg/day from Day 8 through Day 14, and 20 mg/day starting on Day 15.
- Participants randomized to the 30 mg/day dose will initially receive 5 mg/day from Day 1 through Day 7, 10 mg/day from Day 8 through Day 14, 20 mg/day from Day 15 through Day 21, and 30 mg/day starting on Day 22.

Once participants reach their assigned fixed dose, they will continue on that dose for the remainder of the planned 12-week treatment period. No dose adjustments will be allowed. Participants who cannot tolerate their assigned fixed dose of JZP385 will be withdrawn from the study.

Assessments of efficacy, safety, and PK will be conducted as indicated in Section 8.2, Section 8.3, and Section 8.5, respectively, and as described in the Schedule of Activities (SoA) (Section 1.3)

4.2. Scientific Rationale for Study Design

This study was designed to be consistent with the US Food and Drug Administration (FDA) Guidance for Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, the International Conference on Harmonisation (ICH) E1A and E8 Guidance, and with the ethical principles in these guidances that originate in the Declaration of Helsinki.

The target patient population is participants with moderate to severe ET, which was selected to reflect the patient population within clinical practice for whom a therapeutic intervention for ET

would be considered. Patients with mild ET are typically not treated with medication, as the tremor is not usually associated with significant functional disability (Gironell and Kulisevsky, 2009; Louis, 2010; Rajput and Rajput, 2014). Essential tremor severity level in this study will be defined by eligibility criteria on patient-rated (TETRAS-ADL) and clinician-rated (CGI-S) measures of disability. The inclusion of a placebo control group in this study is necessary to determine the efficacy and safety of JZP385.

The 12-week duration (which includes up to 3 weeks of titration and a minimum of 9 weeks at the assigned fixed dose) is considered as adequate duration to detect efficacy and evaluate safety in this phase 2b study. Based on results from the T-CALM study, efficacy signals were observed at both time points tested: the end of Week 2 (at 16 mg/day [8 mg BID]) and the end of Week 4 (at 20 mg/day [10 mg BID]). Adverse events were primarily reported during the first week of treatment and the majority of the commonly reported AEs resolved within a week of onset. A longer treatment duration of 12 weeks with clinic visits to assess safety at multiple time points (Weeks 1, 4, 8, and 12), combined with weekly phone calls for AE reporting, will allow for an adequate assessment of safety and durability of the treatment effect.

The primary endpoint for the study is a composite of the sum of modified items 1 to 11 of the TETRAS-ADL subscale and modified items 6 and 7 of the TETRAS-PS (ie, TETRAS composite outcome score). The TETRAS-ADL subscale is a patient-rated scale of the impact of tremor on day-to-day functioning that is administered by a trained interviewer. The TETRAS-ADL subscale directly measures how a patient functions by assessing activities impacted by tremor, such as eating and drinking, dressing and personal hygiene, carrying items, and finer motor skills (Elble, 2012). The TETRAS-ADL demonstrated sensitivity to change with JZP385 in the T-CALM study (see the JZP385 IB for full results). The TETRAS-PS is a valid and reliable clinical rating scale that has demonstrated sensitivity to change with treatment and is recommended by the Movement Disorder Society (MDS) Task Force to assess tremor severity (Elble, 2013). Items 6 (drawing an Archimedes spiral) and 7 (handwriting) of the TETRAS-PS evaluate the impact of upper limb tremor on performance, and thus represent an objective measure of the impact of upper limb tremor on functional tasks. Together, the items from the TETRAS-ADL subscale and TETRAS-PS that comprise the primary endpoint represent both patient-rated and objective measures of the functional impact of tremor.

The key secondary endpoint is the CGI-S. The clinician-rated CGI-S will specifically evaluate patients' ability to function due to ET and will adequately complement the primary endpoint. In the T-CALM study, a numerically higher percentage of patients reported improvement on the CGI-C when treated with JZP385 at 16 and 20 mg/day (administered as 8 and 10 mg BID, respectively) compared to placebo. Given that the CGI-C score generally correlates with the CGI-S such that improvement in one follows the other (Busner and Targum, 2007), these data provide preliminary support that CGI-S will be sensitive to improvement with JZP385.

4.3. Justification for Dose

The doses of JZP385 being evaluated in the study are 10, 20, and 30 mg/day administered in the morning. In the T-CALM study conducted in patients with ET, daily doses of 16 and 20 mg/day JZP385 (administered as the IR formulation at doses of 8 and 10 mg BID, respectively), improved symptoms of tremor across several clinically meaningful endpoints, including the TETRAS-ADL subscale, and were safe and well tolerated. Preliminary PK data and subsequent

PK simulations from the relative bioavailability study (Study CX-8998-CLN2-005) indicate that the same daily doses of the IR and ER formulations produce similar exposures (ie, steady state daily AUC). Therefore, this study will further evaluate the safety and efficacy of 20 mg/day JZP385, in addition to a higher dose of 30 mg/day and a lower dose of 10 mg/day administered orally, once daily in the morning. Preliminary safety and tolerability data from study JZP385-101, which enrolled 100 healthy older volunteers with a mean age of 44.1 years (median = 42.9 years; range 23 to 76 years) indicate that titrated doses of up to 36 mg were generally safe and well tolerated.

The titration schedule in this protocol is based on the PK of JZP385, as well as the titration experience in previous clinical studies conducted to date. Steady state levels of JZP385 are reached in 5 days. In the T-CALM study in patients with ET, participants received the IR formulation of JZP385 for 1 week each at doses of 8 and 16 mg/day before the final dose of 20 mg/day (doses were administered as 4, 8 and 10 mg BID, respectively). Preliminary safety and tolerability data from study JZP385-101 also indicate that the starting dose of 8 mg/day of the ER formulation of JZP385, with dose escalation at weekly intervals, was generally safe and well tolerated in healthy volunteers. Although these data indicate the 8 mg/day dose is tolerated as a starting dose, all participants in this study will initially receive 5 mg/day for the first week of the treatment period to evaluate whether starting at a lower dose may further improve tolerability.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant remaining in the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are diagnosed with ET (including ET plus) according to the MDS Consensus Statement on the Classification of Tremors from the Task Force on Tremor of the International Parkinson's and Movement Disorder Society (Bhatia, 2018) and centrally reviewed by an Eligibility Adjudication Committee (EAC; see Section 10.1.5).
3. Participants have moderate to severe disability associated with tremor at both the Screening and Baseline visits, as determined by all of the following:
   a. Score of ≥ 22 on the TETRAS-ADL subscale; and
   b. *Note:* This criterion has been removed in Amendment 3.
   c. CGI-S rating of at least moderate for participants' ability to function.

   Note: Participants who need washout of a medication(s) that could impact their tremor assessment (eg, medications that produce tremor **or** that treat tremor but are prohibited because of potential PK drug-drug interactions with study intervention [such as primidone]) at Screening Visit 1 must return to the clinic for a second Screening Visit (Screening Visit 2). For these participants, the Screening TETRAS-ADL subscale and CGI-S assessments that will be used to determine eligibility will be performed at Screening Visit 2, after participants have washed out their medication.

Sex and Contraceptive/Barrier Requirements

4. Participant is male or female.
   a. Male participants:

   Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 30 days after the last dose of study intervention:

   - Refrain from donating sperm.

PLUS, either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom with female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year (as described in Appendix 5) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.
  - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

b. Female participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of non-childbearing potential (WONCBP) as defined in Appendix 5.

OR

- Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of < 1%, as described in Appendix 5 during the study intervention period and for at least 30 days after the last dose of study intervention. *Note:* In addition to hormonal contraception, male partners of WOCBP are required to use barrier protection, eg, condoms, from the first dose of study intervention until 30 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive serum pregnancy test at Screening Visit 1 and negative urine pregnancy tests (unless serum is required by local regulations) at the Screening Visit 2 (if applicable) and at the Baseline Visit, see Section 8.3.5.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
6. Willing and able to comply with the study design schedule and other requirements.

Prior/Concomitant Antitremor Medications

7. If currently treated with antitremor medications, potential participants must be on a stable dosage for at least 6 weeks prior to Screening Visit 1 and must not anticipate making any changes to their antitremor medication for the duration of the study. *Note:* Treatment with some antitremor medications (eg, primidone) is not allowed in accordance with other exclusion criteria. Participants not currently taking antitremor medications who enter the study must have not taken any antitremor medication within 6 weeks prior to Screening Visit 1 and must not take any concomitant antitremor medication during the study.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Female participants who are pregnant, nursing, or lactating, or plan to become pregnant during the study or within 90 days of study completion.
2. Known history or current evidence of other medical or neurological conditions that may cause or explain the participant's tremor in the opinion of the investigator or central reviewer (when applicable), including, but not limited to:
    a. Parkinson's disease or features of atypical parkinsonism
    b. Psychogenic tremor
    c. Clinically significant symptoms or signs of dystonia, myoclonus, or ataxia
    d. Cerebellar disease other than ET
    e. Traumatic brain injury
    f. Alcohol abuse or withdrawal
    g. Mercury poisoning
    h. Hyperthyroidism
    i. Pheochromocytoma
    j. Head trauma or cerebrovascular disease within 3 months before onset of ET
    k. Multiple sclerosis

l. Clinically significant polyneuropathy in the opinion of the investigator, or

m. Family history or diagnosis of Fragile X syndrome

3. Considered at risk of falls in the opinion of the investigator.
4. Has evidence at Screening of severe cognitive impairment as defined by a Montreal Cognitive Assessment (MoCA; score < 20) or has cognitive impairment that in the opinion of the investigator would prevent completion of study procedures (including the ability to accurately self-report on study questionnaires) or the ability to provide informed consent.
5. History or presence of any acutely unstable medical condition, malignancy other than basal cell carcinoma or resected noninvasive cutaneous squamous cell carcinoma, or surgical history that could affect the safety of the participant or interfere with study efficacy, safety, or PK assessments; or the ability of the participant to complete the study per the judgment of the investigator.
6. History or presence of gastrointestinal (including prior bariatric bypass surgery), hepatic (including alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 2 x upper limit of normal [ULN] or total bilirubin ≥ 1.5 ULN), or severe renal impairment or end-stage renal disease, or any other condition that, in the opinion of the investigator, may interfere with absorption, distribution, metabolism, or excretion of drugs. Participants with hyperbilirubinemia who have a history of Gilbert's syndrome may be eligible for the study; participants whose screening laboratory test results demonstrate predominantly unconjugated hyperbilirubinemia must be evaluated to exclude other diagnoses and, subsequently, must have the diagnosis of Gilbert's syndrome established in order to be eligible.
7. Presence of significant cardiovascular disease at Screening including but not limited to the following:

   a. Myocardial infarction within the past year;

   b. Unstable angina pectoris;

   c. Symptomatic congestive heart failure (American College of Cardiology/American Heart Association stage C or D);

   d. Revascularization procedures within the past year;

   e. Ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillator or medication therapy;

   f. Uncontrolled hypertension, or systolic blood pressure ≥ 155 mmHg or diastolic blood pressure ≥ 95 mmHg (based on the average of triplicate assessments at Screening Visit 1, Screening Visit 2, or Baseline);

   g. Clinically significant ECG abnormality per the investigator assessment, or Fridericia's corrected QT interval (QTcF) > 450 msec for men and > 470 msec for women, based on the average of triplicate assessments at Screening or Baseline; or

h. Any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize participant safety in the study

8. History or presence of bipolar and related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria.
9. Current suicidal risk as determined from history, by presence of active suicidal ideation as indicated by positive response to item 4 or 5 on the C-SSRS (within the past 24 months), or any history of suicide attempt; current or past (within 1 year) major depressive episode according to DSM-5 criteria. Participants with stable treated depression are allowed per the judgment of the investigator or the treating medical practitioner and the antidepressant treatment has to be stable for at least 6 months prior to Screening and remain stable for the duration of the study.
10. History (within past 2 years at screening) or presence of a diagnosed substance use disorder (including alcohol, tobacco, and cannabis) according to DSM-5 criteria, known drug dependence, or seeking treatment for alcohol or substance abuse related disorder.

Prior/Concomitant Therapy

For the following exclusion criteria, please refer to the Trial Site Binder for a list of examples of prohibited therapies and medications.

11. Prior magnetic resonance (MR)-guided focused ultrasound thalamotomy, surgical intervention (eg, deep brain stimulation, ablative thalamotomy, gamma knife thalamotomy), or inability to refrain from using a device for treatment of tremor for the duration of the treatment period.
12. Botulinum toxin injection for the treatment of upper limb tremor in the 6 months before screening or planned use at any time during the study.
13. Treatment with any medication that could produce tremor taken within 2 weeks or 5 half-lives (whichever is longer) before the evaluation of tremor at the Screening Visit (Screening Visit 1 or 2, as applicable) or anticipated use at any time during participation in the study. *Note:* Regular use of sleep medications or anxiolytics (eg, benzodiazepines) to improve sleep or anxiety is permitted provided it will continue to be used at stable dosages throughout the study (ie, PRN use is not permitted).
14. Use of prescription or nonprescription drugs or other products known to be inducers of CYP3A4 that are known to decrease AUC by > 30% (eg, primidone) and which cannot be discontinued at least 4 weeks before Baseline or planned use at any time during the study. *Note:* If a potential participant is taking primidone at screening, it must be discontinued at least 4 weeks prior to Screening Visit 2.
15. Use of prescription or nonprescription drugs, or other products (eg, grapefruit, grapefruit juice, or Seville oranges) known to be strong or moderate inhibitors of CYP3A4, that cannot be discontinued 2 weeks or 5 half-lives, whichever is longer, before Baseline or planned use at any time during the study.

16. Use of proton pump inhibitors that cannot be discontinued at least 2 weeks before Baseline, or planned use at any time during the study. Occasional use of antacids or histamine-2 receptor antagonists will be permitted, but antacids should be taken at least 4 hours before or after study intervention; and histamine-2 receptor antagonists should be taken at least 4 hours after and at least 12 hours before study intervention.
17. Inability to refrain from use of medication/substance(s) that might produce tremor or interfere with the evaluation of tremor on study visit days prior to discharge such as, but not limited to, stimulant decongestants, beta-agonist bronchodilators, and alcohol. Participants who consume caffeine or use tobacco should take their regular amount of caffeine or tobacco on the clinic days.

Prior/Concurrent Clinical Study Experience

18. Received an investigational drug 30 days or 5 half-lives prior to the Baseline visit (whichever is longer) or plans to use an investigational drug (other than the study intervention) during the study.
19. Received any study intervention in a previous JZP385 (formerly known as CX-8998 or MK-8998) clinical study.

Diagnostic assessments

20. A fall in blood pressure (ie, a decrease in systolic blood pressure ≥ 20 mm Hg or diastolic blood pressure ≥ 10 mm Hg), or a heart rate increase (ie, > 30 beats per minute) observed on the average of the triplicate orthostatic assessments at Baseline, or in the opinion of the investigator, the participant was symptomatic for orthostatic hypotension.
21. Laboratory value(s) at screening outside the laboratory reference range that is (are) considered clinically significant by the investigator (clinical chemistry, hematology, and urinalysis). *Note:* Screening laboratory tests may be repeated, as needed.
22. Urine drug screen positive at Screening for drugs of abuse (eg, phencyclidine [PCP], cocaine, cannabinoids (including cannabidiol [CBD]), opiates, barbiturates, amphetamines, methadone, or MDMA [Ecstasy]) unless explained by a medication that is being washed out during the Screening Period (eg, primidone) or by use of an allowed prescription medication (eg, benzodiazepine as outlined in Exclusion Criterion #13). *Note:* Medical or recreational use of cannabinoids (including CBD) is not permitted at Screening or throughout the duration of study participation. If the interpretation of positive results is ambiguous, or there are extenuating circumstances, a repeat urine drug screen may be performed if approved by the investigator and the medical monitor.

Other Exclusions

23. Regular use of more than 3 units of alcohol per day (see also Exclusion Criterion 17). A unit of alcohol is defined as a 12-fluid ounce (350 mL) glass of beer (5% alcohol by volume), a 5-fluid ounce (150 mL) glass of wine (12% alcohol by volume), or a 1.5 fluid ounce (44 mL) glass of spirit (40% alcohol by volume).
24. Regular consumption of caffeine > 400 mg/day or > 4 cups of coffee per day.
25. Allergy or sensitivity to any ingredients in the study intervention formulation or placebo.
26. Any other condition and/or situation that causes the investigator or medical monitor to deem a participant unsuitable for the study.

5.3. Lifestyle Considerations

No specific restrictions to lifestyle are required for this study.

5.3.1. Meals and Dietary Restrictions

As noted in Exclusion Criterion 15, refrain from consumption of grapefruit, grapefruit juice, or Seville oranges from 2 weeks before the start of study intervention until after the last dose of study intervention.

Participants will be instructed to take a single oral daily dose of study intervention in the morning, on an empty stomach, upon awakening (and no more than 1 hour after awakening). Participants will also be instructed to abstain from eating or drinking (except water) for 60 minutes after taking the study intervention.

Participants will also be instructed to refrain from eating or drinking (except water) prior to the clinic visit, such that study intervention is taken on an empty stomach in the clinic. Participants should also abstain from eating or drinking (except for water) for 60 minutes after taking study intervention. At clinic visits, a light breakfast should be served approximately 1 hour after dosing and should be consumed within 15 to 20 minutes.

5.3.2. Caffeine, Alcohol, and Tobacco

As noted in exclusion criteria 23 and 24 (Section 5.2), consumption of > 3 units of alcohol or > 400 mg caffeine per day is not permitted during the study. As noted in Exclusion Criterion 17, consumption of alcohol is prohibited on clinic days.

Participants who consume caffeine or use tobacco should take their regular amount of caffeine or tobacco on clinic days, as per their regular schedule.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to receive study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any applicable SAEs (see Section 8.4.1).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once provided rescreening is approved by the medical monitor. Potential participants screened an additional time (rescreened) who had previously met the inclusion criterion relative to ET diagnosis confirmed by the EAC (Inclusion Criterion #2) will not be assessed again relative to that criterion as part of the rescreening process and will not have to complete the TETRAS-PS assessment at Screening Visit 1 or 2, as applicable. Rescreened participants should be assigned a new participant number.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

As indicated in Section 6.5, dose modifications are not permitted. See Section 7.1.2 for details regarding temporary interruption of study intervention.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s)/Treatment(s) Administered

The study interventions planned for use in this study are described in Table 4 below.

Table 4: Study Treatment/Intervention

Treatment Arm	Intervention/ Treatment Name[a]	Formulation	Unit Dose Strength(s)[b]	Dosage Level(s)	Route of Administration	Use	Sourcing	Package	Labeling	Storage Conditions
1	Placebo	Capsule	Placebo	3 x placebo QD	Oral	Placebo comparator	Provided centrally by the sponsor	Placebo capsules will be provided in blister cards; and labeled as required per country requirement.	Double-blind	Store at 2 to 8ºC
2	JZP385 (DR2)	Capsule	Baseline Visit: 5 mg JZP385	1 x 5 mg QD + 2 x placebo QD	Oral	Experimental	Provided centrally by the sponsor	JZP385 capsules will be provided in blister cards; and labeled as required per country requirement.	Double-blind	Store at 2 to 8ºC
			Weeks 2-12: 10 mg JZP385	1 x 10 mg QD + 2 x placebo QD						
3	JZP385 (DR2)	Capsule	Baseline Visit: 5 mg JZP385	1 x 5 mg QD + 2 x placebo QD	Oral	Experimental	Provided centrally by the sponsor	JZP385 capsules will be provided in blister cards; and labeled as required per country requirement.	Double-blind	Store at 2 to 8ºC
			Week 2: 10 mg JZP385	1 x 10 mg QD + 2 x placebo QD						
			Weeks 3-12: 20 mg JZP385	2 x 10 mg QD + 1 x placebo QD						
4	JZP385 (DR2)	Capsule	Baseline Visit: 5 mg JZP385	1 x 5 mg QD + 2 x placebo QD	Oral	Experimental	Provided centrally by the sponsor	JZP385 capsules will be provided in blister cards; and labeled as required per country requirement.	Double-blind	Store at 2 to 8ºC
			Week 2: 10 mg JZP385	1 x 10 mg QD + 2 x placebo QD						
			Week 3: 20 mg JZP385	2 x 10 mg QD + 1 x placebo QD						
			Weeks 4-12: 30 mg JZP385	3 x 10 mg QD						

Abbreviations: mg = milligram; QD = once daily.

[a] The JZP385 DR2 formulation is delayed release formulation 2 ie, capsules containing a combination of IR and DR pellets; details of the formulation can be found in the JZP385 IB.

[b] The dose strength of JZP385 is based on the active moiety in the drug product.

6.2. Preparation/Handling/Storage/Accountability

Further guidance and information for the final disposition of unused study interventions are provided to the sites.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants who sign the informed consent form (ICF) will receive a participant number assigned by interactive response technology (IRT) at screening. The participant number identifies the participant for all study procedures that occur throughout the study. This number is unique and once assigned, cannot be reassigned to another study participant.

Treatment allocation/randomization for this study will occur centrally through the use of an IRT. Participants eligible for the study will be randomized in a 1:1:1:1 ratio to receive once daily doses of 10, 20, or 30 mg JZP385 or placebo. Randomization will be stratified by the TETRAS composite outcome score (≤ 17 or > 17) and the use of concomitant antitremor medication (Yes or No), as assessed at the Baseline Visit.

A double-blind approach will be used throughout the 12-week treatment period. During the study (including the titration period), the number of capsules taken each day will be the same for patients randomized to each treatment. JZP385 and placebo capsules will look and feel identical.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant.

If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and IRT system, as applicable. The participant's treatment assignment may be unblinded for regulatory reporting purposes. Notification of the treatment assignment is only made known to those who require it for safety reporting and submission processes. All other individuals involved in the study, including the investigator, will remain

blinded to treatment assignment. Participants for whom the blind is broken for this reason will not be withdrawn from the study.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.4. Study Intervention/Treatment Compliance

When participants administer study intervention in the clinic (ie, at Week 1, Week 4, Week 8, and Week 12 visits), they will take the last dose from the kit dispensed at the previous visit, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

Participants will take the first dose of study intervention at home in the morning on the day following the Baseline Visit (or Day 1). When participants self-administer study intervention at home, compliance with study intervention will be assessed at each clinic visit. Compliance will be assessed by counting returned capsules during the site visits and documented in the source documents Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of JZP385 or placebo capsules dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates should also be recorded.

6.5. Dose Modification

No dose adjustments or modifications will be allowed. Participants who cannot tolerate their assigned fixed dose of JZP385 will be discontinued from the study intervention (see Section 7.1). Every effort should be made to have the participant attend an Early Discontinuation Visit (see Section 1.3).

6.6. Continued Access to Study Intervention After the End of the Study

There is no continued access to study intervention upon completion of the study. Participants should follow-up with their healthcare provider regarding the resumption of any medications that were discontinued prior to study participation.

6.7. Treatment of Overdose

Any dose greater than the assigned dose that a participant receives in a 24-hour time period will be considered an overdose. In a case of an acute overdose, it is recommended that the stomach is emptied and that oral gavage with activated charcoal is used to reduce absorption of JZP385. See the JZP385 IB for further details.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or discontinued.

- Report any AE/SAE or laboratory abnormalities associated with the overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

Concomitant treatment with some medications/therapies is not permitted during the study (see Exclusion Criteria 11 to 17 in Section 5.2). A full list of prohibited medications is provided in the Investigator Trial Site Binder.

JZP385 has a potential to inhibit P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in the intestine at the studied doses. Therefore, medicines that are known sensitive substrates of P-gp and BCRP should be administered approximately 12 hours apart from study intervention. In vitro data indicate JZP385 is a weak inducer of CYP3A4 and CYP2B6. Therefore, medicines that are sensitive substrates of CYP3A4 and CYP2B6 that are taken concomitantly with JZP385 should be monitored for potential decrease in pharmacological effect.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation from study intervention does not represent withdrawal from the study (Section 7.2). Participants may discontinue from study intervention at any time for any reason, or at the discretion of the investigator. In addition, a participant may be dropped from study intervention by the investigator or sponsor for safety, behavioral, compliance and/or administrative reasons.

For participants who discontinue study intervention, all effort should be made to complete the procedures listed in the Early Discontinuation Visit (Section 1.3). Participants should be asked to return 2 weeks later for the EoS/Safety Follow-up Visit. If the Early Discontinuation Visit occurs 2 or more weeks after the last dose of study intervention, an additional safety follow-up visit is not required.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

A participant must be discontinued from study intervention for any of the following reasons:

- The participant or participant's legal representative requests to discontinue study intervention.
- The participant has an AE that may compromise the participant's continued participation.
- The participant has a suicide risk reported or assessed by the Columbia Suicide Severity Rating Scale (C-SSRS; see Section 8.3.6).
- The participant has a positive serum pregnancy test or becomes pregnant during the study (see Appendix 5 and Section 8.3.5).
- The participant is noncompliant with study intervention or procedures.
- Sponsor decides to terminate the study prior to completion.

7.1.1. Positive Alcohol or Urine Drug Screens

The investigator may discontinue study intervention for any participant with a positive alcohol or urine drug screen. However, if the investigator believes discontinuation of study intervention is not necessary despite a positive alcohol or urine drug screen result, approval from the medical monitor is required in order to retain the participant in the study.

7.1.2. Temporary Discontinuation/Study Intervention Interruption

If a participant must temporarily interrupt study intervention for any reason, the sponsor's medical monitor should be consulted to determine whether the participant will continue in the study.

7.2. Participant Discontinuation/Withdrawal from the Study

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

At the time of discontinuing from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up, and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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 study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

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 study site. The following actions must be taken if a participant fails to return to the clinic for a required study 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 study.
- 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 study.

Discontinuation of specific sites or of the study as a whole are handled as part of Study and Site Start and Closure Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). For clinic visits, participants should be admitted to the study site in the morning. The investigator may opt to have the participant attend an unscheduled visit, if deemed necessary, at any time during the study. Some clinic visits may be conducted remotely, if required due to the COVID-19 pandemic, and with approval from the sponsor's medical monitor, as noted in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the medical monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

After screening procedures have been completed and eligibility criteria have been confirmed, provide eligible participants with instructions on how to discontinue any excluded medications. Document that the investigator has determined that discontinuation is safe and medically appropriate, and the discontinuation is medically supervised. The medical monitor should be contacted if there are any questions regarding discontinuation of excluded medications.

For clinical outcome assessment measures, the same person should perform each assessment for the same participant throughout the duration of the study, whenever possible.

The TETRAS-PS assessment will be administered and scored by a blinded trained rater at the site throughout the study. Blinded raters are defined as clinical site personnel (eg, a nurse, physician, experienced study coordinator) who must have undergone the required training in administration and scoring of the TETRAS-PS. Blinded raters must be restricted from efficacy and safety scale information, AEs, concomitant therapy, laboratory data, imaging data, or any other data that have the potential of revealing the study intervention assignment. Blinded raters must not be involved with any other aspect of participant management/care and must not share any information they collect about participants with other site staff. Principal Investigators should not serve as blinded raters, except when approved by the sponsor. Appropriate training for rating scales will be provided by the rater training vendor. Documentation of how and when data are filed, stored, and transmitted to or from the study site will be provided to the sites. A video recording of the TETRAS-PS conducted at Screening will undergo independent review by an expert rater from the central Eligibility Adjudication Committee (EAC) to confirm a correct diagnosis of ET. This video recording (and subsequent EAC review) will not be needed for rescreening participants who have already completed this process.

Pharmacokinetic results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. The maximum amount of blood collected from each participant over the duration of the study as shown in the SoA (Section 1.3), including any extra assessments that may be required, will not exceed 125 mL (as described in the laboratory manual). However, repeat of unscheduled samples may be taken for safety reasons or for technical issues with samples.

8.1. General Administrative Procedures

8.1.1. Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant/legal representative prior to participation in this study. No study procedures, including washout of prior medications, may be undertaken before signing the ICF. A signed copy of the ICF should be given to the participant and the original should be placed in the participant's medical records.

8.1.2. Assignment of Participant Number

Each participant who signs the ICF will be assigned a unique number that will identify the participant throughout the study. Once a number has been assigned, it cannot be reassigned to another study participant.

8.1.3. Medical History

A medical history will be obtained by the investigator or a medically qualified designee (consistent with local regulations). All active conditions should be recorded and any condition diagnosed within the participant's lifetime that the investigator deems clinically significant. The information will include, but is not limited to, symptoms of ET (current and past, including symptoms experienced prior to any ET treatment); history and treatment (if any) of cardiovascular, pulmonary, gastrointestinal, hepatic, renal, immunologic, neurologic, or psychiatric disease; reproductive status; current contraceptive method (if appropriate); and confirmation of relevant inclusion and exclusion criteria.

8.1.4. Medication Review (Prior and Concomitant Medications)

The investigator or medically qualified designee should review the participant's prior medication use within 30 days (any medication(s) taken for ET should be reviewed within the prior 6 weeks). Medication that is required to be washed out prior to the study should also be recorded. All medications currently being taken by the participant should be recorded.

Additional information related to any medications taken for the treatment of ET since diagnosis (eg, treatment duration, satisfaction) should be collected.

8.1.5. Inclusion and Exclusion Criteria Review

All inclusion and exclusion criteria should be reviewed by the investigator to ensure the participant qualifies for the study. A research diagnostic verification form will be completed by the site within 2 days of completion of the TETRAS-PS assessment, which will be video-recorded at Screening Visit 1 or Screening Visit 2, as applicable (see Section 1.3), and rated by a trained blinded rater on site. To support selection of the appropriate patient population in the study, the video recording of the TETRAS-PS conducted at Screening will undergo central review by an independent expert rater from the EAC to confirm a correct diagnosis of ET. Results of this review will be available in the electronic clinical outcome assessment provider's portal. Screening results from all participants meeting the eligibility requirements will be further assessed for final approval of inclusion in the study. Details of the eligibility review by the EAC will be provided in the EAC Charter.

8.1.6. Timing of Study Intervention Dosing

Participants will be requested to take study intervention in the morning on an empty stomach upon awakening (and no more than 1 hour after awakening). After the Baseline Visit, on days when participants come into the clinic, study intervention will be administered on site on an empty stomach. When participants administer study intervention in the clinic (ie, at the Week 1, Week 4, Week 8, and Week 12 visits), they will take the last dose from the kit dispensed at the previous visit, under medical supervision.

8.1.7. Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is designed as a rapid screening instrument to detect mild cognitive dysfunction. The MoCA test was validated in 2000 and revalidated in 2004 (Nasreddine, 2005). The assessment comprises a 30-question test that can be completed in approximately 10 minutes. The MoCA assesses different cognitive domains, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points; a score of < 20 is considered exclusionary in the current study. According to the DSM-V criteria, people with major neurocognitive disorders typically have scores on cognitive scales that fall at least 2 SD below the mean of a normative sample. The eligibility cutoff of < 20 represents 2 SD below the mean for the highest age group (75 to 85 years) and lowest education level (elementary school or lower) in a rigorously selected normal cognitive population in Sweden (N = 758) (Borland, 2017). In the largest population-based US sample (N = 2,653) where cognitive impairment was not rigorously screened out, the eligibility cut-off of < 20 represents 1 SD below the mean (Rossetti, 2011), lending additional support for this cut-off in a different sample.

A sample MoCA can be found in the Investigator Trial Site Binder.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. Tremor Research Group Essential Tremor Rating Assessment Scale – Activities of Daily Living

The Tremor Research Group first published TETRAS in 2008 (Elble, 2008). TETRAS consists of a 12-item activities of daily living (ADL) subscale, and a 9-item performance subscale (PS). TETRAS was developed as a rapid clinical assessment of ET that requires no equipment other than pen and paper.

The ADL subscale includes many of the items assessed in previously developed scales for the evaluation of tremor (Fahn, 1993; Louis, 2000; Bain, 1993), including eating and drinking, dressing and personal hygiene, carrying items and finer motor skills. Each item in the TETRAS-ADL subscale is rated on a 0 to 4 scale, with 0 representing normal activity and 4 representing severe abnormality. The sum of the individual scores provides the overall score, ranging from 0 to 48. The TETRAS-ADL subscale has face validity, has preliminarily demonstrated test-retest reliability, and is highly correlated with the TETRAS-PS (Elble, 2012; Elble, 2016). It has also demonstrated sensitivity to change with JZP385 treatment in the

T-CALM study. Items 1 to 11 of the TETRAS-ADL subscale assess the impact of tremor on day-to-day functioning, while item 12 assesses the social impact of tremor.

A sample TETRAS-ADL subscale can be found in the Investigator Trial Site Binder.

During the study, the TETRAS-ADL will be administered and scored by a trained rater at the site.

8.2.2. Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale

The TETRAS-PS quantifies tremor in the head, face, voice, limbs, and trunk. Each item on the TETRAS-PS is rated on a 0 to 4 rating scale, with scoring of upper limb tremor allowing for 0.5-point increments. Specific amplitude ranges (measured in centimeters) define the tremor rating. Raters first estimate the maximum amplitude of tremor and then assign the corresponding rating. The sum of the individual rating scores provides the overall performance score, ranging from 0 to 64. Administration of the TETRAS-PS takes approximately 10 minutes. The TETRAS-PS has demonstrated both test-retest reliability and sensitivity to change (Elble, 2012; Study CX-8998-CLN2-001 [T-CALM] – see IB for details) and was given a "recommended" rating as a tremor severity scale by the MDS (Elble, 2013).

TETRAS-PS items 6 and 7 are the Archimedes spiral and handwriting assessments, respectively. Both are rated on a 0 (normal) to 4 (severe) rating scale. The Archimedes spiral is tested in both the right and the left hands, while the handwriting is assessed with the dominant hand only. The sum of the TETRAS-PS items 6 and 7 provides a score ranging from 0 to 12. The Archimedes spiral and handwriting tasks have been integral in the routine examination of patients with tremor for decades, heavily utilized in tremor rating scales beyond the TETRAS (Bain, 1993; Fahn, 1993; Louis, 2001), and have demonstrated sensitivity to change with treatment (Calzetti, 1982; Haubenberger, 2011; Hopfner, 2015; Koller, 1986; Shill, 2004; Tolosa and Loewenson, 1975).

A sample TETRAS-PS can be found in the Investigator Trial Site Binder.

During the study, the TETRAS-PS assessment will be administered and scored by a blinded trained rater at the site throughout the study and conducted as detailed in Table 5.

Table 5: TETRAS-PS Assessments

Visit	Description of Assessment
Screening Visit 1	A blinded rater will assess TETRAS-PS if participant does not need to washout of a medication that impacts tremor. Video record this assessment. Participants who will undergo washout of medications that impact tremor (eg, primidone) are assessed at Screening Visit 2 only.
Screening Visit 2 (if applicable)	A blinded rater will assess TETRAS-PS if participant needs to washout of a medication that impacted tremor reported at Screening Visit 1. Video record this assessment.
Baseline	A blinded rater will assess TETRAS-PS (assess at same time of day as the anticipated 1-hour postdose assessment at post-baseline visits) [Optional] Assess items 6 and 7 of the TETRAS-PS serially across the day at 6 time points: initial assessment, 1 (use assessment from full TETRAS-PS for this time point), 2, 4, 6, and 8 hours after initial assessment
Week 4	A blinded rater will assess TETRAS-PS 1-hour postdose.
Week 8	A blinded rater will assess TETRAS-PS 1-hour postdose. [Optional] Assess items 6 and 7 of the TETRAS-PS serially across the day at 6 time points: predose, 1 (use assessment from full TETRAS-PS for this time point), 2, 4, 6, and 8 hours postdose (time points should correspond to the same time of day as Baseline assessments).
Week 12	A blinded rater will assess TETRAS-PS 1-hour postdose.
E/D Visit	A blinded rater will assess TETRAS-PS 1-hour postdose (assess at same time of day as 1-hour postdose assessment at post-baseline visits).

Abbreviations: EAC = Eligibility Adjudication Committee; ET = essential tremor; TETRAS-PS = The Essential Tremor Rating Assessment Scale - Performance Subscale.
Note: Potential participants screened an additional time (rescreened) who had previously met the inclusion criterion relative to ET diagnosis confirmed by the central EAC (Inclusion Criterion #2) will not have to complete the TETRAS-PS assessment and subsequent central review by the EAC at Screening Visit 1 or 2, as applicable.

8.2.3. Clinical Global Impression of Severity

The CGI-S will be assessed by qualified medical personnel (ie, a clinician) to assess the severity of participants' ET. The severity assessment will rate the participants' ability to function due to their ET.

The CGI-S is a 5-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness. The responses to this clinician-completed scale range from 1 (no limitations) to 5 (severe). The clinician will rate his/her impression of the severity of the participant's current ability to function due to their ET relative to his/her experience with this patient population.

A sample CGI-S can be found in the Investigator Trial Site Binder.

8.2.4. Quality of Life in Essential Tremor Questionnaire

The Quality of life in Essential Tremor Questionnaire (QUEST) was developed to specifically assess the impact of ET on health-related quality of life (Tröster, 2005). The QUEST is a 30-item questionnaire comprising 5 subscales (physical, psychosocial, communication, hobbies/leisure, and work/finance) and a total score, plus 3 additional items relating to sexual function and satisfaction with tremor control and medication side effects. Initial reports provide preliminary support of its reliability and validity. The internal consistency was very good to excellent for 4 of the subscales and the total score, and moderately high for the Work/Finance subscale (Tröster, 2005). The QUEST has also demonstrated sensitivity to change with deep brain stimulation for ET (Sandvik, 2012).

A sample QUEST questionnaire can be found in the Investigator Trial Site Binder.

8.2.5. Clinical Global Impression of Change

The CGI-C will be assessed by qualified medical personnel (ie, a clinician) to assess the change in the participants' ability to function due to ET.

The CGI-C is a 5-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. Clinicians will rate their impression of any change in the severity of the participant's condition since Baseline on a 5-point scale ranging from 1 (much improved) to 5 (much worse). Clinicians' rating will focus on the participants' change in their ability to function due to ET.

A sample CGI-C can be found in the Investigator Trial Site Binder.

8.2.6. Patient Global Impression of Change

The PGI-C is a 5-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. Participants will rate the change in their condition since Baseline on a 5-point scale ranging from 1 (much improved) to 5 (much worse). Participants' rating will focus on the change in their ability to function due to ET.

A sample PGI-C can be found in the Investigator Trial Site Binder.

8.2.7. 36-item Short Form Health Survey Version 2

The 36-item Short Form Health Survey Version 2 (SF-36v2) is a multi-purpose, short form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index (Hays and Stewart, 1992; Ware and Sherbourne, 1992).

A sample SF-36v2 can be found in the Investigator Trial Site Binder.

8.2.8. Essential Tremor Embarrassment Assessment

The Essential Tremor Embarrassment Assessment (ETEA) is a patient-rated questionnaire administered by a health care provider or researcher that contains 14-items assessing embarrassment related to tremor. Participants provide a simple response (disagree or agree) to each of the 14-items, the sum of which yields an initial score (Score A, range = 0 to 14). Participants then provide a more nuanced response to each question on a 0-to-5-point Likert

scale ranging from disagree (0) to agree strongly (5). The sum of the nuanced responses yields a second score (Score B, range = 0 to 70). Higher scores on both the simple and nuanced responses indicate greater embarrassment. The ETEA was developed based on input from both tremor experts and patients and was subsequently validated in 75 patients with ET where it demonstrated high internal consistency (Traub, 2010). The ETEA has also demonstrated sensitivity to change with treatment in patients with ET (Kreisler, 2019).

A sample ETEA questionnaire can be found in the Investigator Trial Site Binder.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems; a genitourinary exam is excluded. Height and weight (in ordinary indoor clothes without shoes) will also be measured and recorded as indicated in the SoA in Section 1.3.

Any abnormalities identified at the screening physical exam should be recorded as medical history.

8.3.2. Vital Signs

Vital signs (to be taken before blood collection, when applicable), including body temperature, respiratory rate, and orthostatic blood pressure, and pulse rate will be assessed at each clinic visit, as indicated in the SoA (Section 1.3).

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Orthostatic blood pressure (systolic and diastolic) and pulse rate will be obtained after the participant has been in a supine position for at least 5 minutes, and again after the participant has been standing for 2 minutes. Baseline and Screening orthostatic assessments will be taken in triplicate (at 15 to 30-minute intervals), and a single orthostatic assessment will be performed at all other visits.

Respiratory rate and body temperature will be assessed after the participant has been resting and seated (or supine) for at least 5 minutes.

8.3.3. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals.

Electrocardiograms will be reviewed, initially interpreted, signed, and dated by the investigator or a designated physician after each ECG collection. All ECGs (with the exception of ECGs for participants who are screen failures) will be transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will conduct a full over-read. A report based on data from this over-read will be issued to the site.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with abnormal values considered clinically significant during participation in the study and considered related to study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 3, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.3.5. Pregnancy Testing

Refer to Section 5.1 for pregnancy testing entry criteria.

Pregnancy testing (urine or serum as required by local regulations) should be conducted as specified in the SoA (Section 1.3). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

JZP385 is considered to be a central nervous system-active study intervention. Participants being treated with JZP385 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of suicidal ideation or behavior, should undergo a risk assessment. All factors contributing to suicidal ideation or behavior should be evaluated and consideration should be given to discontinuation of the study intervention.

Baseline assessment of suicidal ideation and behavior/ intervention emergent suicidal ideation and behavior will be monitored using the C-SSRS. At the Screening Visit, the Baseline/Screening Version of the C-SSRS will be administered to participants to exclude any individuals with active suicidal ideation or behavior.

The Since Last Visit Version of the C-SSRS will be administered to participants at every clinic visit after their Screening visit, including the Baseline and Follow-up visits. At the Baseline Visit, any participant who reports active suicidal ideation (eg, a positive response to Question 4

or 5 on the C-SSRS) or behavior (eg, a positive response to any suicidal behavior question on the C-SSRS) will be excluded. At post-baseline visits, active suicidal ideation or behavior must be recorded as an AE and reported to the sponsor or designee within 24 hours of first knowledge of the event by study personnel. Please refer to Appendix 4 for details on reporting other reportable experiences (OREs).

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 4.

Adverse events 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 all AEs. 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 4.

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

All AEs and SAEs will be collected from the start of study intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and within 24 hours of first knowledge of the event by study personnel, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs. All SAEs that occur after the consent form is signed but before study intervention/treatment must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified study intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading 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 will be followed until resolution, stabilization, the event

is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 4.

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 intervention 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 intervention 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.

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.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

The Reference Safety Information for the determination of expectedness of JZP385 can be found in the IB.

8.4.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 30 days after last study intervention.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered an AE or SAE, any pregnancy complications or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. After obtaining the necessary signed informed consent, the investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor. Neonates will be followed for 6 months following birth.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former study participants/ pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.4.6. Adverse Events of Special Interest and Other Reportable Experiences

The AEOSIs defined for this study are based on observations from the phase 1 and 2 studies that have been conducted with JZP385 to date and consist of the following: hallucinations of any type and syncope (including presyncope).

Additional information regarding the reporting of AEOSIs is provided in Appendix 4.

8.4.7. Other Reportable Experiences: Overdose, Medication Errors, and Misuse

Overdose, (defined as any dose administered or received that was higher than the intended dose), medication errors (defined as any unintentional error in the dispensing or administration of the study intervention), and misuse of the study intervention are considered OREs. The method for completing and transmitting reports of these experiences is provided in Appendix 4. Guidelines for the treatment of overdose are provided in Section 6.7.

If any overdose, medication error, or misuse of the study intervention results in an AE this must be recorded. If the AE is serious, it must also be reported as described in Appendix 4.

8.5. Pharmacokinetics

Blood samples of approximately 3 mL per time point will be collected and processed to measure plasma concentrations of JZP385, and its metabolites, if applicable, as specified in the SoA (Section 1.3). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Instructions for the collection and handling of biological samples will be provided by the sponsor in a Laboratory Manual. Each plasma sample will be divided into 2 aliquots (primary plasma PK sample and a back-up plasma PK sample). Participant confidentiality will be maintained.

Study intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Pharmacogenomics

A blood sample of approximately 10 mL will be collected and analyzed to detect polymorphisms in specific genes and determine if unique single nucleotide polymorphisms or more complex Mendelian factors might be a contributing factor in a patient's response to JZP385.

Participant confidentiality will be maintained at all times by the blinding of samples.

See Appendix 6 for information regarding genetic research. Details on processes for collection and handling of biological samples, as well as shipment and destruction of these samples can be found in the Investigator Trial Site Binder.

8.7. Biomarkers

Biomarkers will not be evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not being conducted in this study.

8.9. Health Economics

Health economics are not being assessed in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The null and alternative hypotheses for analysis of the primary estimand variable are:

$$H_0: u_{JZP385} = u_{Placebo}$$

$$H_1: u_{JZP385} \neq u_{Placebo}$$

Specifically, the null hypothesis states that there is no difference in the mean change on the TETRAS composite outcome score from Baseline to Week 12 between each dose of JZP385 and the placebo control group. The alternative hypothesis is that the mean change on the TETRAS composite outcome score from Baseline to Week 12 is not equal between each dose of JZP385 and the placebo control group.

The null and alternative hypotheses for analysis of the key secondary estimand variable are:

$$H_0: p_{JZP385} = p_{Placebo}$$

$$H_1: p_{JZP385} \neq p_{Placebo}$$

Specifically, the null hypothesis states that there is no difference in the proportion of participants who improved by ≥ 1 point on the CGI-S from Baseline to Week 12 between each dose of JZP385 and the placebo control group. The alternative hypothesis is that the proportion of participants who improved by ≥ 1 point on the CGI-S from Baseline to Week 12 is not equal between each dose of JZP385 and the placebo control group.

Each JZP385 treatment group will be compared individually to placebo. The remaining secondary and exploratory endpoints will not be controlled within the formal hypothesis test for type I error. All safety analyses will be descriptive; no formal statistical testing will be performed.

9.2. Sample Size Determination

A sample size of 80 evaluable participants per treatment group will provide 90% power to detect a difference of 3.1 points for the change from Baseline to Week 12 on the TETRAS composite outcome score between JZP385 and placebo, with a common SD of 6.0 points. This sample size will also provide 91.7% power to detect a 26% between-treatment (assuming JZP385 at 66% versus placebo at 40%) difference in proportion of participants who improved by at least 1 point on the CGI-S from Baseline to Week 12. Assuming a 20% dropout rate, a total of 400 participants (100 participants per treatment group) will be randomized. The sample size calculation for the TETRAS composite outcome score is based on t-test and the CGI-S sample size calculation is based on chi-square test, both tests are 2-sided at the significance level of 0.05.

For the TETRAS composite outcome score, at least 80% power is still achieved if there is a reduction of 0.4 points from the assumption in the difference in mean change from baseline (assuming a constant common standard deviation) or an increase in common standard deviation by 1 point, (assuming a constant difference in means).

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	The Enrolled Analysis Set will include all participants who provide informed consent for this study. This analysis set will be used to summarize participant disposition, major protocol deviations, and inclusion/ exclusion from the analysis sets as well as reasons for exclusion from each analysis set. Summaries will be presented overall and by the randomization group.
Safety	The Safety Analysis Set will include all participants who receive at least 1 dose of study intervention. This analysis set will be used for safety analyses, and participants should be summarized according to actual treatment.
Modified Intent-to-treat (mITT) analysis set	The mITT Analysis Set will include participants who are randomized to any of the JZP385 treatment groups or placebo, receive at least 1 dose of study intervention, and have baseline and at least 1 non-missing within window post-baseline TETRAS composite outcome score. This population will be analyzed for all efficacy endpoints. If a participant in the mITT population does not have any assessment for a particular secondary efficacy endpoint, that participant will be excluded from the analysis of that endpoint.
PK Analysis Set	The PK Analysis Set will include all participants who receive at least 1 dose of study intervention and have at least 1 postdose evaluable PK concentration. All PK analyses will be based on the PK population.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to data base lock and it will include a detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

In general, results will be summarized by treatment group. Categorical variables will be reported as frequency and percent. Continuous variables will be reported as the number of participants, mean, SD, or SE, median, minimum, and maximum. All summaries, statistical analyses, and individual participant data listings described below will be completed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

9.4.1.1. Multiplicity Adjustments

To evaluate the efficacy of JZP385 at doses of 10, 20, and 30 mg/day compared with placebo, pairwise treatment difference between each of the 3 doses and placebo will be tested at the end of Week 12 for the primary and key secondary endpoints.

The family-wise Type I error rate will be controlled at a 2-sided significance level of 0.05. To address the multiplicity issue due to the multiple efficacy endpoints and doses, a fixed

hierarchical testing sequence will be employed. The testing procedure will stop when a p-value exceeds 2-sided significance level of 0.05 (see below).

Statistical hypotheses to be tested (in sequential order):

1. Change in the TETRAS composite outcome score from Baseline to Week 12, 30 mg/day versus placebo.
2. Difference in proportion of participants who improved ≥ 1 point on the CGI-S from Baseline to Week 12, 30 mg/day versus placebo.
3. Change in the TETRAS composite outcome score from Baseline to Week 12, 20 mg/day versus placebo.
4. Difference in proportion of participants who improved ≥ 1 point on the CGI-S from Baseline to Week 12, 20 mg/day versus placebo.
5. Change in the TETRAS composite outcome score from Baseline to Week 12, 10 mg/day versus placebo.
6. Difference in proportion of participants who improved ≥ 1 point on the CGI-S from Baseline to Week 12, 10 mg/day versus placebo.

9.4.1.2. Intercurrent Event Strategies

Discontinuation of study intervention, as specified in Section 7.1, will be considered as intercurrent events.

For the primary and key secondary estimands, the following 2 types of intercurrent events will be considered:

- Discontinuation of treatment due to an AE, for lack of efficacy, or any other reason. Participants who experience this type of intercurrent event will be treated as if they did not experience an intercurrent event (hypothetical strategy). The hypothetical strategy used is defined as the pharmacologic effect of JZP385 compared to placebo assuming the intercurrent event did not happen with continuation of study intervention for the duration of the study. Analyses will be conducted using data collected at time points obtained at or prior to participants' discontinuation of study intervention and combined with imputed values for post-discontinuation time points for which the underlying assumptions are considered appropriate.
- Any change to concomitant antitremor medication use after the initiation of study intervention, including but not limited to the following: 1) starting a new antitremor medication, 2) stopping a concomitant antitremor medication, and 3) a dose or regimen change to current antitremor medication. This type of intercurrent event will be disregarded, and measurements obtained subsequently will be reported and analyzed (treatment policy). Treatment policy is defined as the effect of randomized treatment over the study period regardless of the occurrence of the intercurrent event. In accordance with treatment policy, data collected after this type of intercurrent event will be reported and included in analyses.

If a participant experiences a combination of both types of ICE (eg, change the use of anti-tremor medication and discontinue the study intervention afterwards), each ICE should be treated

independently. Data collected after the change of antitremor medication but on or before the study intervention discontinuation will be included in analyses per treatment policy, the postdiscontinuation data will be handled by hypothetical strategy.

9.4.1.3. Pooling of Investigational Centers

Data from all investigational centers will be pooled for presentation of the main results (eg, demographics, safety, PK, and efficacy). Data may be pooled by region or country as appropriate for exploratory analyses of the primary and key secondary endpoints.

9.4.1.4. Dropouts and Missing Data

The TETRAS composite outcome score will be derived as the sum of items 1 to 11 of the ADL section of TETRAS plus the sum of items 6 (left and right) and 7 of the PS section of the TETRAS (for a total of 14 items on the composite primary outcome). If ≤ 3 items of the TETRAS composite outcome score are missing at a specific time point, the mean of the remaining non-missing TETRAS composite outcome score item scores at that point will be used to impute the missing TETRAS composite outcome score item value. The TETRAS composite outcome score will then be calculated as the sum of the observed and imputed item scores. If ≥ 4 items of the composite primary outcome are missing, the TETRAS composite outcome score will not be calculated.

For the analysis of the TETRAS composite outcome score, the primary analysis will rely on MMRM, assuming participants who early discontinue the study intervention (defined as an intercurrent event) or missed the assessments due to other reasons would have efficacy outcomes like other participants in their treatment group, randomization stratum, and initial trajectory who completed the study. Sensitivity analyses will adopt control-based drop-out imputation methods to assess the impact on the treatment effect of JZP385 when underlying missing at random (MAR) assumption on the primary MMRM analysis shifted accordingly. A tipping point analysis will further assess the robustness of the primary analysis method.

For the analysis of CGI-S, the primary analysis will adopt a 2-step multiple imputation method and assume data to be missing at random. A tipping point analysis will be conducted as sensitivity analysis to assess the robustness of the primary analysis method.

The details will be further described in the SAP.

9.4.2. Primary Estimand

The primary estimand is a composite outcome score of the sum of modified items 1 to 11 of the TETRAS-ADL and modified items 6 and 7 of the TETRAS-PS. For the primary estimand, the scoring of each of the items 1 to 11 of the TETRAS-ADL subscale as well as items 6 and 7 of the TETRAS-PS will be modified. For TETRAS-ADL, each item will be modified from 5 response items to 4 response items by collapsing options 0 and 1 together and for TETRAS-PS, each item will be modified from 9 response items (due to 0.5 scoring increments) to 4 response items. Each item has a maximum score of 3. As item 6 of the TETRAS-PS includes assessments for both hands, there are a total of 3 items from the TETRAS-PS and 11 items from the TETRAS-ADL that contribute to a 14-item TETRAS composite outcome score. The total range of the TETRAS composite outcome score that will be used for the primary analysis will therefore be 0 to 42.

The attributes of the primary estimand are listed below:

- Treatment: 10, 20, and 30 mg/day JZP385 and placebo.
- Population: Adults with moderate to severe ET.
- Variable: Change from Baseline to Week 12 on the TETRAS composite outcome score.
- Intercurrent Events:
  - Discontinuation of study intervention due to an AE, for lack of efficacy, or any other reason. Participants who experience this type of intercurrent event will be addressed by hypothetical strategy.
  - Any change to concomitant antitremor medication use after the initiation of study intervention (refer to Section 9.4.1.2). Participants who experience this type of intercurrent event will be addressed by treatment policy.
- Summary: Difference in the mean TETRAS composite outcome score from Baseline to Week 12 between each dose of JZP385 and placebo.

For the main estimator analysis, a MMRM will be used to include the difference in the TETRAS composite outcome score from the Baseline Visit to Weeks 4, 8, and 12. The model will include fixed effects for treatment group, week, treatment group by week interaction, baseline TETRAS composite outcome score stratification (≤ 17 or > 17), baseline concomitant antitremor medication stratification (Yes or No), baseline TETRAS composite outcome score by week interaction, baseline TETRAS composite outcome score as a continuous covariate, and week repeated within each participant as a repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements.

For sensitivity analyses, a control-based Pattern Mixture Model (PMM) will be used to explore the possibility of data being missing not at random (MNAR). A supplementary analysis will be conducted with only those participants who have Week 12 TETRAS composite outcome scores. Additional details on sensitivity and supplementary analyses will be provided in the SAP.

Subgroup analyses by randomization stratum, sex, age, and region will be conducted as applicable. Further details will be provided in the SAP.

9.4.3. Secondary Estimands and Endpoints

9.4.3.1. Key Secondary Estimand

The attributes of the key secondary estimand are listed below:

- Treatment: 10, 20, and 30 mg/day JZP385 and placebo.
- Population: Adults with moderate to severe ET.
- Variable: Proportion of participants who improved (≥ 1 point improvement) from Baseline to Week 12 on the CGI-S.

- Intercurrent Events:
  - Discontinuation of study intervention due to an AE, for lack of efficacy, or any other reason. Participants who experience this type of intercurrent event will be addressed by hypothetical strategy.
  - Any change to concomitant antitremor medication use after the initiation of study intervention (refer to Section 9.4.1.2). Participants who experience this type of intercurrent event will be addressed by treatment policy.
- Summary: Difference in the proportion of participants who improved (≥ 1 point improvement) from Baseline to Week 12 on the CGI-S between each dose of JZP385 and placebo.

The main estimator will be analyzed using the CMH test adjusting for the stratification factors at randomization (baseline TETRAS composite outcome score [≤ 17 or > 17] and the use of concomitant antitremor medication [Yes or No]). The 2-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, and the associated 2-sided 95% CIs using a normal approximation to the weighted average will be provided.

For the intercurrent event of discontinuation of study intervention due to an AE, for lack of efficacy, or any other reason, under the hypothetical strategy, the primary analysis will adopt a 2-step multiple imputation approach, with MCMC to impute non-monotone intermittent missing followed by a predictive mean matching method to impute the rest monotone missing outcomes.

Sensitivity analysis will be conducted through the tipping point analysis, with further details provided in the SAP.

Supplementary analyses will be performed using the Non-responder Imputation (NRI) method as well as completers analysis with only participants who have Week 12 CGI-S assessment.

9.4.3.2. Secondary Endpoints

For the analysis of CGI-C and PGI-C at Week 12, the CMH test stratified by the randomization stratum will be used for the comparison between each dose of JZP385 and placebo.

For the analysis of change from Baseline to Week 12 on the TETRAS-ADL, TETRAS-PS, TETRAS-PS upper limb score (item 4), and TETRAS total score, the same MMRM models used for the primary estimand will be used.

For the analysis of change of QUEST score from Baseline to Week 12, an analysis of covariance (ANCOVA) model will be used. The model will include treatment group, randomization stratum, and corresponding baseline value as fixed effects.

For the analysis of change of ETEA score from Baseline to Week 12, an ANCOVA model will be used. The model will include treatment group, randomization stratum, and corresponding baseline value as fixed effects.

9.4.4. Tertiary/Exploratory Endpoints

For the analysis of change from Baseline to Weeks 4 and 8 on the TETRAS composite outcome score, TETRAS-ADL, TETRAS-PS, TETRAS upper limb score (item 4), TETRAS total score, the analyses results will be derived from the MMRM used in the Week 12 analysis on the primary estimand and the secondary endpoints.

For the analysis of change from Baseline to Week 12 on modified items 6 and 7 of the TETRAS-PS (where each item is modified from 9 response items [due to 0.5 scoring increments] to 4 response items), the sum of modified items 1 to 11 of the TETRAS-ADL subscale (where each item is modified from 5 response items to 4 response items), and TETRAS total score, the analyses results will be derived from a similar MMRM used in the Week 12 analysis on the primary estimand endpoint.

For the analyses of proportion of participants who improved ≥ 1 point from Baseline to Weeks 4 and 8 on the CGI-S, the CMH test stratified by the randomization stratum will be used for the comparison between each dose of JZP385 and placebo. For the analyses of PGI-C and CGI-C at Weeks 4 and 8, the CMH test stratified by the randomization stratum will be used for the comparison between each dose of JZP385 and placebo.

For the analysis of change in SF-36v2 score from Baseline to Week 12, a descriptive summary at each scheduled visit along with change from Baseline to Week 12 will be tabulated and listed.

The time course efficacy analysis using the sum of modified items 6 and 7 of the TETRAS-PS will be performed with a mixed model. The model will include treatment group, time points, treatment group by time point interaction and the randomization stratum as fixed effects, and participant as a random effect.

9.4.5. Safety Analysis

All safety analyses will be performed on the Safety Population. Safety analyses will be descriptive; no formal statistical testing will be performed.

Adverse Event Analyses:

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The participant incidence of AEs, AEs related to study intervention, SAEs, AEs leading to discontinuation, and fatal AEs will be summarized. This overall summary will also provide AEs by maximum severity.

The participant incidence of AEs, AEs related to study intervention, AEs, and AEs leading to discontinuation will also be presented by SOC and preferred term. Preferred term summaries may also be provided.

The participant incidence of an AE will be summarized; if a participant has multiple events with the same PT occurring in different periods, the event will be reported for each of those periods. Multiple increases in severity will only be counted as one AE.

Vital Signs:

For each vital sign parameter, summary statistics will be provided for observed and change from baseline values by scheduled visit.

Physical Examinations

Observed and change from baseline values for weight will be summarized descriptively by scheduled visit.

12-lead ECG

Observed and change from baseline values for ECG intervals will be summarized descriptively. QT abnormalities will be assessed; the number and percent of participants with values or change from baseline values exceeding certain thresholds will be tabulated.

Laboratory Evaluations

Observed and change from baseline laboratory evaluations will be summarized descriptively.

C-SSRS

Columbia Suicide Severity Rating Scale parameters will be summarized by scheduled visit.

9.4.6. Pharmacokinetic Analysis

Plasma concentrations of JZP385 and its metabolites will be listed and summarized by visit and dose.

Pharmacokinetics parameters (eg, C_{max}, T_{max}, $t_{½}$, C_{tau}, AUC) of JZP385 and its metabolites, if applicable, will be estimated using a population PK model and will be presented separately from the study data.

Population exposure-response analysis for JZP385 and its metabolites, if applicable will be performed and will be presented separately from the study data.

9.5. Interim Analysis

No formal interim analysis will be performed.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the 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 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 study is initiated.

- Protocols and any amendments to the protocol will require IRB/IEC and national regulatory authority approval (as applicable) prior to initiation, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study 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 study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, EU Regulation 536/2014 for clinical studies (when applicable) or EU Directive 2001/20/EC (if still in force), EU Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. 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 study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

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 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study 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 study.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.4. 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 study-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 who will be required to give consent for their data to be used as described in the informed consent.

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.

10.1.5. Committees Structure

Establishing a Data Monitoring Committee is not planned for this study. The sponsor recognizes the importance of ongoing review of the accumulating safety data and will perform periodic data monitoring regularly by data listing review. In addition, safety data from the study will be reviewed on an ongoing basis as part of routine pharmacovigilance and safety surveillance activities. Reports of safety findings (from either single events or based on aggregate review) that suggest a significant risk to humans will be distributed to all participating investigators and to the relevant regulatory authorities and IRBs/IECs.

Eligibility Adjudication Committee:

Select eligibility criteria will be centrally reviewed by an independent expert from the EAC. Details can be found in the EAC Charter.

10.1.6. Dissemination of Clinical Study Data

As the sponsor of the study, Jazz Pharmaceuticals is solely responsible for disclosing results on ClinicalTrials.gov, EudraCT, and other public registries in accordance with applicable global laws and regulations. By signing this protocol, the investigator acknowledges that all posting

requirements are solely the responsibility of the sponsor and agrees not to submit any information about the study or its results.

10.1.7. Data Quality Assurance

Investigators and site staff will be trained on protocol procedures and electronic case report form (eCRF) completion prior to enrolling participants in the study

All participant data relating to the study will be recorded on printed or eCRF 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).

Guidance on completion of CRFs will be provided in the CRF completion guidelines.

The investigator must permit study-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 study including quality checking of the data.

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator, or institution/study site, as applicable, for the period of time established in the clinical study agreement entered into by the investigator's study site unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period or thereafter without the written approval of the sponsor and must be managed and retained in accordance with the terms of the clinical study agreement. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. 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 study. Also, current medical records must be available.

A definition of what constitutes source data can be found in the Monitoring Plan and/or CRF completion guidelines.

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

Study 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 study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first participant has the first visit.

Study/Site Termination

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

The investigator may initiate study 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 study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

APPENDIX 1. ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
AEOSI	Adverse events of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BID	Twice daily
Ca_V3	T-type calcium channel
CBD	Cannabidiol
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
C_{tau}	Concentration at trough
DR	Delayed release
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EAC	Eligibility Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoS	End of study
ET	Essential tremor
ETEA	Essential Tremor Embarrassment Assessment
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Definition
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
H2RA	Histamine-2 receptor antagonists
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IR	Immediate release
IRB	Institutional Review Board
IRT	Interactive response technology
MAR	Missing at random
MDRD	Modification of Diet in Renal Disease
MDS	Movement Disorder Society
MMRM	Mixed-effect model with repeated measures
MNAR	Missing not at random
MoCA	Montreal Cognitive Assessment
OREs	Other reportable experiences
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetics
PK/PD	Pharamacokinetic/ Pharmacodynamic
PMM	Pattern Mixture Model
PRN	As needed
PS	Performance Subscale
QUEST	Quality of life in Essential Tremor Questionnaire
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36v2	36-item Short Form Health Survey Version 2
SoA	Schedule of activities
SOC	System Organ Class
SV	Screening Visit
T-CALM	Phase 2 proof-of-concept study CX-8998-CLN02-001

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
TETRAS	Tremor Research Group Essential Tremor Rating Assessment Scale
TETRAS-ADL	The Essential Tremor Rating Assessment Scale – Activities of Daily Living
TETRAS-PS	The Essential Tremor Rating Assessment Scale – Performance Subscale
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
US	United States
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

APPENDIX 2. REFERENCES

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APPENDIX 3. CLINICAL LABORATORY TESTS

The tests detailed in Table 6 will be performed by the central laboratory, with the exception of urine pregnancy and breath alcohol tests, which will be performed locally. Breathalyzers and urine pregnancy tests will be provided by the 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 study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 6: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	Albumin	ALP	ALT/ SGPT	AST/ SGOT
	BUN	Calcium	CO_2	Chloride
	Creatinine	Creatine kinase	GGT	Glucose
	Lactate dehydrogenase	Phosphorus	Potassium	Prolactin
	Sodium	Total and direct bilirubin	Total cholesterol	Total protein
	Triglycerides	Uric acid	INR	eGFR[b]
Routine Urinalysis	• Appearance, color • Specific gravity • pH, glucose, protein, occult blood, ketones, bilirubin, urobilinogen, nitrite, and leukocytes (by dipstick) • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential)[c] • Serum pregnancy testing is mandatory at screening, and urine is collected thereafter (unless serum is required by local regulations).			
Other Tests	• Urine drug screen (to include at minimum: amphetamines, methadone, MDMA, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine)			

Laboratory Tests	Parameters
	• Breath alcohol test • All study-required laboratory tests will be performed by a central laboratory, with the exception of urine pregnancy and breath alcohol tests

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MDMA = 3, 4,-methylenedioxymethamphetamine; MDRD = Modification of Diet in Renal Disease; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell.

[a] All events of ALT or AST $\geq 3 \times$ upper limit of normal (ULN) and total bilirubin $\geq 2 \times$ ULN (> 35% direct bilirubin) or ALT or AST $\geq 3 \times$ ULN and INR > 1.5 which may indicate severe liver injury (possible Hy's Law), must be reported to the sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

[b] Calculated via central laboratory using the MDRD method.

[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. Serum pregnancy testing for confirmation of positive urine test, as well as locally or IRB/IEC required serum testing will be performed at the central laboratory. Serum pregnancy testing is mandatory at screening, and urine is collected thereafter.

APPENDIX 4. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • 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 intervention.
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 judgment 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 intervention administration even though it may have been present before the start of the study. • 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 intervention 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. • "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 an AE or SAE if they fulfil the definition of an AE or SAE.
Events <u>NOT</u> 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 study 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 or serious adverse event that, at any dose:

- Results in death

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.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (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.

Results in persistent or significant 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.
Is a congenital anomaly/birth defect
Is a suspected transmission of any infectious agent via an authorized medicinal product
Other situations: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention 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. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the required form. • There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. 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 to the sponsor or designee. • 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 study and assign it to one of the following categories: • Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only

- Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. An AE/SAE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- Life-threatening: life-threatening consequences; urgent intervention indicated.
- Fatal: death related to adverse event

When the severity of an AE increases over time, the increase in the severity will be recorded as a new AE and the original AE will stop when the new AE starts.

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 intervention 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 judgment 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 intervention administration will be considered and investigated.
- The investigator will also consult the 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 to the sponsor or designee. 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 to the sponsor or designee.
- 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.

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 designee) 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 submitted documents. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the sponsor or designee
• SAEs must be reported to the sponsor (or designee) using an SAE Reporting Form within 24 hours of first knowledge of the event by study personnel. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The form, instructions on completion, and contact information can be found in the Trial Site Binder. • The SAE Reporting Form should be completed as much as possible before transmittal. • Contacts for SAE reporting can be found in the Trial Site Binder.

Reporting of AEOSIs and OREs

Reporting of AEOSIs and OREs to the sponsor or designee
• AEOSIs and OREs must be reported to the sponsor or its designee using an ORE/AEOSI Reporting Form within 24 hours of first knowledge of the event by study personnel. • The form, instructions on completion and contact information can be found in the Trial Site Binder. • The ORE/AEOSI Reporting Form should be completed as much as possible before transmittal. • Contacts for ORE/AEOSI reporting can be found in the Trial Site Binder.

APPENDIX 5. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions

Woman of Non-childbearing Potential

Women in the following categories are considered women of non-childbearing potential (WONCBP):

1. Premenopausal female with permanent infertility due to one of the following:
2. Documented hysterectomy
3. Documented bilateral salpingectomy
4. Documented bilateral oophorectomy
5. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

6. Postmenopausal female
7. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
8. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
9. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Woman of Childbearing Potential

Women in the following categories are considered women of childbearing potential (WOCBP; fertile):

10. Following menarche
11. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together due to risk of failure from friction.

APPENDIX 6. GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to JZP385 and related diseases. They may also be used to develop tests/assays including diagnostic tests related to JZP385. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed for polymorphisms in calcium channel genes. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to JZP385 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on JZP385 continues but no longer than 15 years from the date of sample collection or other period as per local requirements.

APPENDIX 7. CRITERIA FOR DIAGNOSIS OF ESSENTIAL TREMOR

Movement Disorder Society (MDS) Consensus Statement on the Classification of Tremors from the Task Force on Tremor of the International Parkinson's and Movement Disorder Society (Bhatia, 2018)

Essential Tremor

- Isolated tremor syndrome of bilateral upper limb action tremor
- At least 3 years' duration
- With or without tremor in other locations (eg, head, voice, or lower limbs)
- Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism

Essential Tremor Plus

Tremor with the characteristics of ET and additional neurological signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis. ET with tremor at rest should be classified here.

Exclusion Criteria for Essential Tremor and Essential Tremor Plus

- Isolated focal tremors (voice, head)
- Orthostatic tremor with a frequency > 12 Hz
- Task- and position-specific tremors
- Sudden onset and step-wise deterioration

APPENDIX 8. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 01

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment is being implemented to align with feedback received from the United States Food and Drug Administration (FDA) regarding study endpoints, to correct an error in the hepatic and renal values necessary for participant exclusion, and to add general clarifications throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 3 Objectives, Estimands and Endpoints; 4.2 Scientific Rationale for Study Design; 8.2 Efficacy Assessments; 9.1 Statistical Hypotheses; 9.2 Sample Size Determination; 9.3 Analysis Sets; 9.4 Statistical Analyses	The primary endpoint was changed from the Essential Tremor Rating Assessment Scale – Activities of Daily Living (TETRAS-ADL) to a composite primary endpoint that includes the sum of items 1 to 11 on the TETRAS-ADL subscale and items 6 and 7 of the Essential Tremor Rating Assessment Scale – Performance Subscale (TETRAS-PS).	To align with feedback received from the FDA.
1.1 Synopsis; 3 Objectives, Estimands and Endpoints; 4.2 Scientific Rationale for Study Design; 8.2 Efficacy Assessments; 9.4 Statistical Analyses	The first key secondary endpoint was changed from the Clinical Global Impression of Change (CGI-C) to the Clinical Global Impression of Severity (CGI-S). The second key secondary endpoint (items 6 and 7 of the TETRAS-PS) was removed.	To align with feedback received from the FDA.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 3 Objectives, Estimands and Endpoints; 9.4.4 Tertiary/Exploratory Endpoint(s)	The following endpoints were added under exploratory endpoints: • Items 6 and 7 of the TETRAS-PS, with a change to the analysis to modify from 5 response items to 4 response items • The sum of modified items 1 to 11 of the TETRAS-ADL subscale	To provide clarification regarding the use of original and modified scales.
9.2 Sample Size Determination; 9.3 Analysis Sets; 9.4 Statistical Analyses	New effect sizes for study sample size were calculated, text regarding the impact to power with shifts in assumptions were added, and multiplicity adjustments were revised to reflect the changes to the endpoints.	As a result of changes to the primary endpoint, new effect sizes were calculated. The sample size assumptions and power were also provided for the key secondary endpoint. Changes to the number of key secondary endpoints led to a new multiplicity testing sequence.
1.1 Synopsis; 4.1 Overall Design; 6.3 Measures to Minimize Bias: Randomization and Blinding	The randomization stratum was changed from the TETRAS-ADL subscale to select modified items from the TETRAS-ADL subscale and TETRAS-PS (ie, TETRAS composite outcome score).	To align the randomization stratification with the primary endpoint.
1.3 Schedule of Activities; 8.2.2 Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale; 9.4.4 Tertiary/Exploratory Endpoint(s)	The efficacy assessments and breath alcohol test were removed from the Week 1 clinic visit.	The 5 mg dose that is administered to participants randomized to active treatment arms during the first study week serves as a titration dose only and is not being evaluated for efficacy.
1.3 Schedule of Activities	The CGI-S was added as an assessment at Weeks 4 and 8.	To enable assessment of this new key secondary endpoint at each clinic visit.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities;	Language was added regarding the timing of collection of adverse events (AEs) and serious adverse events (SAEs).	To provide clarification regarding the collection of AEs/SAEs.
1.1 Synopsis; 3 Objectives, Estimands and Endpoints; 9.4 Statistical Analyses	The following endpoints were added under secondary endpoints: • CGI-C • TETRAS-ADL subscale	As a result of changes to the primary and key secondary endpoints, other endpoints were rearranged accordingly.
1.1 Synopsis; 3 Objectives, Estimands and Endpoints; 9.4.3 Secondary Estimands and Endpoints	Analysis of CGI-C and Patient Global Impression of Change (PGI-C) was changed to only include participants with "much improvement."	To align with feedback received from the FDA.
2.3.2 Benefit Assessment	Participation in long-term study was removed.	To not imply a benefit to participants for such a study, which is not part of this protocol.
5.1 Inclusion Criteria	Inclusion criterion #4 was revised to add clarification from Appendix 5 about barrier contraception for male partners of female participants.	To clarify the contraception requirements for female participants with male partners.
5.2 Exclusion Criteria	Exclusion criterion #6 was updated to add estimated glomerular filtration rate (eGFR) exclusionary values and to move the bilirubin exclusionary values into the parenthesis with other values addressing hepatic function.	To clarify the level of renal disease that is considered exclusionary and correct an error on the placement of the exclusionary bilirubin values.
6.8 Concomitant Therapy	Added clarification regarding timing of administration for concomitant medications that are known sensitive substrates of P-glycoprotein (P-gp) and	To align with feedback received from the FDA.

Section # and Name	Description of Change	Brief Rationale
	breast cancer resistance protein (BCRP).	
8.4.5 Pregnancy	The term "participant" was added into the language regarding follow-up of pregnancy outcome and it was specified that the neonate will be followed for 6 months following birth.	To clarify that in addition to the participant's pregnant female partner, the participant herself who may become pregnant needs to be appropriately followed for the pregnancy outcome.
8.3.3 ECGs	Corrected text to indicate that electrocardiograms (ECGs) measurements will be taken in triplicate not as single measurements	To align with the Schedule of Activities (SoA) and clarify that ECG measurements should be taken in triplicate.
Appendix 3; Table 6	The description "fasted state required at Screening only" was removed for glucose testing.	All labs will be fasted (8 hours) prior to visit, as study drug is taken in the fasted state. Therefore, it is redundant to indicate that glucose should be taken in the fasted state.
Appendix 3; Table 6	The eGFR assessment added to Clinical Chemistry.	To clarify the method of eGFR assessment.
Appendix 3; Table 6	Removed "drug" from the list of exceptions for study-required laboratory tests performed by a central laboratory. Also added the clarification that urine pregnancy tests are not performed at the central lab.	To correct an error and clarify the following text in Appendix 3: "The tests detailed in Table 6 will be performed by the central laboratory, with the exception of urine pregnancy and breath alcohol tests, which will be performed locally."
Throughout	The molecule name was changed from CX-8998 to JZP385.	To reference the current molecule name and link it to interchangeable names of CX-8998, suvecaltamide, and MK-8998 and to ensure consistency across JZP385 studies.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amendment 02

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment is being implemented to revise text regarding participant rollover into a separate long-term study, remove CYP2C9 inducers from the exclusion criteria, and to make other minor edits.

Section # and Name	Description of Change	Brief Rationale
Table 3 Overall Study Design; 1.3 Schedule of Activities; 6.6 Continued Access to Study Intervention After the End of the Study	Deleted language regarding direct rollover into a long-term study.	The timing of a long-term extension study is yet to be determined and therefore participants will not have the opportunity to directly roll over into the long-term study after completing the current study.
Table 1 Primary and Key Secondary Objectives and Estimands (footnote); Table 2 Secondary and Exploratory Objectives and Endpoints (footnote); 3 Objectives, Estimands and Endpoints (footnote); 9.4.2 Primary Estimand; 9.4.4 Tertiary/Exploratory Endpoints	Revised language regarding the TETRAS composite outcome score.	To clarify language around modification of the response items for the TETRAS-ADL and TETRAS-PS subscales.
1.2 Schema	Study intervention name was changes from “CX-8998” to “JZP385.”	To ensure consistent nomenclature of study intervention.
2 Introduction Appendix 2 References	Added more recent (2021) ET prevalence data,	To ensure that background information is current.

Section # and Name	Description of Change	Brief Rationale
Table 2 Secondary and Exploratory Objectives and Endpoints; 3 Objectives, Estimands and Endpoints	Added the following items to the list of exploratory objectives and endpoints: • Change from Baseline to Weeks 4 and 8 on the TETRAS composite outcome score, PGI-C, CGI-S, TETRAS-ADL, TETRAS-PS, TETRAS upper limb score (item 4), and total TETRAS score. • Change from Baseline to Week 12 on the 36-item Short Form Health Survey (SF-36) as summarized by each dose of JZP385 and placebo. • Time course analysis on the sum of modified items 6 and 7 of the TETRAS-PS as summarized by each dose of JZP385 and placebo.	These endpoints were inadvertently omitted from the list of exploratory objectives and endpoints.
Table 2 Secondary and Exploratory Objectives and Endpoints; 3 Objectives, Estimands and Endpoints; 8.5 Pharmacokinetics; 9.4.6 Pharmacokinetic Analysis	Pharmacokinetic (PK) endpoints and analysis were revised.	To provide clarification.
1.3 Schedule of Activities, Footnote e	Added “or local requirements” to the footnote regarding the change from telephone to in-clinic visits.	To allow flexibility for study sites.
5.2 Exclusion Criteria, #14 and #15	Removed CYP2C9 inducers from the exclusion criteria and provided additional details.	Definitive in vitro drug-drug interaction studies indicate that JZP385 is predominantly

Section # and Name	Description of Change	Brief Rationale
		metabolized by CYP3A4 and other enzymes play a minor role.
Table 4 Study Treatment/Intervention	Added footnote to clarify that the dose strength of JZP385 is based on the active moiety in the drug product.	To clarify dosage strength of study intervention.
6.4 Study Intervention/Treatment Compliance	Added "clinic" in front of the term "visit" to the sentence regarding at which visits compliance with study intervention will be assessed.	To clarify that compliance with study intervention is only assessed at clinic visits and not at phone visits.
8.1.5 Inclusion and Exclusion Criteria Review	Changed "Study Operations Manual" to "EAC Charter."	To correct the location of details for the participant eligibility review.
8.4.6 Adverse Events of Special Interest	Section heading changed to "8.4.6 Adverse Events of Special Interest and Other Reportable Experiences" and details were added regarding the definition of other reportable experiences (OREs).	To provide clarification about adverse events of special interest (AEOSIs) and OREs.
Appendix 4 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Corrected the reporting period for OREs and AEOSIs from within 72 hours to within 24 hours from the time of site's knowledge of the event.	To indicate that OREs and AEOSIs should be reported within 24 hours.
Appendix 3 Clinical Laboratory Tests	Added that breathalyzers and urine pregnancy tests will be provided by the central laboratory. Specified that serum pregnancy testing is mandatory at screening, and urine is collected thereafter.	To provide clarification
Appendix 3 Clinical Laboratory Tests, Footnote b	Deleted footnote b regarding fractionating for alkaline phosphatase sampling.	Clarification since additional tests may be performed at any time during the study as determined

Section # and Name	Description of Change	Brief Rationale
		necessary by the investigator or required by local regulations.
Appendix 8	Moved Amendment 1 Summary of Changes to Appendix 8.	For clarity.
Throughout	Changed the nomenclature of the primary endpoint from "composite primary endpoint" to "TETRAS composite outcome score."	To ensure that consistent nomenclature is used for the primary endpoint.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amendment 03

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for this amendment is to broaden the eligibility criteria and reduce study burden.

Section # and Name	Description of Change	Brief Rationale
Table 1 Primary and Key Secondary Objectives and Estimands; 3 Objectives, Estimands and Endpoints; 9.1 Statistical Hypotheses; 9.2 Sample Size Determination 9.4.1.1 Multiplicity Adjustments; 9.4.3.1 Key Secondary Estimand	Changed analysis of CGI-S endpoint from a continuous analysis to categorical analysis (ie, a 1-point change). Revised statistical details regarding the key secondary estimand variable. Revised statistical power calculations.	To improve interpretability of the results and ensure that any statistically significant finding will also be meaningful (ie, represent a category change on this ordinal scale). Statistical section updated to reflect the change on key secondary estimand variable CGI-S, along with updated categorical analysis methods and additional revisions to improve interpretability of the results. The statistical power calculations were also revised, accordingly.
Table 1 Primary and Key Secondary Objectives and Estimands; Table 2 Secondary and Exploratory Objectives and Endpoints; 3 Objectives, Estimands and Endpoints; 9.4.2 Primary Estimand; 9.4.4 Tertiary/Exploratory Endpoints	Clarified language around the primary and key secondary estimands. Added separate bullet points for the following exploratory endpoints: Proportion of participants who improved (≥ 1-point improvement) from Baseline to Weeks 4 and 8 on the CGI-S. Proportion of participants reported as much improved on the PGI-C and CGI-C at Weeks 4 and 8.	To better distinguish the difference in the primary and key secondary objectives. To separate categorical endpoints CGI-S, PGI-C, and CGI-C from continuous endpoints and further define them under Tertiary/Exploratory Endpoints
1.3 Schedule of Activities	Specified that the blood sample for genetic testing is optional.	To provide clarification

Section # and Name	Description of Change	Brief Rationale
	Specified that serum pregnancy tests can be conducted at additional visits to confirm positive urine tests.	
1.2 Schema; 1.3 Schedule of Activities; Table 3 Overall Study Design; 2.3.1 Risk Assessment 4.1 Overall Design	Shortened standard screening period to 35 days. Added a footnote to indicate that an additional 28 days are permitted for participants who require longer washout of primidone and reordered the other footnotes accordingly	Screening period has been shortened to avoid an unnecessarily long screening period for most participants. A provision permitting a longer screening period to allow for safe washout of the excluded antitremor medication, primidone, has been added.
1.3 Schedule of Activities; 8.2.2 Tremor Research Group Essential Tremor Rating Assessment Scale – Performance Subscale; Table 5 TETRAS-PS Assessments	Specified serial TETRAS-PS items 6 and 7 are optional and 5 to 8-hour postdose PK sample at Week 8 is optional. Indicated that a light lunch is only provided to those participants who are doing the optional assessments. Clarified in Table 5 that TETRAS-PS assessments are administered by a blinded rater and need to be video recorded at Screening Visit 1 and 2. Revised the nomenclature in Table 5 for the serial item 6 and 7 TETRAS-PS Baseline assessments.	To improve the operational execution and reduce study complexity by making these exploratory endpoints that drive long clinic visit days optional. To clarify that the TETRAS-PS should be performed at the time of the anticipated 1-hour postdose at future visits, and to clarify that participants do not dose at the Baseline visit.
Table 3 Overall Study Design	Added footnote to define the TETRAS composite outcome score.	To provide clarification
2.3.1 Risk Assessment 2.3.3 Overall Benefit: Risk Summary	Added additional detail on the risk-benefit of JZP385.	To provide more specificity in the protocol regarding the risk-benefit in the patient population under study as opposed to referring to the IB.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria #3	Removed Inclusion 3b (Score of > 5 on the sum of items 6 and 7 of the TETRAS-PS).	Inclusion 3a (TETRAS-ADL score ≥ 22) and 3c (CGI-S rating of at least moderate for participants' ability to function) are considered sufficient to enroll a moderate to severe ET population.
5.1 Inclusion Criteria #4b; Table 6 Protocol-required Safety Laboratory Tests	Revised Inclusion 4b to clarify when serum vs urine pregnancy tests are required for WOCBP.	To provide clarification.
5.2 Exclusion Criteria #4; 8.1.7 Montreal Cognitive Assessment	Revised Exclusion #4 to lower MoCA eligibility threshold to < 20 and added clarification that the investigator should ensure participants are able to accurately self-report on study questionnaires.	To better assess and exclude participants with severe cognitive impairment based on more rigorous data on the use of the MoCA and the judgment of the investigator on the individual participant. The original cut-off of < 23 was developed based on a limited study in a convenience sample of participants with Parkinson's disease (N = 114) and healthy controls (N = 47) at a single non-US center. However, a more thorough literature review showed that in a normal cognitive population, MoCA average scores fell within this range, which suggested that the original criteria (< 23) had low specificity to detect severe cognitive impairment.
5.2 Exclusion Criteria #6	Revised Exclusion 6 to remove specified threshold of the eGFR to define renal disease and to add severe renal impairment or end-stage renal disease.	Based on the finding that JZP385 is primarily cleared via metabolism, and that, previously, patients with creatinine clearance ≥ 39 mL/min were allowed in the T-CALM study with no safety concerns, the specific eGFR threshold to define renal disease will be removed from the protocol. The eGFR will still be calculated for each participant as part of the laboratory assessment.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; 5.2 Exclusion Criteria #7f; 8.3.2 Vital Signs	Added triplicate assessments of orthostatic vital signs at Screening Visit and added that Exclusion 7f applies to Screening Visit as well as Baseline.	To clarify criteria should be met at the Screening Visit as well as Baseline.
5.2 Exclusion Criteria #10	Clarified that tobacco and cannabis use disorder are excluded and that a substance abuse disorder should be diagnosed.	To provide clarification.
5.2 Exclusion Criteria #11	Revised Exclusion 11 to clarify that MR-guided focused ultrasound is a thalamotomy.	To provide clarification.
5.2 Exclusion Criteria #12	Revised Exclusion 12 to specify botulinum toxin (ie, Botox) for the treatment of upper limb tremor is exclusionary.	JZP385 is targeting treatment of the core symptom of ET, which is upper limb tremor. Thus, the use of botulinum toxin for other reasons (eg, cosmetic, head tremor, etc.) will not confound this assessment.
5.2 Exclusion Criteria #13b	Revised Exclusion 13b to clarify that PRN use of medications that impact tremor is not permitted.	To provide clarification.
5.2 Exclusion Criteria #16	Revised Exclusion 16 to allow the use of histamine-2 receptor antagonists under the condition they are taken at least 4 hours after and 12 hours before study intervention.	Administering a dose of H2RA at least 12 hours before JZP385 will ensure that H2RA effect has washed out before JZP385 administration. Administration of H2RA 4-hours post-JZP385 dose will ensure that JZP385 has been absorbed or passed through the stomach to the intestine.
5.2 Exclusion Criteria #22	Revised Exclusion 22 to clarify that a positive urine drug screen at Screening that is attributed to a medication	To provide clarification.

Section # and Name	Description of Change	Brief Rationale
	that is being washed out is not exclusionary.	
6.3 Measures to Minimize Bias: Randomization and Binding	Specified that IRT assigns the participant number at Screening.	To provide clarification.
6.8 Concomitant Therapy	Revised the timing of administration for concomitant medications that are known sensitive substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) relative to study drug administration.	To better align with the known PK profile of the ER formulation of JZP385 used in the current study whereby -there is no JZP385 left 12 hours postdose in the intestine to elicit transporter inhibition, permitting safe administration of P-gp/BCRP substrates at that time.
7.1.2 Temporary Discontinuation/Study Intervention Interruption	Specified that the sponsor's medical monitor must be consulted if a participant temporarily interrupts study intervention.	To provide clarification.
8 Study Assessments and Procedures	Specified that Principal Investigators should not serve as blinded raters, except when approved by the sponsor.	To provide clarification.
8.2.3 Clinical Global Impression of Severity 8.2.5 Clinical Global Impression of Change	Revised text to clarify the CGI assessments are rated by qualified medical personnel (ie, a clinician).	To provide clarification.
8.3.2 Vital Signs	Oral temperature was changed to body temperature.	To provide clarification.
8.4.6 Adverse Events of Special Interest	Revised text regarding AEOSIs.	Updated to reflect the most relevant and accurate information based on clinical studies with JZP385.
8.4.7 Overdose, Medication Errors, and Misuse	Renamed section title to include OREs.	Updated to reflect the most relevant and accurate information based on clinical studies with JZP385.

Section # and Name	Description of Change	Brief Rationale
9.4.1.2 Intercurrent Event Strategies	Revised current text.	Added text to further clarify the intercurrent event handling strategy (hypothetical) and removed redundant text covered in Sections 9.4.2 and 9.4.3.
9.4.1.4 Dropouts and Missing Data	Updated analysis methods.	Updated primary and sensitivity analysis methods related to CGI-S. Also clarified the primary and sensitivity analysis approach on the TETRAS composite outcome score.
9.4.2 Primary Estimand	Revised text on sensitivity and supplemental analysis. Text revised to align with the mixed model components.	Updated language to further clarify on sensitivity analysis and supplemental analysis approaches.
10.1.1 Regulatory and Ethical Considerations	Text regarding IRB/IEC and national regulatory authority approval combined into 1 bullet, instead of 2.	To align with the protocol template.
Appendix 4	Revised text regarding AEOSI and ORE reporting.	For clarification and to align with the protocol template.
Appendix 8	Moved Amendment 2 Summary of Changes to Appendix 8.	For clarity.
Throughout	Revised formulation language throughout to change from “delayed release” to “extended-release.”	To improve accuracy of formulation description.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized

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