TITLE PAGE

Protocol Title:

A 17-week, Phase 2, Randomized, Double-blind, Placebo-controlled, Flexible-dosing, Parallel-group, Multicenter Study of the Efficacy and Safety of Suvecaltamide in the Treatment of Moderate to Severe Residual Tremor in Participants with Parkinson's Disease

Study Number: JZP385-202

Protocol and Amendment Number: JZP385-202-01

Amendment Scope**:** Global

Compound: Suvecaltamide (JZP385, formerly CX-8998 and MK-8998)

Brief Title: A Study of Suvecaltamide in Adults with Moderate to Severe Residual Tremor in Parkinson's Disease

Study Phase: Phase 2

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: [redacted]
EU Clinical Trial Number: 2022-001063-27

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, PhD **Sr. Director Clinical Development, Neuroscience**	**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 01	Please see appended electronic signature page.
Original Protocol	16-May-2022

Amendment 01 (Date: Please see appended electronic signature page)

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 and EU Regulation No 5136/2014.

Overall Rationale for the Amendment:

The overall rationale for this amendment is to facilitate participant enrollment by modifying eligibility criteria, including the removal of the TETRAS-PS inclusion criterion and expansion of participant's upper age limit to 85 years.

Section # and Name	Description of Change	Brief Rationale
Signature Page	Updated the name of the Medical Monitor.	To account for change in study personnel.
1.3 Schedule of Activities (Table 4)	Removed the requirement for urinalysis at Week 1.	To reduce burden to the participants and sites. No other safety laboratory assessments are being conducted at this visit.
1.3 Schedule of Activities (Table 4)	Added a reminder to the comments in Table 4 regarding Week 5 for the "Provide instructions for titration" activity.	To provide a reminder regarding titrating to reach an efficacious and tolerable dose.
3 Objectives, Estimands, and Endpoints (Table 6); also updated in 1.1 Synopsis (Table 2)	Changed the order of secondary efficacy endpoints so that TETRAS-PS comes after the PGI-C, PGI-S, and CGI-C endpoints.	Correction to align with the planned order of analysis in the SAP.
	Removed 'physical examination findings' from safety secondary endpoint.	Physical examination findings will be reported as medical history prior to the first dose of study intervention and as AEs after the first dose of study intervention.
	[redacted]	For clarification.

Section # and Name	Description of Change	Brief Rationale
	[redacted]	
4.1 Overall Design; 5.4 Screen Failures	Specified that 'Medical Monitor' is the 'Sponsor Medical Monitor' for rescreening purposes.	For clarification.
4.1 Overall Design; also updated in 1.1 Synopsis	Added text about optimization to Dose Titration and Optimization Period bullet.	For clarification.
4.1 Overall Design; 6.5 Dose Modification; also updated in 1.1 Synopsis	Changed 'continued study participation' to 'continuation of study intervention' for Maintenance Period bullet.	For clarification.
5.1 Inclusion Criteria; also updated in 1.1 Synopsis (Table 3)	Inclusion Criterion #1 – changed the upper age limit from '80 years' to '85 years'.	[redacted] Participant safety will be managed by exclusion criteria for comorbid conditions, and the flexible dosing design will allow participants to be titrated to an optimal dose based on efficacy and tolerability.
5.1 Inclusion Criteria; also updated in 1.1 Synopsis (Table 3)	Inclusion Criterion #3 – changed 'idiopathic PD' to 'PD' and removed the requirement for this diagnosis to occur 'within the past 5 years'.	The term idiopathic was removed to align with the terminology in the MDS 2015 criteria and the past 5 years was removed to correct the timing.
5.1 Inclusion Criteria	Inclusion Criterion #7b – removed criterion for TETRAS-PS score.	Inclusion #7a (TETRAS-ADL score ≥ 22) and #7c (CGI-S rating of at least moderate for participants' ability to function) are considered sufficient to enroll a PD participant with moderate to severe residual tremor.

Section # and Name	Description of Change	Brief Rationale
	Inclusion Criterion #8a – removed the bullet for abstinence from heterosexual intercourse and revised other bullets.	To align with sponsor's standard procedures.
	Inclusion Criterion #8b – updated the note 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.	For clarification and to align with sponsor's standard procedures.
5.2 Exclusion Criteria	Exclusion Criterion #2 – added example medical conditions and a note regarding prior essential tremor diagnosis to criterion.	For clarification.
	Exclusion Criterion #9 – clarified language to align with intent and added note to explain when remote history of cancer may be allowed.	For clarification.
	Exclusion Criterion #10 – added text regarding Gilbert's syndrome, combined criteria #10 and #11, and removed the eGFR threshold.	[redacted]
	Exclusion Criterion #17 – modified to clarify that participants should refrain from using PRN medication(s)/substance(s) that	For clarification.

Section # and Name	Description of Change	Brief Rationale
	may produce tremor or interfere with the evaluation of tremor prior to discharge on study visit days. Also, provided clarification regarding PRN sleep medications and regular benzodiazepine use.	
	Exclusion Criterion #19 – replaced 'PD medications or other anti-tremor medications' with 'medications to treat tremor' and added a note regarding PRN use of dopaminergic rescue medications.	Use of PRN dopaminergic medications can be standard of care for other motor symptoms (eg, rigidity or bradykinesia); therefore, PRN use of dopaminergic medications is allowed for the treatment of non-tremor PD symptoms (rigidity and bradykinesia). PRN use of medications to treat tremor is prohibited.
	Exclusion Criterion #21 – added text regarding permissible uses of botulinum toxin.	For clarification. Suvecaltamide is targeting treatment of tremor in PD. Thus, the use of botulinum toxin for other reasons (eg, cosmetic, excessive salivation, dystonia) will not confound this assessment as long as the location of use is anatomically distinct from the region with tremor.
	Exclusion Criterion #22 – added examples of dopamine receptor antagonists and dopamine depleting medications.	For clarification.
	Exclusion Criterion #28 – revised criterion to include 'known use of recreational drugs'. Added a note regarding opioid use at stable doses.	For clarification and to align with sponsor's standard procedures.
6.3 Measures to Minimize Bias: Randomization and Blinding; 8.1.2 Assignment of Participant Number	Updated first paragraph to specify that a participant number will be assigned by IRT at Screening. Updated second paragraph of Section 6.3 for clarification.	For clarification.

Section # and Name	Description of Change	Brief Rationale
6.8 Concomitant Therapy	[redacted]	For clarification.
7.1.2 Positive Alcohol or Urine Drug Screens; 8 Study Assessments and Procedures	Changed 'Medical Monitor' to 'Sponsor Medical Monitor'.	For clarification.
7.1.2 Positive Alcohol or Urine Drug Screens	Added text to clarify that the urine sample will be sent to the central laboratory.	For clarification.
8 Study Assessments and Procedures	Removed protocol waiver list item.	Protocol waivers are discussed in Section 5.
8.1.1 Informed Consent	Replaced 'medically qualified designee" with 'qualified designee'.	For clarification (qualified designee does not need a medical degree if consistent with local regulations).
8.1.3 Medical History; Appendix 5 Contraceptive and Barrier Guidance	Removed text related to sexual abstinence.	To align with the inclusion criterion changes and the sponsor's standard procedures.
8.1.5 Inclusion and Exclusion Criteria Review	Revised text to clarify that approval of eligibility to attend the Baseline Visit will be obtained from the Medical Monitor. Also, added text to clarify that the sites must re-confirm eligibility at the Baseline Visit prior to randomization.	For clarification and to align with the sponsor's standard procedure.
8.3.2 Vital Signs	Revised text to clarify that vital signs will be taken prior to blood collection when possible.	For clarification.
9.4.1.2 Definition of Study Periods for Analysis	Removed Section 9.4.1.2 from the protocol.	The analysis period definition resides within the contexts of the SAP.
Section 9.4.1.3 Intercurrent Event Strategies (formerly Section 9.4.1.4)	Replaced 'taking rescue medications' with 'PRN use of medications to treat tremor'.	To align with updated Exclusion Criterion #19.
Section 9.4.1.5 Dropouts and Missing Data (formerly Section 9.4.1.6)	Updated the Dropouts and Missing Data section. Updated Figure 1.	For clarification.
9.4.2 Primary Estimand	Updated MMRM model components.	For clarification.

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
10.1.6 Dissemination of Clinical Study Data	Removed 'EudraCT'.	Correction.
Appendix 3 Clinical Laboratory Tests (Table 9)	Added text to clarify that LDL is calculated and added HDL. Revised text so prothrombin time INR is specified separately.	To clarify that both a lipid panel and coagulation parameters will be collected.
Throughout	Minor editorial changes were made throughout the protocol.	For clarification and consistency.

Abbreviations: AEs = adverse events; BID = twice a day; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; eGFR = estimated glomerular filtration rate; EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; HDL = high density lipoprotein; IRT = interactive response technology; LDL = low density lipoprotein; MDS = Movement Disorder Society; MMRM = mixed effect model with repeated measures; PD = Parkinson's disease; PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; [redacted] PRN = as needed; SAP = Statistical Analysis Plan; TETRAS-ADL = The Essential Tremor Assessment Rating Scale, Activities of Daily Living; TETRAS-PS = The Essential Tremor Assessment Rating Scale, Performance Subscale; WOCBP = woman of childbearing potential.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A 17-week, Phase 2, Randomized, Double-blind, Placebo-controlled, Flexible-dosing, Parallel-group, Multicenter Study of the Efficacy and Safety of Suvecaltamide in the Treatment of Moderate to Severe Residual Tremor in Participants with Parkinson's Disease

Brief Title:

A Study of Suvecaltamide in Adults with Moderate to Severe Residual Tremor in Parkinson's Disease

Rationale:

Tremor negatively impacts the ability to perform ADL and negatively impacts psychosocial functioning for patients with Parkinson's disease (PD) throughout the disease course. There are currently no pharmacotherapies specifically approved for treatment of tremor in PD. Dopaminergic therapies (eg, levodopa/carbidopa) are considered the gold standard treatment for motor symptoms (including bradykinesia, rigidity, and tremor). However, tremor response to these pharmacotherapies is highly variable among patients with PD, and tremor often remains inadequately controlled at tolerable doses. This suggests that the underlying pathophysiology for tremor in PD is multifactorial and likely differs from the other motor symptoms of PD. The challenge of adequately treating tremor in PD with the available pharmacotherapies coupled with the significant impact on patient quality of life highlights the considerable need for novel pharmacotherapeutic options for the treatment of tremor in patients with PD.

Suvecaltamide (JZP385, formerly CX-8998 and MK-8998) is a highly selective negative modulator of Ca_V3 channels that shows low nM potency against all 3 Ca_V3 isoforms. Ca_V3 channels are low-voltage-activated T-type calcium channels that are thought to modulate neuronal cell firing and are highly expressed in brain areas that are hypothesized to be important in PD, particularly the subthalamic nucleus, ventrolateral thalamus, and the cerebellar-thalamic-cortical circuit. Numerous lines of evidence suggest that the increased activation of Ca_V3 channels and excessive rhythmicity play a key role in neurological disorders such as tremor in PD. Given that Ca_V3 channels are distributed in regions implicated in the pathophysiology of tremor and have been a pharmacological target in PD, selective targeting of these channels may offer an efficacious and well-tolerated treatment option.

The current study is designed to evaluate the efficacy and safety of suvecaltamide for the treatment of moderate to severe residual tremor in adults with PD that is not adequately controlled by PD medication and that interferes with their ADL and/or with their performance of tasks. [redacted] Representative of the real-world setting, a flexible-dosing regimen based on investigator assessment of clinical response and tolerability will be used. The flexible-dosing regimen further provides a conservative approach for the first larger study in the older PD population who may have other comorbidities and who are also taking PD medications, by starting suvecaltamide in patients at a lower dose and gradually titrating based on clinical response and tolerability.

Objectives, Estimands, and Endpoints:

Table 1: Primary and Key Secondary Objectives and Estimands

Objectives	Estimands and Attributes
Primary	
To evaluate the efficacy of suvecaltamide administered once daily for 17 weeks to improve functional and performance-based impairment due to tremor.	**Treatments:** Suvecaltamide and placebo. **Population:** Participants with PD who are experiencing moderate to severe residual tremor despite being optimally treated on a stable regimen of PD medication(s). **Variable:** Change from Baseline to Week 17 on the TETRAS composite outcome score.[a] **Intercurrent events:** Alternative/additional therapy as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events are provided in Section 9.4.1.3. Participants who experience any intercurrent event will be included in the analysis regardless (treatment policy). **Summary:** Difference in the mean change in the TETRAS composite outcome score[a] from Baseline to Week 17 between suvecaltamide and placebo.
Key Secondary	
To evaluate the efficacy of suvecaltamide administered once daily for 17 weeks to improve functional impairment due to tremor.	**Treatments:** Suvecaltamide and placebo. **Population:** Participants with PD who are experiencing moderate to severe residual tremor despite being optimally treated and on a stable regimen of PD medication(s). **Variable:** Proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 17 on the CGI-S. **Intercurrent events:** Alternative/additional therapy as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events are provided in Section 9.4.1.3. Participants who experience any intercurrent event will be included in the analysis regardless (treatment policy). **Summary:** Difference in the proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 17 in CGI-S scores between suvecaltamide and placebo.

Abbreviations: AE = adverse event; CGI-S = Clinical Global Impression of Severity; PD = Parkinson's disease; TETRAS-ADL = The Essential Tremor Rating Scale, Activities of Daily Living Subscale; TETRAS-PS = The Essential Tremor Rating Scale, Performance Subscale.

[a] The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL and items 6 (6a and 6b) 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. 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 suvecaltamide administered once daily for 17 weeks to improve tremor and the functional impairment due to tremor.	• Change from Baseline to Week 17 on TETRAS-ADL.[a] • Change from Baseline to Week 17 on TETRAS total score (TETRAS-ADL + TETRAS-PS).[a] • Proportion of participants who improved (≥ 1 point) from Baseline to Week 17 on the PGI-S. • Proportion of participants who were much improved on the PGI-C at Week 17. • Proportion of participants who were much improved on the CGI-C at Week 17. • Change from Baseline to Week 17 on TETRAS-PS.[a] • Change from Baseline to Week 17 on the MDS-UPDRS tremor score (items 2.10, 3.15, 3.16, 3.17, and 3.18).
To evaluate the safety and tolerability of suvecaltamide administered once daily for 17 weeks.	Incidence and severity of AEs as well as evaluation of safety laboratory assessments, vital signs, ECG results, C-SSRS, and QUIP-RS.
[redacted]	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: AUC = area under the plasma concentration-time curve; CGI-C = Clinician's Global Impression of Change; C-SSRS = Columbia Suicide Severity Rating Scale; C_{max} = concentration at peak; C_{tau} = concentration at trough; ECG = electrocardiogram; [redacted]
MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD = Parkinson's disease; [redacted] PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; [redacted] QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale; [redacted] $t_{½}$ = terminal half-life; TETRAS-ADL = The Essential Tremor Rating Scale, Activities of Daily Living Subscale; TETRAS-PS = The Essential Tremor Rating Scale, Performance Subscale; T_{max} = time to maximum concentration.

[a] This endpoint uses the unmodified or raw TETRAS score.

[b] For the modified items 1-11 of the TETRAS ADL, each item is modified from 5 response items to 4 by collapsing options 0 and 1 together.

[c] For the modified items 6 (6a and 6b) and 7 of the TETRAS-PS, each item is modified from 9 response items (due to scoring in 0.5 increments) to 4 response items.

Brief Summary:

This is a 17-week double-blind, placebo-controlled, randomized, flexible-dosing, parallel-group, multicenter study of the efficacy and safety of suvecaltamide in the treatment of moderate to severe residual tremor in adult participants with PD. [redacted]

The maximum total duration of the study for each participant will be 23 weeks, with a maximum treatment duration of 17 weeks. For each participant, the study consists of a Screening Period (up to 4 weeks), a 5-week Dose Titration and Optimization Period, a 12-week Maintenance Period,

and a 2-week Safety Follow-up Period. There is no continued access to study intervention upon completion of the study.

Participants eligible for the study will be randomized 1:1 to receive suvecaltamide or placebo and stratified by TETRAS composite outcome score (≤ 17 or > 17) as assessed at Baseline. Suvecaltamide (or matching placebo) will be administered orally [redacted]. Each participant's optimal dose (10, 20, or 30 mg suvecaltamide or matching placebo) will be determined by the investigator during the Dose Titration and Optimization Period, and the participant will receive this optimal dose throughout the Maintenance Period as follows:

- Dose Titration and Optimization Period: study intervention will be titrated by the investigator in collaboration with the participant to individually optimize efficacy and tolerability. Every effort should be made by the investigator to ensure that the maintenance dose is optimized for efficacy and tolerability. Investigators should thoroughly assess whether tremor symptoms have been optimally treated and consider up-titration if therapeutic benefit has not yet been achieved. [redacted]
- Maintenance Period: participants will continue to take study intervention of 1, 2, or 3 capsules of either suvecaltamide (10 mg per capsule) or matching placebo at the optimal dose determined by the investigator at the end of the Dose Titration and Optimization Period (see Table 7). No dose adjustment should occur during the Maintenance Period. If the investigator determines a dose adjustment is indicated for safety reasons, the Medical Monitor should be consulted regarding continuation of study intervention.

A 2-week Safety Follow-up Period (with visit planned at the end of the 2-week period) will be required for participants who either discontinue early or fully complete the Maintenance Period.

Assessments of efficacy, safety, [redacted] will be conducted throughout the study period.

Overall Design:

Table 3: Overall Study Design

Overall Design	
Study Phase	2
Clinical Indication	Suvecaltamide for treatment of moderate to severe residual tremor in participants with PD
Study Type	Interventional
Type of Design	Randomized, placebo-controlled, flexible-dosing, parallel-group, multicenter study. Participants will be stratified by the TETRAS composite outcome score (≤ 17 or > 17) as assessed at Baseline.
Type of Control	Placebo
Study Blinding	Double-blind
Population	Male and female participants ages 40 to 85 years inclusive with a diagnosis of clinically probable or clinically established PD meeting the MDS 2015 criteria (Postuma, 2015) with moderate to severe residual tremor despite treatment with PD medication(s).
Number of Participants	Approximately 160 participants will be randomized (80 to each treatment arm) to achieve 128 participants to complete Week 17 assessments assuming a 20% drop-out rate (see Section 9).
Duration of Participation	The study comprises 4 periods: an up to 4-week Screening Period, a 5-week Dose Titration and Optimization Period, a 12-week Maintenance Period, and a 2-week Safety Follow-up Period. The maximum treatment duration for each participant will be 17 weeks. The maximum total study duration for each participant is 23 weeks.
Number of Treatment Arms	2
Treatment Groups	1. Placebo 2. Suvecaltamide (titrated to optimal once-daily oral dose of 10, 20, or 30 mg)
Data Monitoring Committee	Not applicable.

Abbreviations: MDS = Movement Disorder Society; PD = Parkinson's disease; TETRAS = The Essential Tremor Rating Scale.

1.3. Schedule of Activities

Table 4: Schedule of Activities

	Screening (up to 28 days)	BL	Dose Titration and Optimization Period			Maintenance Period						Efficacy FU Visit[a]	E/D Visit[b]	Safety FU Period	Comments
	SV	BL	W1, W2	W3, W4	W5	W6, W7, W8	W9	W10, W11, W12	W13	W14, W15, W16	W17			W19	See Section 7 regarding d/c of study intervention and participant d/c or withdrawal.
Clinic Visits[c]	X	X	X[d]		X[d]		X[d]		X[d]		X	X[d]	X	X[b, d]	
Phone Visits[c]				X		X		X		X					
Day	-28 to -3	-1	7, 14	21, 28	35	42, 49, 56	63	70, 77, 84	91	98, 105, 112	119			133	
			(-1, +2)			(-3, +2)									Visit windows
ICF	X														
Randomization		X													
I/E criteria	X	X													See Section 5.
Demographics	X														
Medical history	X	X													See Section 8.1.3 and Section 8.4.1.
Complete physical exam	X										X		X	X	See Section 8.3.1.
Height	X														See Section 8.3.1.
Weight	X	X									X		X	X	See Section 8.3.1.
Serum or urine pregnancy test	X														See Section 8.3.5.
Urine pregnancy test[c]		X			X		X		X		X		X	X	See Section 8.3.5
Urine drug screen	X	X			X		X		X		X		X		See Section 7.1.2 and Appendix 3.

	Screening (up to 28 days)	BL	Dose Titration and Optimization Period			Maintenance Period						Efficacy FU Visit[a]	E/D Visit[b]	Safety FU Period	Comments
	SV	**BL**	**W1, W2**	**W3, W4**	**W5**	**W6, W7, W8**	**W9**	**W10, W11, W12**	**W13**	**W14, W15, W16**	**W17**			**W19**	**See Section 7 regarding d/c of study intervention and participant d/c or withdrawal.**
Clinic Visits[c]	**X**	**X**	**X[d]**		**X[d]**		**X[d]**		**X[d]**		**X**	**X[d]**	**X**	**X[b, d]**	
Phone Visits[c]				**X**		**X**		**X**		**X**					
Day	**-28 to -3**	**-1**	**7, 14**	**21, 28**	**35**	**42, 49, 56**	**63**	**70, 77, 84**	**91**	**98, 105, 112**	**119**			**133**	
			(-1, +2)			**(-3, +2)**									**Visit windows**
Breath alcohol test	X	X			X		X		X		X		X		See Section 7.1.2.
Laboratory assessments (chemistry, hematology)	X	X			X		X		X		X		X	X	See Section 8.3.4 and Appendix 3.
Orthostatic blood pressure and pulse	X	X	X		X		X		X		X		X	X	See Section 8.3.2.
Urinalysis	X	X			X		X		X		X		X	X	See Section 8.3.4 and Appendix 3.
Temperature and respiratory rate	X	X	W1 only		X		X		X		X		X	X	See Section 8.3.2.
12-lead ECG	X	X	W1 only				X				X		X	X	See Section 8.3.3.
C-SSRS Screening/ Baseline Version	X														See Section 8.3.6.
C-SSRS Since Last Visit Version		X	X		X		X		X		X	X	X	X	See Section 8.3.6.

	Screening (up to 28 days)	BL	Dose Titration and Optimization Period			Maintenance Period						Efficacy FU Visit[a]	E/D Visit[b]	Safety FU Period	Comments
	SV	**BL**	**W1, W2**	**W3, W4**	**W5**	**W6, W7, W8**	**W9**	**W10, W11, W12**	**W13**	**W14, W15, W16**	**W17**			**W19**	**See Section 7 regarding d/c of study intervention and participant d/c or withdrawal.**
Clinic Visits[c]	**X**	**X**	**X[d]**		**X[d]**		**X[d]**		**X[d]**		**X**	**X[d]**	**X**	**X[b, d]**	
Phone Visits[c]				**X**		**X**		**X**		**X**					
Day	**-28 to -3**	**-1**	**7, 14**	**21, 28**	**35**	**42, 49, 56**	**63**	**70, 77, 84**	**91**	**98, 105, 112**	**119**			**133**	
			(-1, +2)			**(-3, +2)**									**Visit windows**
QUIP-RS		X									X		X	X	See Section 8.3.7.
MoCA	X														See Section 8.1.7.
Instruction on medication washout	X														See Section 5.2 and Section 6.8.
TETRAS-ADL	X	X			X		X		X		X	X	X	X	See Section 8.2.1.
TETRAS-PS	X	X			X		X		X		X	X	X		See Section 8.2.2.
CGI-S	X	X			X		X		X		X	X	X		See Section 8.2.3.
CGI-C							X		X		X	X	X		See Section 8.2.4.
PGI-S	X	X			X		X		X		X	X	X		See Section 8.2.5.
PGI-C							X		X		X	X	X		See Section 8.2.6.
MDS-UPDRS I-IV		X			X		X		X		X		X		See Section 8.2.7.
[redacted]		[redacted]									[redacted]		[redacted]		See Section 8.2.8.
[redacted]		[redacted]									[redacted]		[redacted]		See Section 8.2.9.
[redacted]		[redacted]									[redacted]		[redacted]		See Section 8.2.10.
[redacted]		[redacted]									[redacted]		[redacted]		See Section 8.2.11.

	Screening (up to 28 days)	BL	Dose Titration and Optimization Period			Maintenance Period						Efficacy FU Visit[a]	E/D Visit[b]	Safety FU Period	Comments
	SV	**BL**	**W1, W2**	**W3, W4**	**W5**	**W6, W7, W8**	**W9**	**W10, W11, W12**	**W13**	**W14, W15, W16**	**W17**			**W19**	**See Section 7 regarding d/c of study intervention and participant d/c or withdrawal.**
Clinic Visits[c]	**X**	**X**	**X[d]**		**X[d]**		**X[d]**		**X[d]**		**X**	**X[d]**	**X**	**X[b, d]**	
Phone Visits[c]				**X**		**X**		**X**		**X**					
Day	**-28 to -3**	**-1**	**7, 14**	**21, 28**	**35**	**42, 49, 56**	**63**	**70, 77, 84**	**91**	**98, 105, 112**	**119**			**133**	
			(-1, +2)			**(-3, +2)**									**Visit windows**
Light breakfast, lunch, or snack as needed	X	X	X		X		X		X		X	X	X		Participants will be asked to fast for their Screening Visit only. [redacted]
Dispense study intervention		X	X		X		X		X						Participants should begin taking study intervention at home on Day 1 (the day following the Baseline Visit). Remind participants not to take study intervention prior to clinic visits for Weeks 1, 9, 13, and 17.
Provide instructions for titration		X	X	X	X										For Week 5 Visit, confirm that participant has reached an efficacious and tolerable dose and provide instructions to participant to maintain dose for remainder of study.

	Screening (up to 28 days)	BL	Dose Titration and Optimization Period			Maintenance Period						Efficacy FU Visit[a]	E/D Visit[b]	Safety FU Period	Comments
	SV	**BL**	**W1, W2**	**W3, W4**	**W5**	**W6, W7, W8**	**W9**	**W10, W11, W12**	**W13**	**W14, W15, W16**	**W17**			**W19**	**See Section 7 regarding d/c of study intervention and participant d/c or withdrawal.**
Clinic Visits[c]	**X**	**X**	**X[d]**		**X[d]**		**X[d]**		**X[d]**		**X**	**X[d]**	**X**	**X[b, d]**	
Phone Visits[c]				**X**		**X**		**X**		**X**					
Day	**-28 to -3**	**-1**	**7, 14**	**21, 28**	**35**	**42, 49, 56**	**63**	**70, 77, 84**	**91**	**98, 105, 112**	**119**			**133**	
			(-1, +2)			**(-3, +2)**									**Visit windows**
Collect study intervention/ assess compliance			X		X		X		X		X	X	X		If participants do not return study intervention at the Week 17 or E/D visit, they should be asked to return unused study intervention at the Safety FU Visit or Efficacy FU Visit. See Section 6.4
Administer study intervention on site			W1 only				X		X		X				See Section 8.1.6.
Blood draws for genetic testing			W1 only												See Section 8.6.
[redacted]			[redacted]				[redacted]		[redacted]		[redacted]				See Section 8.5.
AEs			←								→		X	X	See Section 8.4 and Appendix 4.
Prior/ concomitant medications	←										→	X	X	X	See Section 6.8 and Section 8.1.4.

	Screening (up to 28 days)	BL	Dose Titration and Optimization Period			Maintenance Period						Efficacy FU Visit[a]	E/D Visit[b]	Safety FU Period	Comments
	SV	BL	W1, W2	W3, W4	W5	W6, W7, W8	W9	W10, W11, W12	W13	W14, W15, W16	W17			W19	See Section 7 regarding d/c of study intervention and participant d/c or withdrawal.
Clinic Visits[c]	X	X	X[d]		X[d]		X[d]		X[d]		X	X[d]	X	X[b, d]	
Phone Visits[c]				X		X		X		X					
Day	-28 to -3	-1	7, 14	21, 28	35	42, 49, 56	63	70, 77, 84	91	98, 105, 112	119			133	
			(-1, +2)			(-3, +2)									Visit windows
Schedule next visit and/or phone contact	X	X	X	X	X	X	X	X	X	X	X	X			Tentatively schedule all study visits at Screening. Confirm visits at each subsequent visit.

Abbreviations: AEs = adverse events; BL = baseline; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; d/c = discontinuation; ECG = electrocardiogram; E/D = early discontinuation; [redacted] FU = follow-up; ICF = Informed Consent Form; I/E = inclusion/exclusion; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; [redacted] PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; [redacted] QUIP-RS = Questionnaire for Impulsive Control Disorders in PD Rating Scale; [redacted] SV = Screening Visit; TETRAS-ADL = The Essential Tremor Rating Scale, Activities of Daily Living Subscale; TETRAS-PS = The Essential Tremor Rating Scale, Performance Subscale; W = week; WOCBP = women of childbearing potential.

[a] Discontinuation from study intervention does not represent discontinuation from the study. For participants who discontinue study intervention early, every effort should be made to attend Efficacy Follow-up Visits through 17 weeks after the first dose. See Section 7 for additional guidance.

[b] If participant discontinues study intervention early (regardless of whether or not he/she continues in the study), he/she will require an E/D Visit and a Safety FU Visit. The E/D Visit should occur as soon as possible following early discontinuation of study intervention. The Safety FU Visit should occur 2 weeks after the E/D visit.

[c] Additional onsite clinic visits may be scheduled at any time, including in place of scheduled phone contacts, if required due to local requirements (eg, for study intervention dispensation). If performed in-clinic, urine pregnancy testing should be completed for WOCBP.

[d] Clinic visits at Week 1, Week 2, Week 5, Week 9, Week 13, E/D, and Safety FU may be conducted remotely, if required due to the coronavirus 2019 pandemic, and with approval from the Sponsor Medical Monitor. The TETRAS-PS and MDS-UPDRS will not be performed during remote visits [redacted].

2. INTRODUCTION

Suvecaltamide (JZP385, formerly CX-8998 and MK-8998) is a potent, highly selective, state-dependent, negative modulator of low-voltage-activated T-type calcium channels (also known as Ca_V3 channels) that is being developed for once-daily treatment of moderate to severe residual tremor in PD.

2.1. Study Rationale

Tremor negatively impacts the ability to perform ADL and negatively impacts psychosocial functioning for patients with Parkinson's disease (PD) throughout the disease course. There are currently no pharmacotherapies specifically approved for treatment of tremor in PD. Dopaminergic therapies (eg, levodopa/carbidopa) are considered the gold standard treatment for motor symptoms; however, tremor response to these pharmacotherapies is highly variable among patients with PD and often tremor remains inadequately controlled at tolerable doses. This suggests that the underlying pathophysiology for tremor in PD is multifactorial and likely differs from the other motor symptoms of PD. The challenge of adequately treating tremor in PD with the available pharmacotherapies coupled with the significant impact on patient quality of life highlights the considerable need for novel pharmacotherapeutic options for the treatment of tremor in patients with PD.

Suvecaltamide is a highly selective negative modulator of Ca_V3 channels that shows low nM potency against all 3 Ca_V3 isoforms. Ca_V3 channels are low-voltage-activated T-type calcium channels that are thought to modulate neuronal cell firing and are highly expressed in brain areas that are hypothesized to be important in PD, particularly the subthalamic nucleus, ventrolateral thalamus, and the cerebellar-thalamic-cortical circuit. Numerous lines of evidence suggest that the increased activation of Ca_V3 channels and excessive rhythmicity play a key role in neurological disorders such as tremor in PD. Given that Ca_V3 channels are distributed in regions implicated in the pathophysiology of tremor and have been a pharmacological target in PD, selective targeting of these channels may offer an efficacious and well-tolerated treatment option.

The current study is designed to evaluate the efficacy and safety of suvecaltamide for the treatment of moderate to severe residual tremor in adults with PD that is not adequately controlled by PD medications and that interferes with their ADL and/or with their performance of tasks. [redacted] Representative of the real-world setting, a flexible-dosing regimen based on investigator assessment of clinical response and tolerability will be used. The flexible-dosing regimen further provides a conservative approach for the first larger study in the older PD population who may have other comorbidities and who are also taking PD medications, by starting suvecaltamide in patients at a lower dose and gradually titrating based on clinical response and tolerability.

2.2. Background

2.2.1. Parkinson's Disease

Parkinson's disease is a neurodegenerative disease affecting over 1 million patients in the United States, 1.2 million in Europe, and 6.3 million worldwide (Dorsey, 2018). The prevalence of PD is approximately 1% for individuals over 65 years of age, increasing to 3% for octogenarians (Nussbaum and Ellis, 2003).

PD is characterized early on by the classic motor symptom triad of resting tremor, bradykinesia, and rigidity (Postuma, 2015). Tremor is one of the most prominent and visible features of PD and is often the first symptom noticed by patients (Jankovic, 2008). Approximately 75% of patients with PD experience tremor at some point during the disease course (Hughes, 1993; Gupta, 2020). While rest tremor is commonly observed, the majority of patients also experience action and postural tremors (Pasquini, 2018; Gupta, 2020).

In addition to being one of the most visual symptoms of PD, tremor is also ranked as one of the 5 most troubling symptoms by both early and advanced stage patients (Politis, 2010), interfering with the ability to perform ADL and negatively impacting psychosocial functioning, including personal and social relationships, self-image, and overall sense of well-being (Heusinkveld, 2018).

There are currently no pharmacotherapies specifically approved for the treatment of tremor in patients with PD. Unlike other motor symptoms of PD, tremor often does not resolve for many patients despite treatment with standard PD medications including dopaminergic therapies (Yahr, 1969; Helmich, 2018). In addition, higher doses of these therapies are generally needed to address tremor symptoms. As a result, the dose-limiting side effects of nausea, vomiting, dyskinesia, or psychosis can lead to the undertreatment of tremor symptoms (Nonnekes, 2016). Taken together, the pharmacological treatment of tremor in patients with PD remains challenging and coupled with the significant impact on patient quality of life, there is a high unmet need for novel therapeutic options for the treatment of tremor in patients with PD.

2.2.2. Suvecaltamide

Suvecaltamide, a highly selective negative modulator of low-voltage-activated CaV3 channels, shows low nM potency against all 3 CaV3 isoforms. All 3 isoforms of CaV3 are expressed throughout the CNS and the peripheral nervous system. In particular, CaV3 channels are highly expressed in thalamocortical circuitry and tremor network regions, where they mediate subthreshold oscillations and excessive rhythmicity in pathophysiologic states found in movement disorders, such as essential tremor (ET) and PD, neuropathic pain, and epilepsy (Handforth, 2005; Llinás, 2007; Park, 2013). For example, Ca_V3 is highly expressed in brain areas that are hypothesized to be important in tremor in PD, particularly the STN, ventrolateral thalamus, and the cerebellar-thalamic-cortical circuit (Park, 2013). Consistent with these findings, pharmacological inhibition of Ca_V3 channels in the STN rescues locomotor deficits in rat models of PD (Tai, 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 PD. 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; Chang, 2015). Given that Ca_V3 channels

are distributed in regions implicated in the pathophysiology of tremor and have been a pharmacological target in PD, selective targeting of these channels may offer a more efficacious and better-tolerated treatment option.

[redacted]

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

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

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

- The potential risks from treatment with suvecaltamide in participants with PD are expected to be consistent with the known pharmacology and safety profile of suvecaltamide in clinical studies conducted to date. In general, AE profiles were consistent across populations studied (eg, ET, schizophrenia, healthy volunteers). [redacted] Generally, the most commonly reported AEs were in the SOCs of Nervous System Disorders and Psychiatric Disorders and included dizziness, euphoric mood, headache, 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 with PD will be managed and mitigated by the use of exclusion criteria in this clinical study protocol, which will preclude participants 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 studies. In addition, a flexible-dosing regimen and titration schedule will be implemented such that participants will start at a lower dose and titrate up to an individually optimized dose based on tolerability and efficacy. This will help mitigate the potential risk associated with pharmacodynamic interaction between suvecaltamide and concomitant PD medication. Extensive monitoring of AEs, ECGs, orthostatic hypotension, and suicidal ideation and behavior will occur at frequent clinic visits throughout the study. These measures are intended to mitigate potential risks and to more fully assess the risks of using suvecaltamide for this indication.

- For participants who are randomized to receive placebo, the risks may be similar to the risks associated with uncontrolled or inadequately controlled tremor in PD, however, these risks are not worse than the risks faced by the PD population treated according to standard of care. The consequences of inadequately controlling tremor in PD include decreased work productivity, increase psychosocial burden, as well as functional limitations resulting from motor impairment (eg, the inability to attend to personal needs and perform personal hygiene activities), all of which contribute to an overall reduction in quality of life.
- Study procedure-related risks, including risks and/or discomfort associated with blood collection, ECGs, physical examinations, and completion of questionnaires and other assessments (see Section 8 for details of study assessments).

2.3.2. Benefit Assessment

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

- Treatment with suvecaltamide for the study duration may alleviate the significant symptom burden associated with tremor in PD.
- Irrespective of which treatment a participant receives in the study, all participants will contribute to the process of developing new therapies in tremor in PD.
- Participants will receive comprehensive clinical exams and clinical monitoring associated with the study for up to 23 weeks.

2.3.3. Overall Benefit:Risk Summary

Benefits to participants include the potential to receive therapy which may alleviate symptoms of tremor in PD, contribute to the development of new therapeutics in tremor in PD, as well as receiving comprehensive physical examination, clinical safety assessments, and laboratory testing.

Risks to participants include those related to suvecaltamide, the potential to be treated with placebo for the study duration, potential pharmacodynamic interactions between suvecaltamide and concomitant PD medications, and risks related to the study procedures including blood collection. The remaining risks associated with treatment with suvecaltamide are expected to be like those seen in previous clinical studies (see Section 2.3.1).

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of suvecaltamide may be found in the IB and Development Safety Update Report.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Table 5: Primary and Key Secondary Objectives and Estimands

Objectives	Estimands and Attributes
Primary	
To evaluate the efficacy of suvecaltamide administered once daily for 17 weeks to improve functional and performance-based impairment due to tremor.	**Treatments:** Suvecaltamide and placebo. **Population:** Participants with PD who are experiencing moderate to severe residual tremor despite being optimally treated on a stable regimen of PD medication(s). **Variable:** Change from Baseline to Week 17 on the TETRAS composite outcome score.[a] **Intercurrent events:** Alternative/additional therapy as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events are provided in Section 9.4.1.3. Participants who experience any intercurrent event will be included in the analysis regardless (treatment policy). **Summary:** Difference in the mean change in the TETRAS composite outcome score[a] from Baseline to Week 17 between suvecaltamide and placebo.
Key Secondary	
To evaluate the efficacy of suvecaltamide administered once daily for 17 weeks to improve functional impairment due to tremor.	**Treatments:** Suvecaltamide and placebo. **Population:** Participants with PD who are experiencing moderate to severe residual tremor despite being optimally treated and on a stable regimen of PD medication(s). **Variable:** Proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 17 on the CGI-S. **Intercurrent events:** Alternative/additional therapy as well as discontinuation of treatment due to lack of efficacy, an AE, or any other reason. Definitions for all intercurrent events are provided in Section 9.4.1.3. Participants who experience any intercurrent event will be included in the analysis regardless (treatment policy). **Summary:** Difference in the proportion of participants who improved (≥ 1-point improvement) from Baseline to Week 17 in CGI-S scores between suvecaltamide and placebo.

Abbreviations: AE = adverse event; CGI-S = Clinical Global Impression of Severity; PD = Parkinson's disease; TETRAS-ADL = The Essential Tremor Rating Scale, Activities of Daily Living Subscale; TETRAS-PS = The Essential Tremor Rating Scale, Performance Subscale.

[a] The TETRAS composite outcome score is the sum of modified items 1 to 11 of the TETRAS-ADL and items 6 (6a and 6b) 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. For TETRAS-PS, each item is modified from 9 response items (due to 0.5 scoring increments) to 4 response items.

Table 6: Secondary and Exploratory Objectives and Endpoints

Objectives	Endpoints
Secondary	
To evaluate the efficacy of suvecaltamide administered once daily for 17 weeks to improve tremor and the functional impairment due to tremor.	• Change from Baseline to Week 17 on TETRAS-ADL.[a] • Change from Baseline to Week 17 on TETRAS total score (TETRAS-ADL + TETRAS-PS).[a] • Proportion of participants who improved (≥ 1 point) from Baseline to Week 17 on the PGI-S. • Proportion of participants who were much improved on the PGI-C at Week 17. • Proportion of participants who were much improved on the CGI-C at Week 17. • Change from Baseline to Week 17 on TETRAS-PS.[a] • Change from Baseline to Week 17 on the MDS-UPDRS tremor score (items 2.10, 3.15, 3.16, 3.17, and 3.18).
To evaluate the safety and tolerability of suvecaltamide administered once daily for 17 weeks.	Incidence and severity of AEs as well as evaluation of safety laboratory assessments, vital signs, ECG results, C-SSRS, and QUIP-RS.
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: AUC = area under the plasma concentration-time curve; CGI-C = Clinician's Global Impression of Change; C-SSRS = Columbia Suicide Severity Rating Scale; C_{max} = concentration at peak; C_{tau} = concentration at trough; ECG = electrocardiogram; [redacted]
MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD = Parkinson's disease; [redacted] PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; [redacted] QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale; [redacted] $t_{½}$ = terminal half-life; TETRAS-ADL = The Essential Tremor Rating Scale, Activities of Daily Living Subscale; TETRAS-PS = The Essential Tremor Rating Scale, Performance Subscale; T_{max} = time to maximum concentration.

[a] This endpoint uses the unmodified or raw TETRAS score.

[b] For the modified items 1-11 of the TETRAS ADL, each item is modified from 5 response items to 4 by collapsing options 0 and 1 together.

[c] For the modified items 6 (6a and 6b) and 7 of the TETRAS PS, each item is modified from 9 response items (due to scoring in 0.5 increments) to 4 response items.

4. STUDY DESIGN

4.1. Overall Design

This is a 17-week double-blind, placebo-controlled, randomized, flexible-dosing, parallel-group, multicenter study of the efficacy and safety of suvecaltamide in the treatment of moderate to severe residual tremor in adult participants with PD. [redacted]

The maximum total duration of the study for each participant will be 23 weeks, with a maximum treatment duration of 17 weeks. For each participant, the study consists of a Screening Period (up to 4 weeks), a 5-week Dose Titration and Optimization Period, a 12-week Maintenance Period, and a 2-week Safety Follow-up Period. There is no continued access to study intervention upon completion of the study.

During the Screening Period, all participants will be evaluated for eligibility (including an assessment of their concomitant PD medication use) and will washout any prohibited medications. Participants may be allowed to rescreen once if the rescreening is approved by the Sponsor Medical Monitor.

Participants eligible for the study will be randomized 1:1 to receive suvecaltamide or placebo and stratified by TETRAS composite outcome score (≤ 17 or > 17) as assessed at Baseline. Suvecaltamide (or matching placebo) will be administered orally [redacted]. Each participant's optimal dose (10, 20, or 30 mg suvecaltamide or matching placebo) will be determined by the investigator during the Dose Titration and Optimization Period, and the participant will receive this optimal dose throughout the Maintenance Period as follows:

- Dose Titration and Optimization Period: study intervention will be titrated by the investigator in collaboration with the participant to individually optimize efficacy and tolerability. Every effort should be made by the investigator to ensure that the maintenance dose is optimized for efficacy and tolerability. Investigators should thoroughly assess whether tremor symptoms have been optimally treated and consider up-titration if therapeutic benefit has not yet been achieved. The starting dose is 5 mg suvecaltamide or 1 matching placebo capsule once daily. After 7 to 14 days, the dose of study intervention will be increased to 10 mg suvecaltamide (or 1 matching placebo capsule) [redacted]. If needed, participants will be able to titrate down to a minimum of 10 mg suvecaltamide (or a minimum of 1 matching placebo capsule) per day at any time following consultation with the investigator. Participants not tolerating a once-daily dose of 5 mg suvecaltamide after 2 weeks of treatment will be discontinued from the study.
- Maintenance Period: participants will continue to take study intervention of 1, 2, or 3 capsules of either suvecaltamide (10 mg per capsule) or matching placebo at the optimal dose determined by the investigator at the end of the Dose Titration and

Optimization Period (see Table 7). No dose adjustment should occur during the Maintenance Period. If the investigator determines a dose adjustment is indicated for safety reasons, the Medical Monitor should be consulted regarding continuation of study intervention.

A 2-week Safety Follow-up Period (with visit planned at the end of the 2-week period) will be required for participants who either discontinue early or fully complete the Maintenance Period.

Assessments of efficacy, safety, [redacted] will be conducted as described in Section 8.2, Sections 8.3/8.4, and Section 8.5, respectively, and as described in the SoA (Section 1.3). Note that to ensure study intervention is taken in the morning, clinic visits should take place in the morning.

4.2. Scientific Rationale for Study Design

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

The target patient population for this study is adults with moderate to severe residual tremor in PD that interferes with their ADL and/or function. This represents a subset of the overall population of patients with PD-related tremor. Approximately 75% of the patients with PD-related tremor are anticipated to have a tremor that would impact their ADL (Pasquini, 2018; Gupta, 2020); the majority of these patients are expected to have residual tremor that is not adequately controlled by PD medications (Raethjen, 2005; Sung, 2008; Zach, 2020).

The severity of the functional impact of tremor in PD will be defined by eligibility criteria on patient interview (TETRAS-ADL), clinician-rated (CGI-S), and objective measures of disability (TETRAS-PS items 6 [6a and 6b] and 7). The inclusion of a placebo control group in this study is necessary to determine the efficacy and safety of suvecaltamide.

The 17-week treatment duration (5-week Dose Titration and Optimization Period and 12-week Maintenance Period) is to ensure adequate duration to evaluate efficacy and safety of suvecaltamide in this phase 2 study.

Tremor may have a pathophysiology different from other motor symptoms (Helmich, 2012). First, tremor does not progress as quickly as bradykinesia, rigidity, gait, and balance (Louis, 1999). Second, tremor severity does not correlate with the severity of other motor symptoms (Louis, 2001). Third, tremor can occasionally impact the body contralateral to the otherwise most affected side, ie, where bradykinesia and rigidity are most prominent. Finally, tremor responds less well to dopaminergic treatment than bradykinesia and rigidity (Koller, 1994; Fishman, 2008). While the clinical presentation of tremor can be different, there is evidence to suggest that the underlying pathophysiology of ET and tremor in PD is similar (Filip, 2022). As a result, the proof-of-concept findings from a phase 2, randomized, double-blind, multicenter, placebo-controlled, dose titration study of suvecaltamide in adults with ET (Study CX-8998-CLN2-001 [T-CALM]), provide some support for the study of tremor in PD. The results of the 4-week T-CALM demonstrated that reduction in tremor with daily doses of 16 and 20 mg suvecaltamide is observed within several weeks, although the durability of the effect is unknown. In the T-CALM study, doses were titrated for the first 2 weeks and the

final target dose was maintained for 2 additional weeks; efficacy assessments were taken at the end of Weeks 2 and 4. Despite not meeting statistical significance on the primary endpoint (TETRAS-PS, as rated by independent video raters), numerical improvements favoring suvecaltamide over placebo were observed on TETRAS-PS as rated by the investigators at both timepoints. Numerical improvements were also observed on the TETRAS-ADL subscale at both timepoints. The 12-week Maintenance Period in the present study is of sufficient duration to permit assessment of the durability of efficacy of suvecaltamide for the treatment of moderate to severe residual tremor in PD.

From a safety perspective, AEs in the T-CALM study were primarily reported during the first week of treatment. Most of the commonly reported AEs resolved within a week of treatment initiation despite continued dosing with suvecaltamide. The 17-week treatment duration of the present study, with multiple clinic visits to assess safety as well as phone visits for AE reporting, will allow for adequate assessment of safety.

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 (6a and 6b) and 7 of the TETRAS-PS (ie, TETRAS composite outcome score). The TETRAS-ADL subscale is a scale that assesses the impact of tremor on day-to-day functioning that is administered by a trained interviewer. It 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 suvecaltamide in the T-CALM study (see the suvecaltamide IB). 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 (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 clinician-rated and objective measures of the functional impact of tremor.

The key secondary endpoint is the CGI-S. The clinician-rated CGI-S will complement the primary endpoint and specifically evaluate the clinician's assessment of the participants' ability to function due to tremor in PD. In the T-CALM study, a numerically higher percentage of clinicians reported participant improvement on the CGI-C when treated with 16 and 20 mg suvecaltamide per 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 suvecaltamide.

4.3. Justification for Dose

Since this is a flexible-dose study, during the Dose Titration and Optimization period, participants will be titrated to their optimally effective and tolerable dosing regimen of 10, 20, or 30 mg suvecaltamide administered [redacted] (see Section 4.1). Participants will enter the Maintenance Period on their optimized dose and will remain on their optimal dose until the end of treatment.

The flexible-dosing regimen is the optimal design to adequately detect efficacy and minimize the potential for issues related to safety and tolerability in the PD population. Flexible dosing based on clinical response has been used in the registrational studies used to support the approval of pharmacotherapies for PD as well as in clinical studies of PD tremor therapies (Pogarell, 2002). Likewise, optimizing dose based on clinical response using a titration schedule (starting participants at a low dose and titrating up slowly as needed) is consistent with clinical practice. Thus, the approach is representative of how a patient with PD would be treated with suvecaltamide in a real-world setting.

In the T-CALM study, daily doses of 16 and 20 mg suvecaltamide per day (administered as the [redacted] 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 well tolerated. [redacted]

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 (Section 1.3).

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

5. STUDY POPULATION

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

Inclusion and exclusion criteria must be evaluated during the Screening Period and rechecked before randomization and/or first dose of study intervention.

5.1. Inclusion Criteria

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

1. Male and female participants ages 40 to 85 years inclusive, at time of signing the ICF.
2. Body mass index from 17 to 45 kg/m^2 (inclusive) at Screening.
3. Diagnosis of clinically probable or clinically established PD meeting the MDS 2015 criteria (Postuma, 2015).
4. Participants must be individually optimized on PD medications for the treatment of other cardinal signs of PD (bradykinesia, rigidity) per the judgement of the investigator. Optimized treatment is defined as the maximum therapeutic effect obtained with PD medications when no further improvement is expected regardless of any additional adjustments to these medications or when the PD medications or adjustments to these medications are anticipated to result in intolerable side effects. This will be based on the investigator's clinical judgement.
5. Participants must be on a stable dosing regimen of their permitted PD and/or other tremor (eg, propranolol) medications for the treatment of motor symptoms for at least 6 weeks prior to Screening and do not anticipate the need to make any changes for the duration of the study. A lack of use of medications used to treat motor symptoms also must be stable for 6 weeks prior to Screening and remain stable for the duration of the study (eg, participants who tried PD medications and are no longer taking them must be off of these medications and stable for 6 weeks prior to Screening).
6. For participants who experience motor fluctuations, tremor must also be present during "ON" periods and participants should be able to have tremor symptoms evaluated during "ON" periods, as determined by the investigator, in relation to the participant's PD medications. If necessary, participants may take their PD medications in the clinic during visits where tremor symptoms are evaluated (timing of PD medications relative to tremor evaluations can be determined by the investigator).
7. Participants have moderate to severe impairment associated with tremor at both the Screening and Baseline Visits, as determined by all the following:
    a. A score of > 21 on the TETRAS-ADL subscale; and
    b. This criterion has been removed.
    c. CGI-S rating of tremor severity of > 2 (at least moderate for participants ability to function).

8. Contraception:

   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
   - Use contraception/barrier as follows:
     - 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 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 1 of the following conditions applies:

   - Is a 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% per year, preferably with low user dependency, as described in Appendix 5, during the study intervention period and for at least 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. 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.
   - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at Screening and at the Baseline Visit before the first dose of study intervention (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 described 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.

9. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

10. Willing and able to comply with the study design schedule and other requirements.

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, including, but not limited to: psychogenic tremor; myoclonus or ataxia; cerebellar disease; traumatic brain injury; alcohol abuse or withdrawal; mercury poisoning; hyperthyroidism; pheochromocytoma; multiple sclerosis; clinically significant polyneuropathy in the opinion of the investigator; or family history or diagnosis of Fragile X syndrome.

   Note: Participants with a history of essential tremor are eligible.
3. Hoehn & Yahr stage 5 (confinement to bed or wheelchair unless aided).
4. Participants who only experience tremor during their "OFF" periods.
5. Severity of motor fluctuations or medication-induced dyskinesia that would interfere with the assessment of tremor and/or "ON"/"OFF" periods that are unpredictable per the opinion of the investigator.
6. Clinically significant symptomatic orthostatic hypotension in the opinion of the investigator.
7. Has evidence at Screening of cognitive impairment as defined by a MoCA score < 22 or has cognitive impairment that in the opinion of the investigator would prevent completion of study procedures or the ability to provide informed consent.
8. Received any study intervention in a previous suvecaltamide (JZP385, formerly CX8998 and MK-8998) clinical study.
9. Presence of any unstable medical or surgical history that could affect the safety of the participant or interfere with study efficacy, safety[redacted]; or the ability of the participant to complete the study per the judgment of the investigator. Examples of this may include, but are not limited to, untreated or currently treated malignancy or chronic infection, including human immunodeficiency virus. Note: Participants with a remote history of cancer may be eligible if the cancer has resolved and is not expected to impact safety, efficacy[redacted].
10. History or presence of gastrointestinal disease (including prior bariatric bypass surgery), hepatic (including ALT or AST ≥ 2 × 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 the absorption, distribution, metabolism,

or excretion of suvecaltamide. 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.

11. This criterion has been combined with the criterion above.
12. Presence of significant cardiovascular disease at Screening including but not limited to the following:
    a. Myocardial infarction within the past year;
    b. Revascularization procedure(s) within the past year;
    c. Unstable angina pectoris;
    d. Symptomatic congestive heart failure (American College of Cardiology/American Heart Association Stage C or D);
    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 or Baseline);
    g. Markedly abnormal ECG per the Investigator assessment, or QTcF > 450 msec for men and > 470 msec for women, based on the average of triplicate assessments at Screening or Baseline.
13. History or presence of bipolar and related mood disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
14. 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; the participant's antidepressant treatment must be stable for at least 6 months prior to Screening and expected to remain stable for the duration of the study.
15. History (within past 2 years at Screening) or presence of substance use disorder (including alcohol) according to DSM-5 criteria, known drug dependence, or seeking treatment for alcohol or substance abuse related disorder. Nicotine use disorder would not be exclusionary if it does not impact tremor per the judgement of the investigator.

Prior/Concomitant Therapy

16. Treatment-naïve patients (ie, those who have never tried PD medication) are excluded from participating in the study.
17. Use of PRN medication/substance(s) that might produce 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, alcohol, or caffeine. Participants who consume caffeine or use tobacco should take their regular amount of caffeine or tobacco on the clinic days.
    Note: Use of PRN sleep medications is permitted (including the night before a study visit day) if it does not impact tremor per the judgement of the investigator. Regular use of sleep medications or anxiolytics (eg, benzodiazepines) to improve sleep or anxiety is also permitted provided it will continue to be used at stable dosages throughout the study.
18. Prior or planned surgical intervention to treat PD, including but not limited to magnetic resonance-guided focused ultrasound thalamotomy, deep brain stimulation, ablative thalamotomy, and gamma knife thalamotomy. A history of implantation of an infusion pump for delivery of PD medications, or percutaneous endoscopic gastrojejunostomy for delivery of PD medications including levodopa-carbidopa intestinal gel would not be exclusionary if these medication delivery systems are no longer being utilized.
19. Use of PRN medications to treat tremor or continuous infusion of PD medications.

    Note: Use of dopaminergic rescue medications (eg, PRN use of carbidopa/levodopa, including levodopa inhalation powder) for non-tremor PD symptoms (eg, rigidity or bradykinesia) is permitted.
20. Inability to refrain from using a mechanical device for the management of tremor (eg, weighted bracelet) during the study.
21. Botulinum toxin injection for the treatment of tremor in the 6 months before Screening or planned use at any time during the study. Note: Use of botulinum toxin for other reasons (eg, cosmetic, excessive salivation, dystonia) is permitted as long as the location of use is anatomically distinct from the region with tremor.
22. Currently taking dopamine antagonists or depleting medications including antipsychotics such as clozapine, olanzapine, risperidone, or inhibitors of vesicular monoamine transporter 2 such as tetrabenazine, deutetrabenazine, and valbenazine, and other adrenergic reuptake inhibitors such as reserpine.
23. Use of prescription or nonprescription drugs or other products (eg, St. John's Wort) known to be inducers of CYP3A4 (cause > 30% reduction of sensitive substrates AUC), which cannot be discontinued at least 4 weeks before Baseline, or planned use at any time during the study.
24. Use of prescription or nonprescription drugs or other products (eg, grapefruit) known to be strong or moderate inhibitors of CYP3A4, which cannot be discontinued 2 weeks or 5 half-lives, whichever is longer, before Baseline, or planned use at any time during the study.

25. Use of proton pump inhibitors, which cannot be discontinued at least 2 weeks before Baseline, or planned use at any time during the study. (Occasional use of antacids or H_2 receptor antagonists will be permitted, but antacids should be taken at least 4 hours apart from study intervention; and H_2 receptor antagonists should be taken at least 4 hours after and/or 12 hours before study intervention).

Prior/Concurrent Clinical Study Experience

26. Received an investigational drug in the past 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.

Diagnostic Assessments

27. Laboratory value(s) at Screening outside the laboratory reference range that is/are considered markedly abnormal by the investigator (clinical chemistry, hematology, and urinalysis).

    Note: Screening laboratory tests may be repeated once.

28. Known use of recreational drugs, inclusive of the following: phencyclidine, cocaine, opioids, barbiturates, amphetamines, or 3,4-methylenedioxymethamphetamine [ecstasy]. 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.

    Note: Opioid use at stable doses, either regularly or PRN, for pain management, as prescribed, is permitted. Use of cannabinoids (including cannabidiol) is permitted if there is no impact to tremor symptoms per the judgement of the investigator.

Other Exclusions

29. Daily or near-daily use of more than 2 units of alcohol per day. 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).
30. Regular consumption of > 600 mg caffeine per day or > 6 cups of coffee per day.
31. Allergy or sensitivity to any ingredients in the study intervention formulation or placebo.
32. 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

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of Seville oranges, grapefruit, or grapefruit juice from 2 weeks before the start of study intervention until after the final dose.
- Participants will be instructed to take a single oral daily dose of study intervention [redacted]. At clinic visits, a light breakfast, lunch, or snack will be provided as needed. See Section 8.1.6 for a description of timing of study intervention dosing.
- Participants will be asked to fast for their Screening Visit only.
- Note that per exclusion criterion 25, occasional use of antacids or H_2 receptor antagonists will be permitted, but antacids should be taken at least 4 hours apart from study intervention and H_2 receptor antagonists should be taken at least 4 hours after and/or 12 hours before study intervention.

5.3.2. Caffeine, Alcohol, and Tobacco

As noted in exclusion criteria 29 and 30, respectively, daily or near-daily use of more than 2 units of alcohol per day or regular consumption of > 600 mg of caffeine (or > 6 cups of coffee) per day is not permitted during the study. Participants must abstain from alcohol at least 12 hours prior to each clinic visit.

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if the rescreening is approved by the Sponsor Medical Monitor. 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 during the Maintenance Period. See Section 7.1.3 for details regarding temporary interruption of study intervention.

6. STUDY INTERVENTIONS 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 Interventions Administered

The study interventions planned for use in this study are described in Table 7.

Table 7: Study Interventions

Treatment Arm	Intervention/ Treatment Name[a]	Formulation	Unit Dose Strength(s)[b]	Dosage Level(s)	Route of Admin.	Use	Sourcing	Package	Labeling	Storage Conditions
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment Arm	Intervention/ Treatment Name[a]	Formulation	Unit Dose Strength(s)[b]	Dosage Level(s)	Route of Admin.	Use	Sourcing	Package	Labeling	Storage Conditions
			[redacted]							
			[redacted]	[redacted]						

Abbreviations: admin = administration; [redacted] QD = once daily.

[redacted]

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

6.2. Preparation/Handling/Storage/Accountability

1. Further guidance and information for the final disposition of unused study intervention are provided in the Trial Site Binder.
2. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
3. Only participants enrolled in the study may dose with study intervention.
4. At clinic visits, only authorized site staff may dispense or administer study intervention.
5. 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.
6. 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). Refer to the Pharmacy Manual for details.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants who sign the ICF will receive a participant number by 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 ratio to receive once-daily doses of suvecaltamide or placebo. Randomization will be stratified by the TETRAS composite outcome score (≤ 17 or > 17) as assessed at Baseline. A double-blind approach will be used throughout the 17-week treatment period (ie, during the Dose Titration and Optimization Period as well as the Maintenance Period). During the Dose Titration and Optimization Period the number of capsules of suvecaltamide or placebo taken each day will be titrated based on efficacy response and tolerability. Participants will enter the Maintenance Period on 1, 2, or 3 capsules of either suvecaltamide (10 mg per capsule) or placebo. Suvecaltamide and placebo capsules will appear 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 participants' 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

For clinic visits where participants are dosed at the site (ie, during Weeks 1, 9, 13, and 17), participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose of study intervention administered in the clinic will be recorded in the source documents. In addition, the time of last meal and last dose of study intervention taken prior to the clinic dose will be recorded in the source documents. The dose of study intervention and study participant identification should be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

For clinic visits where participants dose at home (ie, during Weeks 2, and 5), participants will self-administer study intervention at home and compliance with study intervention will be assessed at each clinic visit. The date and time of the dose of study intervention on the day of the clinic visit will be recorded in the source documents. Compliance will be assessed by direct questioning and counting returned capsules during the clinic visits and documented in the source documents. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of suvecaltamide (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, including dates for intervention delays (see Section 7.1.3) should also be recorded as applicable.

6.5. Dose Modification

Titration and optimization of study intervention dose during the Dose Titration and Optimization Period will occur as outlined in Section 4.1. During the Maintenance Period, participants will take suvecaltamide or placebo at the optimal dose determined by the investigator at the end of the Dose Titration and Optimization Period (10, 20, or 30 mg once daily). No dose adjustment should occur during the Maintenance Period. If the investigator determines a dose adjustment is indicated for safety reasons, the Medical Monitor should be consulted regarding continuation of study intervention.

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 PD medications following study participation.

6.7. Treatment of Overdose, Medication Errors, or Misuse

For this study, any dose of suvecaltamide (or placebo) greater than the assigned dose that a given participant takes within a 24-hour period will be considered an overdose. In 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 suvecaltamide. Attendant signs and symptoms should be managed expectantly. See the IB for 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.
- Closely monitor the participant for any AE/SAE and/or laboratory abnormality.
- 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; and
- Dosage information including dose and frequency.

Concomitant treatment with certain medications/therapies is not permitted during the study (see Section 5.2).

Participants will continue their permitted PD medication(s) at the same stable dose(s) and regimen(s) as in the 6 weeks immediately prior to the study and will remain on the same dose(s) and regimen(s) of these medication(s) until the end of the study. On clinic visit days, site staff will record the time of the last dose(s) of PD medication(s) prior to the efficacy assessments. For all participants, efficacy assessments should occur during “ON” periods, as determined by the investigator, in relation to the participant’s PD medication(s).

[redacted]

Refer to the permitted, prohibited, and cautionary list of medications in the Trial Site Binder.

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

7.1. Discontinuation of Study Intervention

In some instances, it may be necessary for a participant to permanently discontinue study intervention.

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

- The participant or their legally authorized 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 C-SSRS (see Section 8.3.6).
- The participant has a positive serum pregnancy test (Appendix 5 and Section 8.4.5).
- The participant is noncompliant with study intervention or procedures.
- The sponsor decides to terminate the study prior to completion.
- The investigator determines the participant should not continue study intervention.

7.1.1. Participants Remaining in the Study After Study Intervention Discontinuation

Discontinuation from study intervention does not represent discontinuation from the study. For participants who discontinue study intervention early, every effort should be made to attend Efficacy Follow-up Visits through 17 weeks after the first dose of study intervention. After completing the E/D visit, if the participant is willing to attend Efficacy Follow-up Visits after the study intervention is discontinued, the guidelines for scheduling efficacy visits are as follows:

- For participants who discontinue study intervention prior to the Week 9 Visit, it is encouraged to schedule 3 additional Efficacy Follow-up Visits at 9, 13, and 17 weeks after first dose.
- For participants who discontinue study intervention after the Week 9 Visit but prior to the Week 13 visit, it is encouraged to schedule 2 additional Efficacy Follow-up Visits at 13 and 17 weeks after first dose.
- For participants who discontinue study intervention after the Week 13 Visit but prior to the Week 17 Visit, it is encouraged to schedule an additional Efficacy Follow-up Visit at 17 weeks after first dose.
- Participants should be scheduled for the Safety Follow-up Visit 2 weeks after the last dose of study intervention. However, 1 of the Efficacy Follow-up Visits can be combined with the participant's Safety Follow-up Visit if the Efficacy Follow-up Visit is scheduled to occur within 2 weeks after the participant's last dose of study intervention.

7.1.2. Positive Alcohol or Urine Drug Screens

Participants must abstain from alcohol at least 12 hours prior to each clinic visit. 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 Sponsor Medical Monitor is required to retain the participant in the study. If the investigator suspects a false positive urine drug screen, he/she is encouraged to send a portion of the same urine sample to the central laboratory for confirmatory testing (eg, GCMS).

7.1.3. Temporary Discontinuation/Study Intervention Interruption

If a participant must temporarily interrupt study intervention for any reason, the Medical Monitor should be consulted to determine whether the participant will resume study intervention.

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.
- At the time of discontinuing from the study, an E/D Visit should be conducted. In addition, a Safety Follow-up Visit should be conducted as shown in the SoA (Section 1.3). See the SoA for data to be collected at the time of study discontinuation and at the Safety Follow-up Visit 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.
- The site must 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). After trying to contact the participant, the investigator should reach out to the contact provided by the participant. 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 and lost to follow-up.

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 coronavirus 2019 pandemic, and with approval from the Sponsor Medical Monitor, as noted in the SoA.
- Immediate safety concerns should be discussed with the sponsor 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, the investigator should provide eligible participants with instructions on how to discontinue any excluded medication(s). Document that the investigator has determined that discontinuation is safe and medically appropriate, and the discontinuation is medically supervised. The Sponsor Medical Monitor should be contacted if there are any questions regarding discontinuation of excluded medication(s).
- [redacted]
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 125 mL (see Laboratory Manual). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with samples.
- For clinical outcome assessment measures that are rated by specially qualified and trained interviewers/raters, 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 who have undergone the required training in administration and scoring of the TETRAS-PS. The blinded rater who rates the TETRAS-PS for a participant may not rate/administer other scales for that participant nor be involved in other procedures for that participant. Blinded raters must not share any information they collect about participants with other site staff, except when required to ensure participant safety. 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 in the Trial Site Binder.

8.1. General Administrative Procedures

8.1.1. Informed Consent

The investigator or qualified designee (consistent with local requirements) must obtain documented consent from each potential participant/legal representative prior to participation in this study. 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 by IRT at Screening 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) during the Screening Period and updated at the Baseline Visit. All active conditions should be recorded as well as any condition diagnosed within the participant's lifetime that the investigator deems clinically significant.

Medical history information will include, but is not limited to, symptoms of PD (current and past, including symptoms experienced prior to any PD treatment); history and treatment (if any) of cardiovascular, pulmonary, gastrointestinal, hepatic, renal, immunologic, neurologic, or psychiatric disease; reproductive status; current contraceptive method; confirmation of relevant inclusion and exclusion criteria; and any events that occur during the Screening Period and prior to the participant's first dose of study intervention (see Appendix 4).

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. Medication that is required to be washed out prior to the study should also be recorded. All medication(s) currently taken by the participant, as well as all concomitant medication(s) taken during the study, should be recorded (see Section 6.8).

Additional information related to any medications taken for the treatment of PD and/or other treatments specific for tremor (eg, propranolol, primidone) since diagnosis should also 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 Participant Eligibility Form will be completed for all participants considered by the investigator to meet the eligibility requirements at Screening. The site will submit the form to the Medical Monitor for review. The Medical Monitor will provide approval of eligibility to proceed

to the Baseline Visit. Some inclusion and exclusion criteria must be re-assessed at the Baseline Visit by the investigator or designated study site staff to confirm eligibility prior to randomization (see Section 5).

8.1.6. Timing of Study Intervention Dosing

Participants will be instructed to take a single oral daily dose of study intervention [redacted]. Participants should also take their daily dose of PD medication(s) at the clinic, if necessary, to ensure assessments of efficacy can occur during "ON" periods (as determined by the investigator).

At clinic visits, a light breakfast, lunch, or snack will be provided as needed. Participants will be asked to fast for their Screening Visit only.

8.1.7. Montreal Cognitive Assessment

The 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 26 or above is considered normal.

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

8.2. Efficacy Assessments

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

On clinic visit days, site staff will record the time of the participant's dose of study intervention as well as the time of the last dose(s) of PD medication(s) prior to the efficacy assessments. For all participants, assessment of efficacy should occur during "ON" periods, as determined by the investigator, in relation to the participant's PD medication(s).

Note that the primary endpoint is the TETRAS composite outcome score. First published in 2008 and designed as a 10-minute clinical assessment of tremor (Elble, 2008; Elble, 2012), the TETRAS consists of a 12-item ADL subscale and a 9-item PS. The TETRAS composite score utilized in the present study is comprised of the sum of modified items 1 to 11 of the TETRAS-ADL subscale (see Section 8.2.1) and modified items 6 (6a and 6b) and 7 of the TETRAS-PS (see Section 8.2.2). While the TETRAS has not been validated in a PD population, many of the ADL and functional tasks assessed by the composite outcome score have been shown to be impacted by tremor in PD (Elble, 2016; Louis and Machado, 2015).

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

The TETRAS-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 (normal activity) to 4 (severe abnormality) scale. 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 in the ET population (Elble, 2012; Elble, 2016). It has also demonstrated sensitivity to change with suvecaltamide treatment in the T-CALM study in participants with ET. 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 Trial Site Binder.

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. Blinded 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. The TETRAS-PS has demonstrated both test-retest reliability and sensitivity to change in the ET population (Elble, 2012; suvecaltamide IB T-CALM study) and was given a "recommended" rating as a tremor severity scale by the MDS for ET (Elble, 2013).

TETRAS-PS items 6 (6a and 6b) 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 (ie, item 6a) and the left (ie, item 6b) hands, while the handwriting is assessed with the dominant hand only. The sum of the TETRAS-PS items 6 (6a and 6b) 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 in the ET population (Calzetti, 1982; Haubenberger, 2011; Hopfner, 2015; Koller, 1986; Shill, 2004; Tolosa and Loewenson, 1975).

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

8.2.3. Clinical Global Impression of Severity

The CGI-S will be assessed by qualified personnel to assess the severity of the impact of tremor in PD on the participants' ability to function. The CGI-S is a 5-point Likert-type rating scale and is widely used in clinical psychopharmacology trials to assess severity of illness. The responses to this investigator-completed scale range from 1 (no limitations) to 5 (severe). The investigator will rate his/her impression of the severity of the impact of tremor in PD on the participant's current ability to function relative to his/her experience with this patient population.

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

8.2.4. Clinical Global Impression of Change

The CGI-C is a 5-point Likert-type rating scale widely used to assess efficacy in clinical drug trials. Investigators as trained raters 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). Investigators' rating will focus on the participants' change in their ability to function due to tremor in PD.

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

8.2.5. Patient Global Impression of Severity

The PGI-S is a 5-point Likert-type rating scale, with response options ranging from 1 (no limitations) to 5 (severe). The participant will rate his/her impression of the severity of the impact of their tremor in PD on their current ability to function.

A sample PGI-S can be found in the 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 tremor in PD.

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

8.2.7. Movement Disorder Society Unified Parkinson's Disease Rating Scale

The MDS-UPDRS is the most widely used clinical rating scale for tracking PD progression (Goetz, 2008; Ramaker, 2002). The scale takes approximately 30 minutes to complete and consists of 4 parts:

- Part I: non-motor aspects of experiences of daily living;
- Part II: motor aspects of experiences of daily living;
- Part III: motor examination; and
- Part IV: motor complications (dyskinesias and motor fluctuations including "OFF" state dystonia).

Note that the Part I, II, III, and IV scores, total score, and the tremor score (items 2.10, 3.15, 3.16, 3.17, and 3.18) will be calculated (see other secondary endpoints, Section 3).

A sample MDS-UPDRS can be found in the Trial Site Binder.

[redacted]

[redacted]

8.3. Safety Assessments

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

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.

- Investigators should pay special attention to clinical signs related to previous clinically significant or serious illnesses.
  - Any abnormalities identified at the Screening Visit physical exam should be recorded as medical history.

8.3.2. Vital Signs

- Vital signs (to be taken prior to blood collection, when possible) including oral temperature, pulse rate, respiratory rate, and orthostatic blood pressure (systolic and diastolic) will be assessed at each clinic visit as indicated in the SoA.
- 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 the supine position for at least 5 minutes, and again in the standing position after the participant has been standing for 2 minutes. At Screening and Baseline, orthostatic assessments will be taken in triplicate (at intervals of 15 to 30 minutes). All 3 measurements should be recorded. The average of the 3 measurements will be automatically calculated. At all other visits, orthostatic blood pressure and pulse assessments will consist of a single post-dose measurement.
- 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

- [redacted] will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (ie, QTc), QTcF intervals.
- [redacted]
- Each ECG will be reviewed, initially interpreted, signed, and dated by the investigator or a designated physician after collection. All ECGs (except for 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.
- Additional ECGs may be obtained at any time per the investigator's judgement.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
  - Screening laboratory assessments should be conducted under fasting conditions. Record if the participant was fasting or non-fasting.

  - Screening laboratory assessments (including urinalysis) should be repeated at the Baseline Visit if the visit occurs outside of the Screening Period.

- The investigator must review the laboratory report, document this review, and record any markedly abnormal changes occurring during the study as an AE. Laboratory reports must be filed with the source documents. Note: any markedly abnormal laboratory findings or other abnormal safety assessments that are associated with a specific diagnosis would not be reported as an AE. (The specific diagnosis would be reported as an AE if the event occurred after the participant received his/her first dose of study intervention; see Appendix 4.)
- Laboratory findings associated with the underlying disease are not considered markedly abnormal unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with markedly abnormal values during participation in the study and considered by the investigator to be related to study intervention should be repeated until the values return to normal or baseline or are no longer considered markedly abnormal by the investigator or Medical Monitor.
  - If markedly abnormal values do not return to normal/baseline within a period 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.

8.3.5. Pregnancy Testing

Pregnancy testing is applicable only for WOCBP.

- Refer to Section 5.1 for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted as outlined in the SoA.
  - In the event of a positive urine pregnancy test, confirmatory serum pregnancy test must be conducted.
- Additional serum or urine pregnancy tests may be performed, as determined by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study, and in addition to laboratory testing, the investigator must take appropriate steps to confirm, evaluate, and manage the potential pregnancy, including referral, when indicated.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Suvecaltamide is considered a CNS-active study intervention. Participants being treated with suvecaltamide 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 intervention, or at the time of dose changes (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 during the study using the C SSRS administered by a qualified and appropriately trained rater. At the Screening Visit, the Screening/Baseline Version of the C SSRS will be administered to participants to exclude any individual 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 Visit. 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 postbaseline visits, 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) 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.

8.3.7. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale

The QUIP-RS is a rating scale designed to measure the severity of, and support a diagnosis of, impulse control and related disorders in PD. It can also be used to monitor changes in symptom severity over time (Weintraub, 2012).

The QUIP-RS is a brief, self-rated questionnaire. It consists of 4 primary questions (pertaining to commonly reported thoughts, urges/desires, and behaviors associated with ICDs), each applied to the 4 ICDs (gambling, sex, buying, and eating) and 3 related disorders (hobbyism, punding, and medication use). It uses a 5-point Likert scale (scored 0 [never] to 4 [very often] for each question) to gauge the frequency of behaviors.

A copy of the QUIP-RS is found in the Trial Site Binder.

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 (see Section 8.4.3).

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 Adverse Event and Serious Adverse Event Information

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

Note: All SAEs that occur after the ICF 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 if they are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

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 will be recorded and reported to the sponsor or designee 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.

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 should promptly notify the sponsor.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

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. However, after an occurrence is identified, more specific questions should be asked to obtain adequate information to ensure participant safety by providing proper diagnosis and treatment, and specific, accurate reporting of the event.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

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 Serious Adverse Events

- 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, IRB/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 will 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 suvecaltamide 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 to be an AE or SAE, any pregnancy complication 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. 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 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, 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

The AEOSIs defined for this study are [redacted]. Additional information regarding 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 OREs are 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.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

[redacted]

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.9. Health Economics

Health economics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

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

H0: $m_{suvecaltamide} = m_{control}$

H1: $m_{suvecaltamide} \neq m_{control}$

Specifically, the null hypothesis states that there is no difference in the mean change on the TETRAS composite outcome score (primary estimand) from Baseline to Week 17 between the suvecaltamide and control (placebo) groups. The alternative hypothesis is that the mean change on the TETRAS composite outcome score from Baseline to Week 17 is not equal between the suvecaltamide and control (placebo) groups.

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

H0: $p_{suvecaltamide} = p_{control}$

H1: $p_{suvecaltamide} \neq p_{control}$

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 17 between the suvecaltamide and control (placebo) groups. The alternative hypothesis is that the proportion of participants who improved by ≥ 1 point on the CGI-S from Baseline to Week 17 is not equal between the suvecaltamide and control (placebo) groups.

There are no hypotheses to be tested for the remaining secondary or exploratory endpoints. All safety analyses will be descriptive; no formal statistical testing will be performed.

[redacted]

[redacted]

9.3. Analysis Sets

For the purposes of analysis, the analysis sets are defined as shown in Table 8.

Table 8: Analysis Sets

Participant Analysis Set	Description
Enrolled Analysis Set	All participants who sign the ICF.
Full Analysis Set	All participants who are randomized. Participants will be analyzed according to randomized treatment.
Safety Analysis Set	All participants who are randomized and 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 ITT Analysis Set	All participants who are randomized, receive at least 1 dose of study intervention, and have baseline and at least 1 non missing evaluable postbaseline TETRAS composite outcome score. Participants will be analyzed according to randomized treatment.
[redacted]	[redacted]

Abbreviations: ICF = Informed Consent Form; ITT = intention to treat; [redacted] TETRAS = The Essential Tremor Assessment Rating Scale.

9.4. Statistical Analyses

The SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

In general, results will be summarized by treatment group. Categorical variables will be reported as frequency and proportion. 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 will be completed using Version 9.4 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

9.4.1.1. Multiplicity Adjustments

A fixed sequence hierarchical testing strategy will be implemented to preserve the family-wise type 1 error rate at the significance level of 0.05. Testing will begin with the comparison of suvecaltamide versus placebo for the primary efficacy variable followed by sequential testing of

the key secondary efficacy variable. 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 TETRAS composite outcome score from Baseline to Week 17, suvecaltamide versus placebo.
2. Proportion of participants who improved by ≥ 1 point on the CGI-S from Baseline to Week 17, suvecaltamide versus placebo.

For the secondary and exploratory endpoints, there will be no control for multiple comparisons.

9.4.1.2. Statistical Methods

Refer to the SAP for a detailed description of statistical methods.

9.4.1.3. Intercurrent Event Strategies

For the primary and key secondary estimands, the following ICEs should be considered:

- Treatment discontinuation due to lack of efficacy or AE; and any other reason including study intervention noncompliance, and other significant protocol deviations.
- Additional/alternative therapies including PRN use of medications to treat tremor, changing background PD treatments, and switching PD treatments.

The ICEs will be handled using 2 approaches:

- As the main approach, treatment policy will be used to address the ICEs. Treatment policy is defined as the effect of the randomized treatment over the study period regardless of whether randomized treatment is continued. Per the treatment policy, data collected (during Efficacy Follow-up Visits) after participants experience a treatment discontinuation ICE will be included for analysis.
- As a supplemental approach, additional analyses of the primary and key secondary estimands will use the hypothetical strategy to address the ICEs. This strategy is defined as the pharmacologic effect of suvecaltamide compared to placebo assuming the intercurrent event did not happen with continuation of randomized treatments for the duration of the study. Analyses will be conducted using data collected at time points that are obtained at or prior to participants discontinuing from randomized treatment and combined with modeled values for post-discontinuation timepoints where the underlying assumptions are considered as appropriate.

In summary, ICEs will be addressed using the treatment policy estimand for the main analysis of the primary and key secondary endpoints and using the hypothetical strategy estimand for supplemental analyses.

9.4.1.4. Pooling of Investigational Centers

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

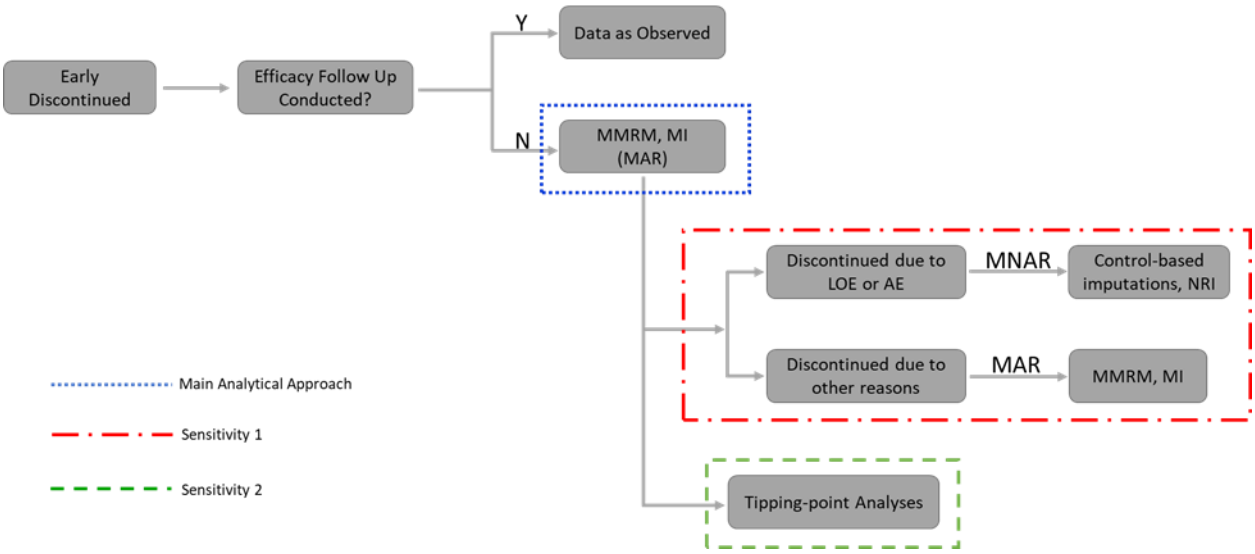
9.4.1.5. Dropouts and Missing Data

Every effort will be made to limit premature discontinuation of the study and ascertain completeness of the data collection. Efficacy Follow-up Visits at Weeks 9, 13, and 17 will be conducted as needed for participants who discontinue study intervention but remain in the study to complete scheduled efficacy assessments (see Section 1.3).

However, missing data caused by reasons defined outside the scope of intercurrent events can still occur (eg, intermittent missing data due to noncompliance). In that case, the MAR assumption will be considered appropriate and missing data will be handled accordingly by MMRM or MI.

Figure 1 provides a flowchart depicting how missing data due to early discontinuation will be addressed for the main analyses of the primary and key secondary efficacy estimands.

Figure 1: Handling of Missing Data Due to Early Discontinuation for the Primary and Key Secondary Efficacy Endpoints



Abbreviations: AE = adverse event; LOE = lack of efficacy; MAR = missing at random; MI = multiple imputation; MMRM = mixed-effect model with repeated measures; MNAR = missing not at random; NRI = non-responder imputation.

Under the main analytical approach, missing data will be assumed to be MAR for participants who do not complete the Efficacy Follow-up Visit(s). The MMRM (for the TETRAS composite outcome score) and MI (for CGI-S response) assume participants with missing data would have efficacy outcomes similar to those participants in their respective study intervention group, randomization stratum, and initial trajectory who completed the study. The MMRM produces an estimate of the treatment effect via restricted maximum likelihood estimation, and a 2-step MI method produces a group of statistical estimates and will be pooled using Rubin's rule.

Under the sensitivity analyses, control-based imputations (for TETRAS composite outcome score) and NRI (for CGI-S response) will be used to treat missing data among participants discontinued due to an AE or lack of efficacy. Tipping-point analyses will be further conducted to assess the robustness of the underlying MAR assumption used in MMRM and MI.

9.4.2. Primary Estimand

The attributes of the primary estimand are listed in Section 3.

For the main estimator analysis, a MMRM will be used to include the change in the TETRAS composite outcome score from Baseline to Weeks 5, 9, 13, and 17. The model will include treatment group, visit, treatment-by-visit interaction, baseline-by-visit interaction, and randomization stratum as fixed effects; baseline TETRAS composite outcome scores as a covariate; and week repeated within each participant as repeated effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment of degrees of freedom along with REML will be used to make proper statistical inference. Within-group LS means and the associated 2-sided 95% CIs, treatment difference in LS means and associated 2-sided 95% CIs and p-values will be reported.

Per the treatment policy, the main analyses will include data collected during the Efficacy Follow-up Visits for participants who experience ICEs. However, for participants who experience ICEs and do not attend Efficacy Follow-up Visit(s), missing data will be handled per Section 9.4.1.5.

For sensitivity analysis, control-based imputation methods (Roger, 2012) will be used to handle missing observations in addition to treatment policy. Details will be further defined in SAP.

For supplementary analysis, a hypothetical strategy will be used to include data points up to the timepoint when a participant experiences an ICE into the MMRM specified above. This will serve as complementary analysis and will ignore observations collected after an ICE.

9.4.3. Secondary Estimand and Endpoints

9.4.3.1. Key Secondary Estimand

The attributes of the secondary estimand are listed in Section 3.

The main estimator will be analyzed using the CMH test adjusting for the stratification factor at randomization (Baseline TETRAS composite score ≤ 17 or > 17). 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.

Per the treatment policy, the main analyses will include data collected during the Efficacy Follow-up Visits for participants who experience ICEs. However, for participants who experience ICEs and do not attend Efficacy Follow-up Visit(s), missing data for CGI-S will be imputed using a 2-step MI method based on similar participants who remained in the study. Further details will be provided in the SAP.

Sensitivity analyses will be conducted to account for missing data using the NRI method and the tipping point analysis, with further details provided in the SAP.

For supplementary analysis, a hypothetical strategy will be used to include data points up to the timepoint when a participant experiences an ICE into the CMH test specified above. This will serve as a complementary analysis and will ignore observations collected after an ICE; the missing observations will be further imputed using 2-step MI.

9.4.3.2. Secondary Endpoints

Refer to Section 3 for a complete list of other secondary endpoints.

Unless otherwise specified, continuous efficacy endpoints will be analyzed using a MMRM as the primary method. The model will include treatment group, visit, treatment-by-visit interaction, and randomization stratum as fixed effects, and Baseline as a covariate, and participant as a random effect. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment of degrees of freedom along with REML will be used to make proper statistical inference. Within-group LS means and the associated 2-sided 95% CIs, treatment difference in LS means and associated 2sided 95% CIs, and nominal p-values will be reported.

Binary efficacy endpoints will be analyzed using the CMH test adjusting for the stratification factor at randomization (Baseline TETRAS composite score ≤ 17 or > 17). 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, along with the associated 2-sided 95% CIs using a normal approximation to the weighted average will be provided.

Per the treatment policy, the main analyses will include data collected during the Efficacy Follow-up Visit(s) for participants who experience ICEs. However, for participants who experience ICEs and do not attend Efficacy Follow-up Visit(s), missing data will be handled per Section 9.4.1.5. No additional sensitivity or supplementary analyses are planned for these secondary endpoints.

For safety endpoints, please refer to Section 9.4.5.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]ho

[redacted]

9.4.5. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety analyses will be descriptive; no formal statistical testing will be performed. These analyses will be performed as outlined below, with further details provided in the SAP.

Adverse events:

All AEs will be mapped to SOC and PT using the MedDRA classification system. 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. Note summaries will be provided by treatment group, study period, and time of onset.

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

If a participant has multiple events with the same PT occurring in different study periods, the event will be reported for each of those periods. Multiple increases in severity will be counted as 1 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 proportion 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. Markedly abnormal laboratory findings will be summarized separately.

C-SSRS and QUIP-RS:

The CSSRS parameters and QUIP-RS scores will be summarized descriptively by scheduled visit.

9.4.6. Other Analyses

Subgroup analyses and additional analyses of secondary and exploratory endpoints will be further described in the SAP.

9.5. Interim Analysis

No 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 International Ethical Guidelines;
  - Applicable ICH Good Clinical Practice (GCP) Guidelines; and
  - 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 and national regulatory authority (as applicable) 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; and
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU regulation 536/2014 for clinical studies, 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 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 (as applicable) of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, General Data Protection Regulation, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before any study activities were performed unless otherwise allowed by protocol criteria, and must also include 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 that 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. Committee Structure

Establishing a Data Monitoring Committee is not planned for this trial. 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.

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 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 he/she 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 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 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/site as applicable, for the period 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. 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.
- 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

10.1.9.1. First Act of Recruitment

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

10.1.9.2. 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; and/or
- 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 assure appropriate participant therapy and/or follow-up.

APPENDIX 1. ABBREVIATIONS AND DEFINITIONS

Abbreviation or Term	Definition/Explanation
ADL	Activities of daily living
Admin.	Administration
AE	Adverse event
AEOSI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
[redacted]	[redacted]
BID	Twice a day
BL	Baseline
BUN	Blood urea nitrogen
Ca_V3	T-type calcium channel
CFR	Code of Federal Regulations
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression of Severity
CI	Confidence interval
C_{max}	Concentration at peak
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CO_2	Carbon dioxide
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
C_{tau}	Concentration at trough
CYP	Cytochrome
d/c	Discontinuation
DNA	Deoxyribonucleic acid
[redacted]	[redacted]
[redacted]	[redacted]
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

Abbreviation or Term	Definition/Explanation
ECG	Electrocardiogram
E/D	Early Discontinuation
eGFR	Estimated glomerular filtration rate
ER	Extended release
ET	Essential tremor
[redacted]	[redacted]
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FU	Follow-up
GCMS	Gas chromatography-mass spectrometry
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
H_2	Histamine receptor type 2
hCG	Human chorionic gonadotropin
HDL	High density lipoprotein
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
I/E	Inclusion/exclusion
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International normalized ratio
[redacted]	[redacted]
IRB	Independent Review Board
IRT	Interactive response technology
ITT	Intention to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system

Abbreviation or Term	Definition/Explanation
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LOE	Lack of efficacy
LS	Least squares
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCMC	Markov chain Monte Carlo
MCV	Mean corpuscular volume
MDMA	3,4,-methylenedioxymethamphetamine
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MedDRA	The Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple imputation
MMRM	Mixed-effect model with repeated measures
MNAR	Missing not at random
MoCA	Montreal Cognitive Assessment
NA	Not applicable
NRI	Non-responder imputation
ORE	Other reportable experience
PCP	Phenylcyclidine
PD	Parkinson's disease
[redacted]	[redacted]
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
[redacted]	[redacted]
[redacted]	[redacted]
PRN	As needed
PT	Preferred term
QD	Once daily
[redacted]	[redacted]

Abbreviation or Term	Definition/Explanation
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale
RBC	Red blood cell
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
[redacted]	[redacted]
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of activities
SOC	System organ class
STN	Subthalamic nucleus
$t_{½}$	Terminal half-life
TETRAS	The Essential Tremor Assessment Rating Scale
TETRAS-ADL	The Essential Tremor Assessment Rating Scale, Activities of Daily Living
TETRAS-PS	The Essential Tremor Assessment Rating Scale, Performance Subscale
T_{max}	Time to maximum concentration.
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Woman of nonchildbearing potential

APPENDIX 2. REFERENCES

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APPENDIX 3. CLINICAL LABORATORY TESTS

- The tests detailed in Table 9 will be performed by the central laboratory, except for urine pregnancy and breath alcohol tests, which will be performed locally. Breathalyzers and urine pregnancy tests will be provided by the central laboratory.
- Laboratory assessments at Screening should be conducted under fasting conditions. Record if the participant was fasting or non-fasting. Repeat laboratory assessments at the Baseline Visit if the visit occurs outside of the screening window.
- 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.
- All events of ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 × 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.

Table 9: Protocol-Required Safety Laboratory Tests

Laboratory Test(s)	**Parameters**			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH % Reticulocytes		WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	Albumin	ALP	ALT/SGPT	AST/SGOT
	BUN	Calcium	CO_2	Chloride
	Creatinine	eGFR[a]	GGT	Glucose
	Lactate dehydrogenase	Phosphorus	Potassium	Prolactin
	Sodium	Total and direct bilirubin	Total cholesterol	Total protein
	Triglycerides	Uric acid	HDL	LDL (calculated)
	Prothrombin time INR			
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 WOCBP)[b] Serum pregnancy testing is mandatory at Screening; urine is collected thereafter			

Laboratory Test(s)	Parameters
Other Screening tests	Urine drug screen (to include at minimum: amphetamines, methadone, MDMA, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and PCP) Breath alcohol test FSH to evaluate postmenopausal status (female participants only; see Appendix 5)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; HDL = high density lipoprotein; IEC = Independent Ethics Committee; IRB = Independent Review Board; INR = international normalized ratio; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MDMA = 3,4,-methylenedioxymethamphetamine; PCP = phenylcyclidine; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal; WBC = white blood cell; WOCBP = women of childbearing potential.

[a] Calculated via central laboratory using the Modification of Diet in Renal Disease method.

[b] 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 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 markedly abnormal in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting 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 intervention 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 markedly abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Any markedly abnormal laboratory findings or other abnormal safety assessments that are associated with a specific diagnosis. (The specific diagnosis would be reported as an AE if it occurred during the study.) • 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.

Events NOT Meeting the AE Definition
• 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 preexisting 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 SAE 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 preexisting 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) that 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.

An SAE is defined as any untoward medical occurrence SAE that, at any dose:
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 sponsor or designee. In this case, all participant identifiers, except for 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 assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories*:
    - Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental 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 AE

  * These categories are based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 or higher.
- 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 assess 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 considering 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 via an Electronic Data Collection Tool

- 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 AEOSI/ORE 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 AEOSI/ORE Reporting Form should be completed as much as possible before transmittal. • Contacts for AEOSI/ORE reporting can be found in the Trial Site Binder.

APPENDIX 5. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy
   d. 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.
2. Postmenopausal female
   a. 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 hormonal replacement therapy (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 must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal 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 hormonal replacement therapy (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
• 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
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable

[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 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 are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

APPENDIX 6. [redacted]

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