

PD	pharmacodynamic(s)
PET	positron emission tomography
PGIC	Patient Global Impression of Change scale
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PROMIS-29	29-item Patient-Reported Outcomes Measurement Information System, version 2.1
PTE	pretreatment event
PTZ	pentylenetetrazol
PWT	paw withdrawal threshold
QD	once daily
QTcF	QT interval with Fridericia's correction method
RO	receptor occupancy
SAE	serious adverse event
SOP	standard operating procedure
SRD	single-rising dose
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UK	United Kingdom
US	United States

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

- Change and percent change from baseline of mean PGIC to the end of Part A (Week 15).
- Change and percent change from baseline of mean CSS in subjects to the end of Part A (Week 15).

5.2.3 Exploratory Endpoints

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5.2.4 Safety Endpoints

- Percentage of subjects with at least 1 treatment-emergent adverse event (TEAE) in Part A and Part B.
- Percentage of subjects with at least 1 markedly abnormal value for clinical laboratory evaluations, vital signs, body weight/body mass index (BMI), and electrocardiogram (ECG) parameters after treatment in Part A and Part B.
- Change from baseline in clinical laboratory evaluations, vital signs, body weight, Columbia-Suicide Severity Rating Scale (C-SSRS), and ECG parameter values after treatment in Part A and Part B.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2a randomized, double-blind, placebo-controlled, parallel-group study in adult subjects (≥ 18 -75 years inclusive) with chronic (symptoms ≥ 6 months) CRPS. The objective will be to evaluate the ability of TAK-935 as adjunctive therapy to reduce pain as measured by the NPS (an 11-point scale by electronic pain diary). This study will also evaluate efficacy of TAK-935 as measured by PROMIS-29 version 2.1, PGIC, and CSS.

Approximately 24 subjects will be randomized to ensure 21 completers in the double-blind phase of the study. Randomization will be 2:1 (16 treatment: 8 placebo).

This study consists of 2 parts:

- Part A: Double-Blind Treatment
 - 2- to 4-week screening period.
 - 3-week titration period.
 - 12-week maintenance period.
 - Taper period (maximum 6 days)/Follow-up (15 days after last dose of study drug) if the subject does not continue into the open-label extension (see Section [9.3.4](#) for details).
- Part B: Open-Label Extension
 - 2-week titration period.
 - 12-week open label.
 - Taper period (maximum 6 days)/Follow-up (15 days after last dose of study drug).

Part A: Double-Blind Treatment (19-21 weeks including the screening period and follow-up if the subject does not continue into the open label extension)

At Visit 1 (screening), after obtaining informed consent, subjects will undergo screening procedures to assess subject eligibility in accordance with study entry criteria. Subjects who fulfill the CRPS Budapest Criteria, have symptoms for ≥ 6 months and meet all inclusion criteria and none of the exclusion criteria at the screening visit will be eligible for entry into the study. For a minimum of 6 of the last 7 screening days prior to randomization at Visit 2 (Day 1) into the study, baseline current pain intensity will be collected 3 times a day to provide an average daily 24-hour pain intensity (NPS; an 11-point scale by electronic pain diary). The baseline will be defined as the mean of the average screening 24-hour pain intensity score for the last 7 days before the first dose. During Part A, average 24-hour pain intensity will be calculated as the mean of 3 measurements collected during a day. The average pain intensity score will be calculated as the mean of the average 24-hour pain intensity score collected during the last 7 days before Visit 5 (Day 21, Week 3) and Visit 8 (Day 105, Week 15) (or the last dose in Part A), which will be used for the primary endpoint analysis.

At the end of the prospective screening period, subjects will return to the clinic (Visit 2, Day 1) and if a subject does not meet the eligibility criteria the subject will be discontinued from the study and considered a screen failure.

On Visit 2 (Day 1), the subjects who meet the entry criteria will be randomized in a 2:1 ratio to double-blind treatment with investigational product (IP), either TAK-935 100 mg tablets or matching placebo, for 15 weeks (3-week titration period and 12-week maintenance period).

All screening/baseline assessments will be collected prior to initiating treatment.

At Visit 2 (Day 1), after randomization and all predose procedures have been performed, subjects will be started on 100 mg BID IP (either TAK-935 100 mg tablets or matching placebo) for approximately 1 week. The first dose on Day 1 will be taken in the clinic (except for Visit 4 [Day 14], Visit 6 [Day 49], and Visit 13 (Day 203), when subjects will be instructed to take their dose on site at their study visit). The subject will take the second dose on Day 1 and the remaining daily doses at home. The site will contact the subject by telephone on Day 4 to determine safety and tolerability.

At Visit 3 (Day 7, Week 1), safety and tolerability will be assessed and if the drug is well tolerated, the dose will be increased to 200 mg BID. The site will contact the subject by telephone on Day 10 to determine safety and tolerability of this dose. Any subjects who continue with 100 mg BID and still cannot tolerate the minimum daily dose of 100 mg BID, will be withdrawn from the study.

At Visit 4 (Day 14, Week 2), safety and tolerability will be assessed and if the drug is well tolerated with no continuing pain, the subject will remain at 200 mg BID. If the subject continues to need a higher dose in the PI's opinion, the dose will be increased to 300 mg BID. The site will contact the subject via phone on Day 17 to determine the safety and tolerability of this dose. Subjects that do not require the dose to be increased to 300 mg BID will still be required to complete a 21-day titration period in order to confirm the tolerated dose prior to entering the maintenance phase. After completing 1 week for each dose adjustment at 100 mg BID increments to 300 mg BID depending on tolerance, the 3-week titration period will be completed and the subject will return to the site for Visit 5 (Day 21, Week 3) to begin the 12-week maintenance period.

After Visit 5 (Day 21, Week 3), subjects will visit the clinic approximately every 4 weeks (Visit 6 [Day 49, Week 7] and Visit 7 [Day 77, Week 11]). The current pain intensity will be collected 3 times a day using the electronic pain diary. From this data, an average 24-hour pain intensity score can be calculated.

If at any time during either the titration period or the maintenance period the subject cannot tolerate the dose, the dose may be decreased to the previous tolerated dose. The subject may return to the clinic for an unscheduled visit at any time during either the titration period or the maintenance period if dose adjustments are needed between scheduled visits. If the subject cannot tolerate the minimum daily dose of 100 mg BID, the subject will be withdrawn from the study. If the dose is decreased due to inability to tolerate the dose based on the investigator's review, the dose may be increased to the next highest dose 1 time during the titration. Dose modifications during the maintenance period should be discussed with the medical monitor.

6.2.2 Dose

Dose selection is based on a comprehensive analysis of the safety, tolerability, PK and pharmacodynamic (PD) data from 4 completed single- and multiple-dose phase 1 studies in healthy subjects, and a safety, tolerability, and PK data from the phase 1b/2a study of TAK-935 as adjunctive therapy in adult subjects with DEEs.

The up-titration scheme and target dose regimen were chosen to maximize target engagement (ie, CH24H enzyme occupancy) and downstream changes in plasma 24HC levels for optimal drug response, while ensuring an acceptable clinical safety profile in the target patient population. A population PK/enzyme occupancy (EO)/PD model, using the totality of the information available in healthy subjects was built to characterize TAK-935 PK, and describe its relationships with brain CH24H EO and subsequent reduction in plasma 24HC levels (PD). This integrated model consists of a 2-compartment PK model with (1) transit compartments to account for the delayed absorption of the new tablet formulation (to be used in this study) relative to the oral solution (used in previous phase 1 studies) and (2) dose as a covariate on clearance parameters and peripheral volume of distribution to describe TAK-935 nonlinear PK. A sigmoid E_{max} (maximum drug-induced effect) model using an effect-site compartment described the temporal relationship between TAK-935 concentrations and brain EO, while the relationship between 24HC plasma levels and TAK-935 concentrations was characterized by an indirect inhibitory response PK/PD model. Standard goodness-of-fit diagnostics, parameter precision and visual predictive checks demonstrated the appropriateness of the population PK and PK/EO/PD models.

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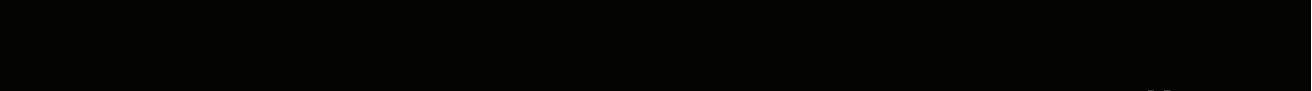


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6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Study Termination related to Drug-Related Events

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6.3.2 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the TAK-935, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.3 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.4 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

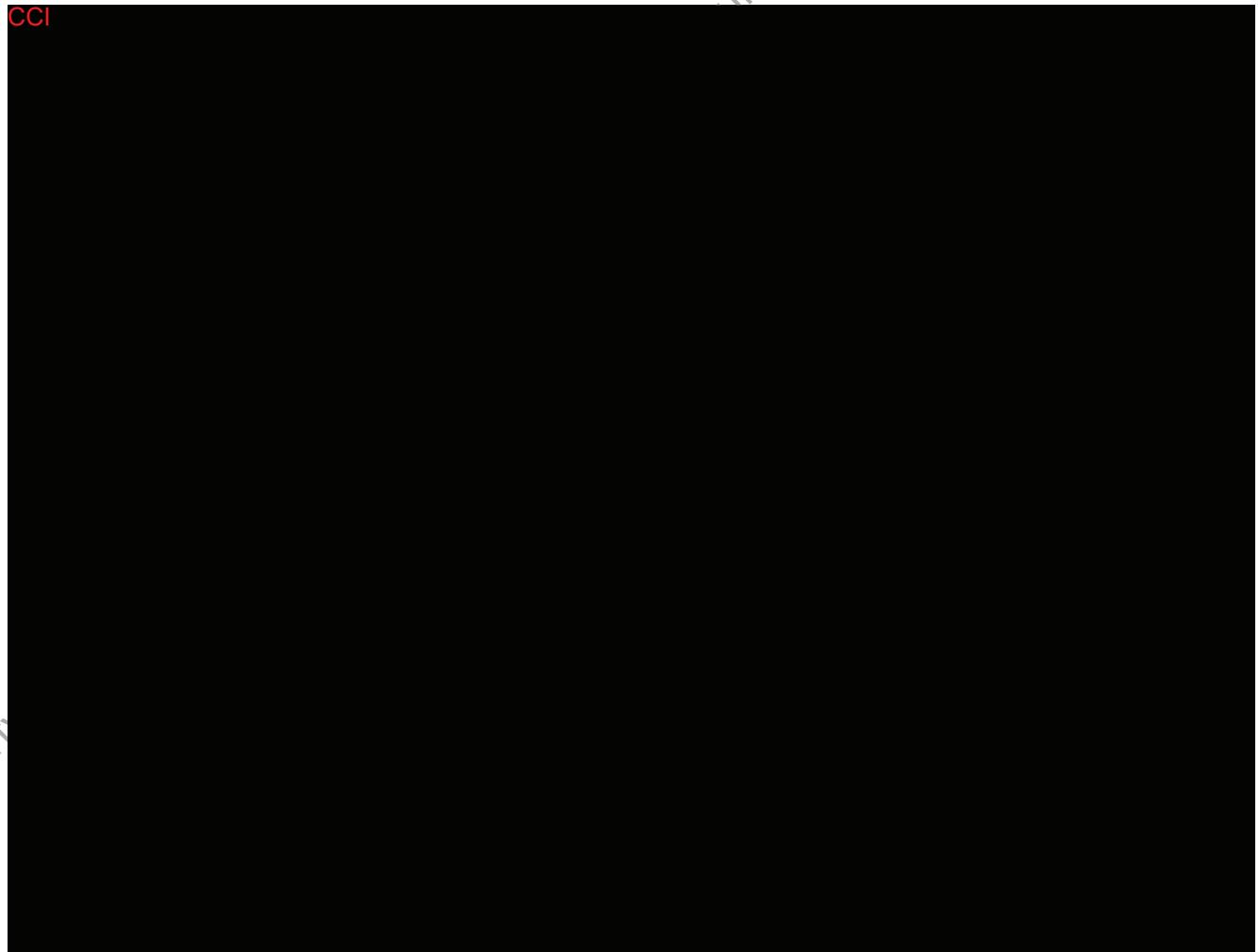
All entry criteria, including test results, need to be confirmed prior to first dose of study drug.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures, including requesting that a subject fast for any clinical laboratory evaluations.
3. The subject is a male or female aged ≥ 18 to 75 years inclusive at the time of informed consent.
4. The subject meets the Budapest clinical diagnosis of CRPS at the screening visit, and is at least 6 months since onset of symptoms.

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In addition to collecting the pain intensity at the time of recording, the electronic pain diary will collect number of flare-ups experienced that day.

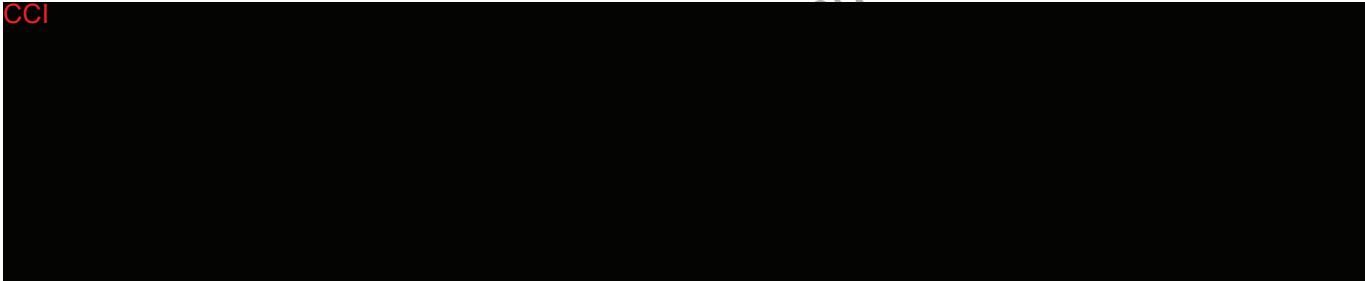
9.1.8.2 PROMIS-29

The PROMIS-29 (version 2.1), a generic health-related quality of life survey, assesses each of the 7 PROMIS domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities) with 4 questions per domain. The questions are ranked on a 5-point Likert scale.

9.1.8.3 PGIC

The PGIC is a 7-point Likert scale to address the following question: Since beginning treatment at this clinic would you describe any changes (if any) in activity, limitations, symptoms, emotions and overall quality of life related to your painful condition compared to before treatment? Very much improved; moderately improved; slightly improved; no change; slightly worse; moderately worse; very much worse.

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9.1.9 Documentation of Concomitant Medications

Concomitant medication is any drug ongoing at the time the informed consent, as well as given in addition to the study drug during the study. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.10 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening/baseline examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described and recorded on the medical history form.

Pain medications and nondrug treatments must be regimented per prescription for 1 month prior to screening, and prescriptions should not be altered during Part A. Concurrent treatment regimen data will be collected throughout the study. The use of rescue pain medications will be assessed at each visit.

During Part A, all subjects will continue to enter the current pain intensity score 3 times a day using the NPS in the electronic pain diary. This data will be captured daily during Part A.

9.3.4 End of Part A or Early Termination

At the end of Part A, subjects will return to the clinic on Day 105 (Week 15, Visit 8) to complete all scheduled assessments.

Subjects will have the option to continue into Part B, a 14-week open-label extension study, or to enter a follow-up period which includes a double-blind taper period (maximum 6 days) followed by a 2-week follow-up period off IP.

In all subjects choosing the taper period, the IP dose will be reduced to the next lower dose every 3 days (or less frequently based on the investigator's discretion) until IP dose is discontinued.

Subjects who withdraw early from Part A of the study will undergo dose tapering and complete all procedures scheduled for the end of Part A/early termination visit (Visit 8) at time of withdrawal. The investigator in consultation with the medical monitor will evaluate the possible effects of rapid withdrawal from the study drug versus the risk of continuing the drug.

9.3.5 Part B

Because treatment assignment in Part A will remain blinded, all subjects who choose to continue into Part B will start at 200 mg BID TAK-935 (100 mg tablets). Subjects should remain at this dose for 1 week. The site will contact the subject by phone on Day 108 to determine safety and tolerability. The subject will return to the clinic on Day 112 (Week 16, Visit 9) to complete all scheduled assessments, assess safety and tolerability, and adjust study drug dosing as needed. The dose may be decreased from 200 mg BID to 100 mg BID based on tolerability at Visit 9 (Day 112, Week 16). After Visit 9, subjects will visit the clinic approximately every 4 weeks (Visit 10 [Day 119, Week 17], Visit 11 [Day 147, Week 21], Visit 12 [Day 175, Week 25], and Visit 13 [Day 203, Week 29]). The current pain intensity will be collected 3 times a day using the electronic pain diary daily. From this data an average 24-hour pain intensity score can be calculated.

9.3.6 End of Part B or Early Termination

The end of Part B (Visit 13) is on Day 203 (Week 29), at which time the appropriate dose de-escalation schedule begins. Subjects return to the clinic to complete all scheduled assessments.

During the taper period, the IP dose will be reduced to the next lower dose every 3 days (or less frequently based on the investigator's discretion) until IP dose is discontinued.

Subjects who withdraw early from Part B of the study should undergo dose tapering and complete all procedures scheduled for the final follow-up visit (Visit 13) at time of withdrawal. The

10.0 PRETREATMENT EVENTS AND AEs

10.1 Definitions

10.1.1 Pretreatment Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

10.1.3 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed

early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs. Procedures for CRPS are not allowed during the study, by consent.
- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on the appropriate eCRF page. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
 - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires subject HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Includes any event or synonym described in the Takeda Medically Significant AE List ([Table 10.a](#)).

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix B](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB

IRBs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and

Study Period	Screening	Part A, Double-Blind Treatment										Part B, Optional Open-Label Extension										218 (±7) Final Follow-up (Part B) ^c
		1 Rand- omization	4 (±2)	7 (±2)	10 (±2)	14 (±2)	17 (±2)	21 (±2)	49 (±2)	77 (±2)	105 (±5) ^a Start Part B	108 (±2)	112 (±2) ^b	115 (±2)	119 (±2)	147 (±7)	175 (±2)	203 (±7)				
Day	-28 to -1																					
Week	-4 to -1			1		2		3	7	11	15		16		17	21	25	29	31			
Study Visit	1	2	PC ^d	3	PC ^d	4	PC ^d	5	6	7	8	PC ^d	9	PC ^d	10	11	12	(ET)	PC			
Concomitant medications	X-																					
12-lead ECG ^f	X	X (pre dose)							X		X								X			
24-hour pain intensity NPS ^g	X	X-																				X
PROMIS-29	X											X										X
PGI-C												X										X
CRPS Severity Scale	X											X										X
C-SSRS	X	X (pre dose)		X		X		X	X	X	X		X		X	X	X	X			X	
Safety/tolerability assessment ^h	X-																					
Clinical laboratory evaluations ⁱ	X	X (pre dose)				X						X										X
Urine drug screen	X												X									
Serum pregnancy test (hCG) for females of childbearing potential	X												X									X
PD (24HC), PK ^j		X (pre dose)				X			X													X
Plasma protein binding assessment ^k						X																
PGx assessment ^l	X																					
Access IWRS	X	X		X		X		X		X		X		X		X		X	X	X	X	
Study drug dispensing and accountability		X		X		X		X		X		X		X		X		X	X	X	X	
AE assessment	X-																					

Footnotes are on the following page.

4.0 INTRODUCTION

4.1 Background

Complex regional pain syndrome (CRPS) was initially identified by Claude Bernard (1813-1878) when he noted that extreme pain could be associated with abnormalities in the autonomic nervous system. Mitchell (1829-1914) coined the term ‘causalgia’ to describe this constellation occurring in veterans of the American Civil War. The term ‘reflex sympathetic dystrophy’ was used until recently when CRPS was agreed upon. CRPS can be subdivided into 3 types: (1) CRPS-I: previously known as reflex sympathetic dystrophy; (2) CRPS-II, previously known as causalgia and defined as CRPS with clinical and/or electrodiagnostic evidence of nerve damage; and (3) CRPS (not otherwise specified) which only partially meets diagnostic criteria, but no better diagnosis can be discerned [3]. CRPS-I and CRPS-II have similar outcomes and response to pain medication. Autonomic changes are often required for the diagnosis and may distinguish between acute CRPS ('hot' limb with edema and red coloration) and chronic ('cold' limb with atrophy and blue coloration). Although there is significant involvement of the peripheral nervous system, chronic CRPS is thought to be a central neurological disease with demonstrated alterations in both central nervous system (CNS) function as well as structural changes including alterations in cortical representations in both sensory and motor cortex [4]. CRPS is known as one of the most painful disorders and the risk of suicide is significantly higher in patients with CRPS with one study demonstrating that 75% of patients had a high risk for suicide [5]. Due to the severity of the pain, amputation is rarely being considered as a therapeutic option [6]. Although the pathophysiology has not been established, overactivity of the *N*-methyl-D-aspartate (NMDA) receptors are thought to play a role [7] and while no drugs are approved for CRPS, ketamine, a NMDA receptor antagonist, has established efficacy in a randomized control trial [8]. Use of an NMDA antagonist along with morphine, decreased pain and cerebral pain representation consistent with brain involvement in CRPS [9].

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The subject should be instructed not to alter their dose without prior approval from the investigator. Any change in dose will be documented in the subject's clinic chart and electronic diary.

Pain medications and nondrug treatments must be stable (regimented per prescription) for 1 month prior to screening and should remain stable throughout Part A. Pain medication use may be adjusted under supervision during Part B. Concurrent treatment regimen data will be collected throughout the study.

A single effective rescue medication must be identified for each subject for use during the study. The prescribed maximum dose must remain stable during Part A. The use of rescue pain medications will be assessed at each visit; subjects requiring significant increase of rescue medication (frequency or dose 50% over pre-enrollment levels or over the prescribed maximum) during Part A will be considered for withdrawal from the study at the investigator's and sponsor's discretion.

During Part A, all subjects will continue to enter the current pain intensity score as described 3 times a day using the NPS in the electronic pain diary.

An unblinded interim analysis will be conducted when all subjects have completed Part A (Double-Blind Treatment).

Following completion of Part A, subjects will have the option to continue into Part B, a 14-week open-label drug extension, or to enter a double-blind taper period (maximum 6 days).

For all subjects that choose not to enter into Part B (Open-Label Extension), the IP dose will be reduced to the next lower dose every 3 days (or less frequently based on the investigator's discretion) until IP dose is discontinued. After tapering, the subjects will complete a safety follow-up phone call approximately 15 days after the last dose of IP.

Part B Open-Label Extension (14 weeks):

Because the Part A treatment assignments will remain blinded, all subjects who choose to continue into Part B will start at 200 mg BID TAK-935 (100 mg tablets), regardless of the treatment they were on in Part A at Visit 8 (Day 105, Week 15). Subjects will remain at this dose for 1 week. The site will contact the subject by telephone, 3 days after initiation of this dose, on Day 108 to determine safety and tolerability.

At Visit 9 (Day 112, Week 16), safety and tolerability will be assessed and if the drug is well tolerated and the subject continues to need a higher dose in the PI's opinion, the dose will be increased to 300 mg BID. The dose may also be decreased based on tolerability at Visit 9 (Day 112, Week 16). The site will contact the subject on Day 115 to determine the safety and tolerability of this dose.

After completing 1 week at 300 mg BID, the 2-week titration period will be completed and the subject will return to the site for Visit 10 (Day 119, Week 17) to begin the 12-week maintenance period.

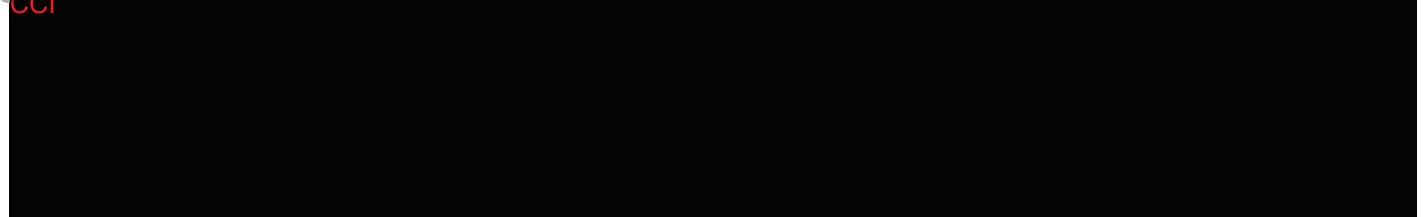
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6.2.2.1 *Clinical Safety*

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- d. No other diagnosis that better explains the signs and symptoms.
5. The subject has a history of failure of one or more standard of care therapies for the treatment of CRPS as judged by the investigator.
6. The subject's pain medications and nondrug treatments must be stable (regimented per prescription) for 1 month prior to screening and remain stable throughout Part A.
7. The subject agrees to use a single previously prescribed rescue medication within the prescribed dose during Part A of the study and to record the daily use of these medications.
8. The subject must have an average 24-hour pain intensity score ≥ 4 and ≤ 9 on the 24-hour average pain intensity NPS during screening/baseline. This score will be calculated by averaging the daily 24-hour pain intensity scores for the past seven days prior to randomization. The subject must have daily 24-hour pain intensity scores recorded for at least 6 of the past 7 days.
9. The subject is not involved in active litigation related to CRPS.
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- 10.
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7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Currently receiving intravenous (IV) or oral ketamine, history of IV or oral ketamine use within the past 6 weeks prior to screening, or planned use of IV or oral ketamine during this study.
2. The subject has received any excluded medications, procedures, or treatments during the time periods listed in Section 7.3.
3. The subject has any unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, or endocrine disease or other abnormality which may impact the ability to participate in the study or that may potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance.

9.1.11 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual. The approximate volume of blood collected at any single visit and the approximate total volume of blood collected in the study will be given in the laboratory and/or study manual.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

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investigator in consultation with the medical monitor will evaluate the possible effects of rapid withdrawal from the study drug versus the risk of continuing the drug.

9.3.7 Final Follow-up

After tapering, the subjects will complete a safety follow-up phone call approximately 15 days after the last dose of IP.

9.3.8 Unscheduled Visit

Subjects may return to the study center for unscheduled visits as needed. Unscheduled study visits can be performed when the subject has a study related issue in between regular study visits.

The following procedures should be performed during this visit:

- Concomitant medications.
- AE assessment.
- Other procedures, including dose adjustments, as deemed appropriate by the investigator.

9.3.9 Poststudy Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

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AEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 AEs of Special Interest

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disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

AE: adverse event; BID: twice daily; BMI: body mass index; CRPS: complex regional pain syndrome; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; ET: early termination; hCG: human chorionic gonadotropin; ID: identification; IWRS: interactive web response system; NPS: Numeric Pain Scale; PC: Phone Call; PGIC: Patient Global Impression of Change; PGx: Pharmacogenomics; PROMIS-29: 29-item Patient-Reported Outcomes Measurement Information System, version 2.1.

^a Subjects who do not continue into Part B will undergo the dose taper procedures and will then proceed to the follow-up period. The timing of the follow-up phone call and follow-up period will be 15 days after the last dose of study medication. Subjects who are on the lowest administered dose of TAK-935 during the taper period will not undergo dose taper.

^b Dosing of TAK-935 will be started at 200 mg BID when subjects enter Part B. After 7 days, doses may be increased to a maximum of 300 mg BID. If at any time during either the titration period or the maintenance period subjects cannot tolerate the dose, the dose may be decreased to the previous tolerated dose. If subjects cannot tolerate the minimum daily dose of 100 mg BID, then subjects will be withdrawn from the study.

^c All subjects will undergo dose taper procedures and will then proceed to the follow-up period. The timing of the follow-up phone call and follow-up period will depend on the dose taper procedures followed. In all subjects choosing the taper period, the IP dose will be reduced to the next lower dose every 3 days (or less frequently based on the investigator's discretion) until IP dose is discontinued. After tapering, the subjects will complete a safety follow-up phone call approximately 15 days after the last dose of IP. Subjects who are on the lowest administered dose of TAK-935 at the end of Part B will not undergo dose taper. The follow-up visit may be eliminated for subjects enrolled in the open-label extension.

^d The phone call should be made by an experienced healthcare provider who can review study drug dosing.

^e Height will only be measured at Screening (Visit 1).

^f A standard 12-lead ECG will be recorded at Screening to evaluate subject's eligibility. A standard 12-lead ECG will be recorded in triplicate at predose at Visit 2, and predose and between 30 to 45 min postdose ($\sim T_{max}$) at Visit 5, 8, and 13.

^g For a minimum of 6 of the last 7 screening days prior to enrollment into the study, baseline average daily 24-hour pain intensity will be collected (NPS; an 11-point scale by electronic pain diary). During the study, 24-hour pain intensity will be collected 3 times a day.

^h Safety and tolerability will be continuously evaluated throughout the study. A formal documented safety and tolerability analysis will be conducted at Visit 4 before advancing subjects from 200 mg BID to 300 mg BID.

ⁱ Blood samples for clinical safety laboratory tests including hematology and chemistry, will be collected at Visit 1, Visit 2 (predose), Visit 4 during Part A, Visit 8 (end of Part A/early

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