Title: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 as an Adjunctive Therapy in Adult Subjects With Chronic Complex Regional Pain Syndrome

NCT Number: NCT03990649

Protocol Approve Date: 16 December 2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 as an Adjunctive Therapy in Adult Subjects With Chronic Complex Regional Pain Syndrome

Study of TAK-935 as an Adjunctive Therapy in Adult Subjects With Complex Regional Pain Syndrome

Sponsor:	Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceuticals Company Limited 40 Lansdowne Street Cambridge, MA 02139, USA
Study Number:	TAK-935-2008
EudraCT Number:	2018-004750-21
Compound:	TAK-935
Date:	16 December 2019 **Amendment Number:** 03

Amendment History:

Date	Amendment Number	Region
30 January 2019	Initial protocol	Global
08 May 2019	01	Global
01 July 2019	02	Global
16 December 2019	03	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Pharmaceuticals Company Limited (TDC) sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories, as applicable, can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

PPD

1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes to the protocol incorporating Amendment No. 03. The primary reason for this amendment is to update the dose selection rationale based on new data from the TAK-935-2001 study.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix F.

Changes in Amendment 03:

1. Updated the dose selection rationale.
2. Clarified the schematic of study design.
3. Replaced ‘dosing card’ with ‘electronic diary’.
4. Moved a secondary objective to an exploratory objective to align with endpoints.
5. Modified Figure 4.a.
6. Clarified the rationale for the study.
7. Moved the detail on pharmacogenomic analysis.
8. Revised contraceptive requirements.
9. Modified the detail regarding blood volumes collected during the study.
10. Clarified the ECG procedures for specific visits.
11. Clarified the efficacy analysis.
12. Clarified the exploratory analysis.
13. Clarified the interim analysis.
14. Clarified when blood samples for plasma protein binding assessment will be collected.

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.2 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator. (Appendix B)

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceuticals Company Limited 40 Lansdowne Street Cambridge, MA 02139, USA	**Compound:** TAK-935
Title of Protocol: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 as an Adjunctive Therapy in Adult Subjects With Chronic Complex Regional Pain Syndrome	**EudraCT No.:** 2018-004750-21
Study Number: TAK-935-2008	**Phase:** 2a

Study Design:

This is a phase 2a randomized, double-blind, placebo-controlled, parallel-group study in adult subjects (≥18 years) with chronic (symptoms ≥6 months) complex regional pain syndrome (CRPS). The objective will be to evaluate the ability of TAK-935 as adjunctive therapy to reduce pain as measured by the Numeric Pain Scale ([NPS], an 11-point scale by electronic pain diary). The study will also evaluate efficacy of TAK-935 as measured by the 29-item Patient-Reported Outcomes Measurement Information System (PROMIS-29, version 2.1), Patient Global Impression of Change (PGIC) scale, and CRPS Severity Score (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 (to occur 15 days after last dose of study drug) if the subject does not continue into the open label extension).

Part B: Open-Label Extension

2-week titration period.

12-week open label period.

Taper period (maximum 6 days)/Follow-up (to occur 15 days after last dose of study drug).

<u>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)</u>

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 before 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 prior to 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), 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 twice daily (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. The subject will take the second dose on Day 1 and the rest of the doses at home (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 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 increment 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 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 has been 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.

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. This data will be captured daily during Part A.

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 to 100 mg BID based on tolerability at Visit 9 (Day 112, Week 16). If the subject tolerates the 200 mg BID dose without continuing pain, the dose will remain at 200 mg BID. 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.

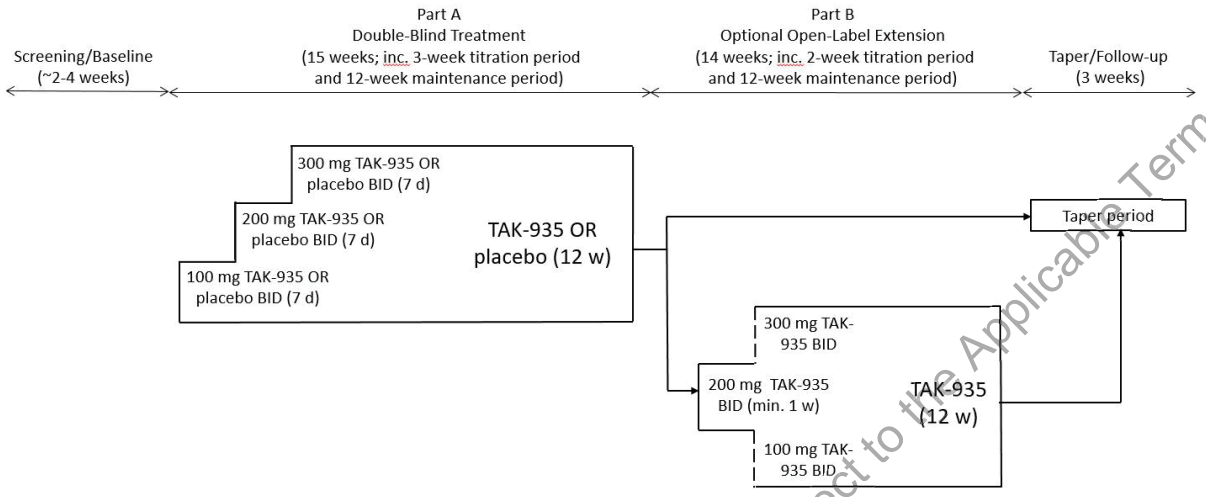
If at any time during either the titration period or the maintenance period the subject cannot tolerate the dose, the dose may be decreased to the previous tolerated dose. The subject may return to the clinic for an unscheduled visit at any time during either the titration period or the maintenance period 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.

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.

After Visit 10 (Day 119, Week 17), the subjects will visit the clinic approximately every 4 weeks (Visit 11 [Day 147, Week 21] and Visit 12 [Day 175, Week 25]). The current pain intensity will be collected daily, 3 times a day, using the electronic pain diary until the end of the study. From these data an average 24-hour pain intensity score can be calculated. In addition, using the data collected in the last 7 days prior to Visit 11 (Day 147, Week 21) and Visit 13 (Day 203, Week 29) (or the last dose in Part B), the average pain score prior to these visits will be derived.

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

The total period of evaluation from screening to the final follow-up in Part B will be approximately 34-36 weeks.



BID: twice daily.

Primary Objective:

- To investigate the effect of TAK-935 on calculated 24-hour average pain intensity by the NPS (an 11-point scale).

Secondary Objectives:

- To investigate the effect of TAK-935 on overall function using the PGIC and the PROMIS-29 scale.
- To investigate the effect of TAK-935 on the CRPS CSS score.
- To investigate the effect of TAK-935 on responder rate (responder is defined as ≥30% improvement in the 24-hour pain intensity).

Exploratory Objectives:

CCI [redacted]

Safety Objective: To evaluate safety and tolerability of TAK-935 in subjects with CRPS.

Subject Population: Adult subjects aged ≥18 to75 years with chronic (symptoms ≥6 months) of CRPS.

Number of Subjects: Total of approximately 24 subjects randomized in Part A: 2 (TAK-935): 1 (placebo).	**Number of Sites:** Approximately 10 sites
Dose Levels: Part A: TAK-935 100 mg BID to 300 mg BID (100 mg tablets) or matching placebo Part B: TAK-935 100 mg BID to 300 mg BID (100 mg tablets)	**Route of Administration:** Oral
Duration of Treatment: Part A: 15 weeks (Titration and Maintenance) Part B: 14 weeks (Titration and Maintenance) and	**Period of Evaluation:** ~36 weeks (including up to 4-week screening/baseline period, 15-week double-blind treatment period [3-week titration and 12-week maintenance periods], 14-week open-label

maximum 6 days (Taper period).	period [2-week titration and 12-week maintenance periods]), and 3-week taper/follow-up period.

Main Criteria for Inclusion (see Section 7.1 for full inclusion criteria):

- The subject is a male or female aged ≥18 to 75 years inclusive at the time of informed consent.
- The subject meets the Budapest clinical diagnosis of CRPS at the screening visit, and is at least 6 months since onset of symptoms.
- CCI
- 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.
- The subject's pain medications and nondrug treatments must be stable (regimented per prescription) for 1 month prior to screening and should remain stable throughout Part A.
- The subject agrees to use a single previously prescribed rescue medication within the prescribed dose during Part A of the trial and to record the daily use of these medications.
- 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.

Main Criteria for Exclusion (see Section 7.2 for full exclusion criteria):

- Currently receiving intravenous (IV) or oral ketamine or other infusion therapy, history of IV or oral ketamine use within the past 6 weeks prior to screening, or planned use of IV or oral ketamine during the study.
- 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.
- CCI .
- The subject has any history of alcohol, opioid, or other moderate to severe substance use disorder (except

nicotine), as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, within the 2 years immediately prior to the screening visit (Visit 1).

- Subject is receiving chronic opioid treatment at a dose that has not been stable over the past 28 days.
- Subject is receiving chronic opioid treatment >160 mg of morphine equivalent per day.
- The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within the past year prior to screening. Subjects who have positive answers on item number 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), based on the past year, prior to randomization are excluded.
- CCI
-

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

- Change in mean 24-hour pain intensity NPS from baseline to the end of Part A (Week 15).

Secondary Endpoints:

- Percent change in mean 24-hour pain intensity NPS score from baseline to the end of Part A (Week 15).
- Percent of responders (defined as ≥30% improvement on the 24-hour pain intensity NPS) by the end of Part A (Week 15).
- Change and percent change from baseline of mean total score of the PROMIS-29 version 2 to the end of Part A (Week 15).
- 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 to the end of Part A (Week 15).

Exploratory Endpoints:

CCI

Safety Endpoints:

- Percentage of subjects with at least 1 treatment-emergent adverse event 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, and electrocardiogram parameters after treatment in Part A and Part B.
- Change from baseline in clinical laboratory evaluations, vital signs, body weight, C-SSRS, and electrocardiogram parameter values after treatment in Part A and Part B.

Statistical Considerations:

Efficacy Analysis:

For the primary efficacy endpoint, only subjects with a baseline and at least 1 postdose value will be included in the summary and analyses. The data from the last 7 days prior to the visits on Day 21 (Week 3), Day 105 (Week 15) (or the last dose in Part A, whichever is earlier), Day 147 (Week 21), and Day 203 (Week 29) (or the last dose in Part B,

whichever is earlier) will be used to derive the mean 24-hour pain intensity for the corresponding visits.

For Part A, summary statistics will be provided for the observed values of the efficacy measures at baseline and each of postdose visits by treatment group. Change from baseline and percent change from baseline will also be summarized with descriptive statistics by treatment group.

For Part B, summary statistics will be provided for the observed values of the efficacy measures at each of the postdose visits for all subjects, as well as by treatment group in Part A. Change from baseline and percent change from baseline will also be summarized with descriptive statistics. Baseline will be the baseline for Part A.

For the mean 24-hour pain intensity derived above in Part A, linear mixed models for repeated measurements will be used to evaluate the effect of TAK-935 on the primary and secondary endpoints. The change from baseline in the 24-hour mean pain intensity to the scheduled visits (Day 21, Week 3) and Day 105, Week 15) will be the response in the model; baseline, site, visit (Day 14 (Week 2) and Day 105 (Week 15), treatment, and treatment by visits interaction will be the fixed effects; and a completely unstructured covariance matrix will be assumed. The treatment effect at each visit will be evaluated using the difference in the least-square means of the change from baseline between TAK-935 and placebo. 95% confidence intervals for the differences and p-values will also be provided. Percent of responders will be summarized and compared between treatment arms in Part A.

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Safety Analyses: Descriptive statistics will be used to summarize all safety endpoints, by treatment group. Data summaries will be displayed for incidence of adverse events, clinical laboratory variables, vital signs, body weight and body mass index, and electrocardiogram parameters.

Interim Analysis: An unblinded interim analysis will be conducted after all subjects have completed Part A. All planned efficacy analysis for the primary and secondary endpoints will be performed for the data collected during Part A. Safety and PK/PD summaries will also be performed for Part A. Since this analysis will be conducted at the end of the double-blind period, this analysis will be considered as the primary efficacy assessment of TAK-935 on CRPS relative to placebo. No alpha spending or adjustment to sample size will be needed based on the results of this analysis.

Sample Size Justification: Assuming a standard deviation of 2 and a 12% drop-out rate, a sample size of 24 subjects in total with randomization ratio of 2:1 is sufficient to achieve at least 65% power to detect a difference of 2 between TAK-935 and placebo by a 2-sample t-test on the change from baseline to Week 15 in mean 24-hour pain intensity NPS score at 0.10 2-sided significance level. A difference of 2 is within the accepted range of minimally clinically important difference for the 11-point NPS [1,2].

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

24HC	24S-hydroxycholesterol
AAP	alpha-1-acid glycoprotein
Ab	antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
BID	twice daily
BMI	body mass index
CH24H	cholesterol 24-hydroxylase
C_{max}	maximum observed concentration
CNS	central nervous system
CPIP	chronic postischemic pain
CRPS	complex regional pain syndrome
CRPS-I	CRPS, presenting as reflex sympathetic dystrophy
CRPS-II	CRPS, with clinical and/or electrodiagnostic evidence of nerve damage
CSS	CRPS Severity Score
C-SSRS	Columbia-Suicide Severity Rating Scale
DEE	developmental and epileptic encephalopathy
ECG	electrocardiogram
eCRF	electronic case report form
EO	enzyme occupancy
FAS	full analysis set
FDA	[United States] Food and Drug Administration
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ID	identification
IV	intravenous
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MRD	multiple-rising dose
NMDA	*N*-methyl-D-aspartate
NPS	Numeric Pain Scale

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

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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[redacted]

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CCI

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TAK-935 is also being evaluated for the treatment of rare pediatric epilepsies.

For further information, refer to the TAK-935 Investigator's Brochure.

4.2 Rationale for the Proposed Study

In phase 1 studies in healthy adult subjects and in a phase 1b/2a study in adult subjects with DEEs, acceptable pharmacokinetic (PK) and safety characteristics have been observed.

This study will be the first phase 2a study to test the efficacy, safety, and tolerability of TAK-935 in adults with CRPS. Based on the mechanism of action, preclinical data on a pertinent model to CRPS and the safety characteristics of the completed and ongoing studies, we propose this phase 2a study that will test the efficacy, safety and tolerability of TAK-935 in adults with CRPS, a highly impacted population with great unmet need.

CCI

[redacted]

CCI

[redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To investigate the effect of TAK-935 on calculated 24-hour average pain intensity by the Numeric Pain Scale (NPS) (an 11-point scale).

5.1.2 Secondary Objectives

- To investigate the effect of TAK-935 on overall function using the Patient Global Impression of Change (PGIC) and the Patient-Reported Outcomes Measurement Information System (PROMIS-29) scale.
- To investigate the effect of TAK-935 on the CRPS Severity Score (CSS).
- To investigate the effect of TAK-935 on responder rate (responder is defined as ≥30% improvement in the 24-hour pain intensity).

5.1.3 Exploratory Objectives

CCI

[redacted]

5.1.4 Safety Objective

- To evaluate safety and tolerability of TAK-935 in subjects with CRPS.

5.2 Endpoints

5.2.1 Primary Endpoint

- Change in mean 24-hour pain intensity NPS from baseline to the end of Part A (Week 15).

5.2.2 Secondary Endpoints

- Percent change in mean 24-hour pain intensity NPS score from baseline to the end of Part A (Week 15).
- Percent of responders (defined as ≥30% improvement on the 24-hour pain intensity NPS) by the end of Part A (Week 15).
- Change and percent change from baseline of mean total score of the PROMIS 29 version 2.1 to the end of Part A (Week 15).

- 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

CCI

[redacted]

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).

<u>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)</u>

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.

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.

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.

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.

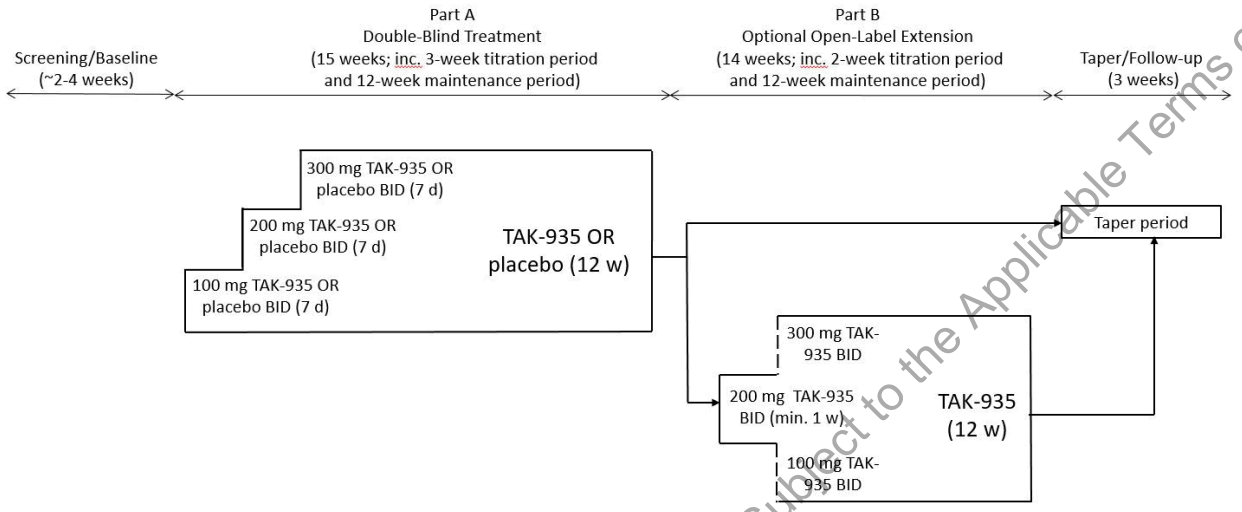
After Visit 10 (Day 119, Week 17), the subjects will visit the clinic approximately every 4 weeks (Visit 11 [Day 147, Week 21] and Visit 12 [Day 175, Week 25]). The current pain intensity will be collected daily, 3 times a day, using the electronic pain diary until the end of the study. From these data an average 24-hour pain intensity score can be calculated. In addition, using the data collected in the last 7 days before Visit 11 (Day 147, Week 21) and Visit 13 (Day 203, Week 29) (or the last dose in Part B), the average pain score prior to these visits will be derived.

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

The total period of evaluation from screening to the final follow-up in Part B will be approximately 34-36 weeks.

A schematic of the study design in shown in Figure 6.a. A schedule of study procedures is listed in Appendix A.

Figure 6.a Schematic of Study Design



BID: twice daily.
During the titration periods of both Part A and Part B, safety and tolerability will be assessed at each visit and if the drug is well tolerated and the subject continues to need a higher dose (ie, the subject still has pain), the dose will be increased to a maximum dose of 300 mg BID.
Starting doses for Part A and optional open-label extension Part B are shown.
Following completion of Part A, subjects will have the option to continue into Part B, a 14-week open-label drug extension study part or to enter a double-blind taper period.
All subjects will undergo dose taper procedures and will then proceed to the follow-up period. During the taper period, 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 are on the lowest administered dose of IP will not undergo dose taper.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension part to further examine the safety, tolerability, and preliminary efficacy of TAK-935 as adjunctive therapy in the treatment of subjects with chronic CRPS (symptoms ≥6 months, diagnosed using the Budapest criteria). Since in a majority of CRPS subjects, symptoms resolve within the first 6 months, the large unmet need is for those subjects with chronic disease.

As this is proof of concept study, statistical power of 65% was considered adequate with an alpha level of 0.10.

During this study, subjects will continue their current medications; therefore, placebo was chosen as the control group to provide maximum difference between the treatment and control arms.

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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6.2.2.1 Clinical Safety

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[redacted]

6.2.3 Endpoints

The safety-related endpoints of TEAEs, clinical laboratory test results, vital sign measurements, C-SSRS, and ECG parameters selected for this study are standard methods for assessing safety and tolerability in clinical studies.

The primary endpoint (24-hour average pain intensity scale as measured on an 11-point scale [0-10]), and secondary endpoints (PROMIS-29 version 2.1, PGIC, and CSS) are well-characterized and accepted endpoints for pain studies.

Measurements of plasma 24HC levels will be included in this study as a PD biomarker related to the mechanism of action of TAK-935. The conversion of cholesterol to 24HC is a critical process in maintaining cholesterol homeostasis in the brain and its release into the cerebrospinal fluid and plasma. Evidence suggests that plasma 24HC levels are correlated with brain 24HC levels in healthy subjects and are largely derived from the CNS. Data from SRD and MRD studies showed a decrease in plasma 24HC levels after administration of TAK-935 in healthy subjects, which was correlated with the changes in EO% measured in the brain using the PET radioligand displacement approach (Study TAK-935-1003).

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Pharmacogenomic analysis may be conducted to investigate the contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study subjects in pharmacogenomic sample collection is optional.

As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

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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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.
10. CCI
11. [redacted]
12. [redacted]

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.

4. CCI [redacted]
5. The subject has any history of alcohol, opioid, or moderate to severe substance use disorder (except nicotine and cannabis), as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, within the 2 years immediately prior to the screening visit (Visit 1).
6. Subject is receiving chronic opioid treatment at a dose that has not been stable 28 days prior to screening.
7. Subjects is receiving chronic opioid treatment >160 mg of morphine equivalent per day (refer to Appendix E for conversion table).
8. The subject has a positive drug screen for phencyclidine, amphetamine/ methamphetamine, or cocaine at screening. Cannabis is allowed.
9. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within the past year prior to screening. Subjects who have positive answers on item number 4 or 5 on the C-SSRS (based on the past year) prior to randomization are excluded.
10. CCI [redacted]
11. [redacted]
12. The subject is positive for hepatitis B or hepatitis C infection at screening. (Note that subjects who have been vaccinated against hepatitis B [hepatitis B surface antibody {Ab}-positive] who are negative for other markers of prior hepatitis B infection [eg, negative for hepatitis B core Ab] are eligible. Also, note that subjects who are positive for hepatitis C Ab are eligible if they have a negative hepatitis C viral load by quantitative polymerase chain reaction).
13. The subject has abnormal and clinically significant ECG abnormality at screening as determined by the investigator. Subject has a QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females), confirmed with 1 repeat testing, at screening.
14. The subject has abnormal clinical laboratory test results at screening that suggest a clinically significant underlying disease that would compromise the well-being of the subject (if the subject has alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] >2.5 × the upper limit of normal [ULN], the medical monitor should be consulted).
15. The subject has a known hypersensitivity to any component of the formulation of TAK-935.
16. The subject has been part of a clinical study involving another investigational product in the previous 3 months prior to screening or subject is currently receiving an investigational product.
17. The subject has received TAK-935 in a previous clinical study or as a therapeutic agent.

18. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
19. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 30 days after participating in this study; or intending to donate ova during such time period.
20. If male, the subject intends to donate sperm during the course of the study or within 90 days after the last dose of study drug.

7.3 Excluded Medications, Procedures, and Treatments

Ketamine use is excluded from the screening until the end of the follow-up visit.

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The subject may be currently receiving nondrug interventions (eg, physical therapy, occupational/physical therapy, biofeedback, cognitive behavioral therapy, and/or yoga/meditation), which must have been started 90 days prior to randomization and continue throughout the duration of the study.

Subjects should be advised to not consume alcohol or illicit drugs during the study. Cannabis is allowed. Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

Elective procedures for CRPS are not allowed during the study, by consent.

7.4 Diet, Fluid, Activity Control

There are no restrictions on diet, fluids, or activity during this study. Subjects should continue their current nondrug interventional therapies (eg, physical/occupational therapy, pain management, etc.).

7.5 Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.20.

1. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
   - Liver test abnormalities

     Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.11), if the following circumstances occur at any time during study drug treatment:
     - ALT or AST >8 × ULN, or
     - ALT or AST >5 × ULN and persists for more than 2 weeks, or
     - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
     - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
2. Subjects who cannot tolerate the 100 mg BID dosing will be withdrawn from the study and should undergo all procedures scheduled for the final visit at the time of withdrawal.
3. Drug-related SAE or drug-related significant non-serious AE, which in the opinion of the study physician or principal investigator, warrants discontinuation of the study for the subject's wellbeing.
4. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

5. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
6. Withdrawal by subject. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category.
7. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
8. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.17.
9. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.
10. The subject has received ketamine therapy during the study.
11. Other. Subjects requiring significant increase of rescue medication (frequency or dose 50% over pre-enrollment levels or over prescribed maximum) will be considered for withdrawal from the study at the investigator's discretion.

    Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation. Subjects who withdraw early from the study should undergo dose tapering and complete all procedures scheduled for the final visit (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. Discontinued or withdrawn subjects may be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

The sponsor will supply the study sites with TAK-935 100 mg tablets and matching placebo tablets. TAK-935 100 mg tablets and matching placebo tablets are manufactured by Takeda Pharmaceutical Company, Ltd, Osaka, Japan. Study drug will be supplied in high-density polyethylene bottles with induction seal and child-resistant caps. Each bottle will contain a label that includes pertinent study information and caution statements.

8.1.1.2 Rescue Medication

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) in Part A will be considered for withdrawal from the study at the investigator's discretion.

Rescue medication will not be supplied by the sponsor.

8.1.1.3 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

- TAK-935 100 mg tablets.
- Matching placebo tablets.

8.1.2 Storage

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Study drug must be kept in an appropriate, limited-access, secure place until it is dispensed and after returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every day.

8.1.3 Dose and Regimen

Each subject will be instructed to administer study drug, orally, at the same time each day with or without food. The study site personnel will indicate how many tablets should be taken per day on the bottle label, per information provided by the Interactive Web Response System (IWRS).

The investigator or designee will instruct the subject on the dosing procedures and study drug storage requirements. Subjects should return unused study drug at each study visit to allow the investigator or designee to evaluate subjects' compliance with the dosing instructions. Number of dispensed and returned tablets will be recorded on the eCRF.

The planned daily dose and tablet count to be administered to subjects in each part of the study is shown in Table 8.a.

Table 8.a Dose and Regimen

Study Part	Dose	Treatment Description [a]
Part A (double-blind)	TAK-935 100 mg BID or matching placebo BID	1 TAK-935 100 mg tablet BID for 7 days or 1 placebo tablet BID for 7 days
	TAK-935 200 mg BID or matching placebo BID	2 TAK-935 100 mg tablets BID for 7 days or 2 placebo tablets BID for 7 days
	TAK-935 100, 200, or 300 mg BID or matching placebo BID	1, 2, or 3 TAK-935 100 mg tablets BID for 7 days (titration period), followed by 84 days (maintenance period)
		or 1, 2, or 3 placebo tablets BID for 7 days (titration period), followed by 84 days (maintenance period)
Part B (open-label extension)	TAK-935 100, 200, or 300 mg BID	Initiate with 2 TAK-935 100 mg tablets BID for 7 days. Dose may be adjusted per investigator's discretion to a maximum of 3 TAK-935 100 mg tablets BID.

BID: twice daily; IP: investigational product.
[a] Planned dose titration is presented. If at any time during Part A titration or maintenance period the subject cannot tolerate the dose, the dose may be decreased to the previous tolerated dose. During the titration period, safety and tolerability will be assessed at each visit and if the drug is well tolerated and the subject continues to need a higher dose (ie, the subject still has pain), the dose will be increased to a maximum dose of 300 mg BID.
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.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented in the eCRF. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

Sites should follow the IWRS manual for specific instructions (IWRS manual provided separately). For Part A, subjects will be assigned to receive their treatment according to the randomization schedule. The investigator or investigator's designee will access the IWRS at the Visit 1 (screening) to obtain the subject number. At Visit 2 (Day 1, Randomization), the investigator or the investigator's designee will use the IWRS to randomize eligible subjects into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication identification (ID) number of the study drug to be dispensed will then be provided by the IWRS. At subsequent drug-dispensing visits, the investigator or designee will again contact the IWRS to request additional study drug for a subject. The medication ID number of the study drug to be dispensed will again be provided by the IWRS. The medication ID number will be entered onto the eCRF. If sponsor-supplied drug (TAK-935 100 mg or matching placebo tablets) is lost or damaged, the site can request a replacement from the IWRS (refer to the IWRS manual provided separately).

Each subject should be instructed as follows:

- Keep sponsor-supplied drugs in original containers until the time of dosing.
- Administer study drug as instructed. If the subject misses a dose, he or she should not be given twice the dose the next day.
- Store sponsor-supplied drugs according to the label and keep them out of the reach of children.
- Return unused sponsor-supplied drugs at each clinic visit.
- Record the number of tablets taken (AM and PM) in the electronic diary.

8.3 Randomization Code Creation and Storage

For Part A, the randomization will be stratified by the investigation site. The dummy randomization schedules will be developed by IWRS and approved by the sponsor. All randomization information will be stored in IWRS.

Study drug will be administered in a double-blind manner in Part A. The study drug blind will be maintained by IWRS. The principal investigator at each study site will receive instructions for obtaining the study drug assignment through the IWRS. During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform an inventory of assigned and unassigned bottles of study drug. All assigned/unassigned study drug bottles will be reconciled before destroying at site (permitted if internal standard operating procedure [SOP] is in place) or returning to the sponsor or a designee before study closure.

Study drug will be administered in an open-label manner in Part B. During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform an inventory of assigned and unassigned bottles of study drug. All assigned/unassigned study drug bottles will be

reconciled before destroying at site (permitted if internal SOP is in place) or returning to the sponsor or a designee before study closure.

8.4 Unblinding Procedure

If the investigator deems it necessary to unblind the study drug used by the subject to determine the dosage administered for the medical treatment of the subject in case of emergency, for example, the occurrence of SAEs, the investigator must complete the unblinding process within the IWRS as outlined in the IWRS manual. The sponsor/designee must be notified immediately if the study drug blind is broken. The date, time, and reason the blind was broken must be recorded in the source documents and on the appropriate eCRF.

If any site personnel is unblinded, it is recommended that the study drug be tapered down in consultation with the medical monitor, and the subject must be withdrawn from the study. However, 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.

The reason for withdrawal should be recorded as, "Protocol Deviation." Subjects who are withdrawn early from the study should undergo all procedures scheduled for the final visit at the time of withdrawal.

Only the responsible investigator or delegate and the respective subject's code will be unblinded. Other study site personnel and sponsor personnel directly associated with the conduct of the study should not be unblinded. The investigator will follow the early termination procedures and withdraw the subject from the study.

8.5 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being destroyed at site or returned to the sponsor or designee. NOTE: Destruction at site is permitted if internal SOP is in place by providing copy of certificate of destruction or memo confirming the destruction to be stored in the trial master file.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (TAK-935 100 mg or matching placebo tablets), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, destruction at site and/or return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot (or medication ID number) used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (TAK-935 100 mg and matching placebo tablets) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date, date and amount dispensed including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are destroyed at site, or returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

In the event of expiry date extension of sponsor-supplied drug already at the study site, Takeda or its designee will provide a memo stating the new extended expiry date.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The schedule of study procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject ID number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.10).

Medication history information to be obtained includes any medication relevant to eligibility criteria and the efficacy or safety evaluations stopped or started within 6 months prior to signing of informed consent.

Subjects will be asked if they have used ketamine therapy within the past 6 weeks prior to screening, how long ago was the therapy provided, what formulation was used, whether the therapy provided relief, and why the therapy was stopped. Subjects will be asked if they experience flare-ups in their pain and, if so, how frequently.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of a general examination of the following body systems: (1) ears, nose, throat; (2) cardiovascular system; (3) respiratory system; (4) gastrointestinal system; (5) dermatologic system; (6) extremities; (7) musculoskeletal system; (8) lymph nodes; and (9) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination. The physical examination must be captured in the source document and eCRF.

9.1.4 Neurological Examination Procedure

A separate neurological examination will be performed and collected in the eCRF. This will include testing mental status, gait, cerebellar function, cranial nerves, motor function (including strength and reflexes), and sensation. As part of the neurological exam, vision testing is recommended to include fundoscopy and best corrected visual acuity using a pocket vision screening card, if possible.

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9.1.6 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height = 176 cm (1.76 meters) and weight = 79.2 kg, then $BMI = 79.2/1.76^2 = 25.56818$ kg/m^2, which will be rounded to 25.6 kg/m^2.

9.1.7 Vital Sign Procedure

Vital signs will include oral body temperature, respiratory rate, blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (bpm).

9.1.8 Primary Efficacy Measurements

9.1.8.1 NPS

The 24-hour average pain intensity (NPS, an 11-point scale) will be calculated from current pain intensity scores collected 3 times a day as measured by the electronic pain diary daily during Parts A and B. Pain intensity will be evaluated on the affected limb. If more than 1 limb is involved, the subject and the investigator will determine which limb is the most problematic and the pain intensity will be evaluated for that limb throughout the study. For both Parts A and B, 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 Day 21(Week 3), Day 105 (Week 15) (or the last dose in Part A), which will be used for the primary endpoint analysis, as well as Day 147 (Week 21) and Day 203 (Week 29) (or the last dose in Part B).

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.

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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The local laboratory will perform all laboratory tests including hematology, serum chemistries, and urinalysis. The results of laboratory tests will be provided to the investigator, who is responsible for reviewing and filing these results. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase, and international normalized ratio) should be performed preferably within 48 to 72 hours and no later than 5 days after the abnormality was noted.

(Refer to Section 7.5 for discontinuation criteria and Section 10.2.3 for requirements related to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 for reporting requirements).

For female subjects, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the investigator prior to randomization.

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9.1.16 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for up to 90 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during the course of the study and for 90 days after the last dose of study drug. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below. From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (from the list below). In addition, they must be advised not to donate ova during this period.

* Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as ≥1 year since last regular menses with a follicle-stimulating hormone level >40 IU/L or ≥5 years since last regular menses, confirmed before any study drug is administered).

**Sterilized males should be ≥1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

A highly effective method of contraception is defined as one that has no higher than a 1% failure rate per year when used consistently and correctly. In this study, the only acceptable methods of contraception are as follows:

Hormonal contraception:

- Combined (estrogen and progesterone containing) hormonal contraception associated with the inhibition of ovulation:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - Oral.

- Injectable.
- Implantable.

Double-barrier methods (each time the subject has intercourse):

- Sponge (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.
- Cap (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom with or without spermicidal cream or jelly.

Intrauterine devices:

- Copper T PLUS condom.
- Intrauterine hormone-releasing system.

Sterilization:

- Bilateral tubal occlusion.
- Vasectomized partner (provided that the partner is the sole sexual partner of the study participant and the absence of sperm in the ejaculate has been confirmed).

Abstinence:

- Sexual abstinence, if it is the preferred and usual lifestyle of the subject, will be considered an acceptable method of contraception on a case-by-case basis upon prior approval by the medical monitor. Subjects practicing abstinence as a method of contraception must refrain from heterosexual intercourse throughout the duration of the study (for female and male subjects) and for 30 (female subjects) or 90 (male subjects) days after last dose of study drug.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for:

- avoidance of pregnancy (during the course of the study and for 30 (female subjects) or 90 (male subjects) days after the last dose of study drug).
- donation of ova (during the course of the study and for 30 days after the last dose of study drug).
- sperm donation (during the course of the study and for 90 days after the last dose of study drug).

All female subjects of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at screening (Visit 1). During the study, subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the

study procedures. An additional serum hCG pregnancy test will be performed at the end of Part A/start of Part B (Visit 4).

9.1.17 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, eg, after Visit 2 or within 90 days for a male subject OR within 30 days for a female subject, of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.18 ECG Procedure

A standard 12-lead ECG will be recorded at Visit 1 (Screening) to evaluate subject's eligibility. A standard 12-lead ECG will be recorded in triplicate at predose at Visit 2, and at predose and between 30 to 45 min postdose (~T_{max}) at Visits 5, 8, and 13. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The interpretation of the ECG will be recorded in the source documents and in the eCRF. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval with QTcF, and corrected QT interval. ECG traces recorded on thermal paper will be photocopied to avoid degradation of trace over time.

9.1.19 Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed using the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) [20].

Two versions of the C-SSRS will be used in this study: the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS.

9.1.20 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is withdrawn at the screening visit, the investigator should complete the eCRF. The IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- AE.
- Did not meet entrance criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Withdrawal by subject.
- Study terminated by sponsor.
- Other (specify reason).

Subjects may be rescreened after consultation with the medical monitor.

Subject ID numbers assigned to subjects who fail screening should not be reused. If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were 2 separate subjects. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject ID number and treated as a stand-alone subject.

9.1.21 Documentation of Randomization

Only subjects who meet all the inclusion criteria and none of the exclusion criteria are eligible for randomization into the Part A double-blind treatment period.

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

If the subject is found to be not eligible, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study drug containers/unused study drug and the daily recording in the electronic diary to each dispensing site visit. All subjects should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s). Sequencing of visits per the schedule of assessments shall not be adjusted and must be maintained in order despite the allowance for visit window creating the ability to overlap.

9.3.1 Screening

Eligibility of subjects will be assessed in accordance with predefined inclusion and exclusion criteria as described in Section 7.0 at the screening visit (Visit 1). See Section 9.1.20 for procedures for documenting screening failures. At the screening visit, subjects will be trained on how to use the electronic pain diary. Subjects will be instructed to record pain 3 times a day for a minimum of 6 of the last 7 screening days prior to enrollment into the study and daily (3 times a day) throughout the study after the consent has been signed.

Eligible subjects will be notified by phone of their study entry, after completing the baseline period.

9.3.2 Randomization

Randomization for eligible subjects will take place on Day 1 in Part A (Visit 2), before subjects take the first dose of study drug in the clinic.

If the subject has satisfied all the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IWRS, as described in Section 8.2.

9.3.3 Part A

On Day 1 (Visit 2), after randomization and all predose procedures have been performed, subjects will receive the first dose of double-blind IP (TAK-935 100 mg or matching placebo tablets). The site will contact the subject by phone on Days 4, 10, and 17 to assess safety and tolerability, and discuss adjusting the study drug dosing as needed. The subject will return to the clinic on Visits 3 (Day 7, Week 1), 4 (Day 14, Week 2), 5 (Day 21, Week 3), 6 (Day 49, Week 7), and 7 (Day 77, Week 11) to complete all scheduled assessments, assess safety and tolerability, and adjust study drug dosing as needed.

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

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.

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).

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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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10.1.6 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time informed consent is provided at screening (Visit 1) and continue until early termination or until the follow-up visit (Visit 13, Week 29). For subjects who discontinue prior to study drug administration, AEs are collected until the subject discontinues study participation.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment.

The electronic pain diary will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied (see Section 10.1.2).

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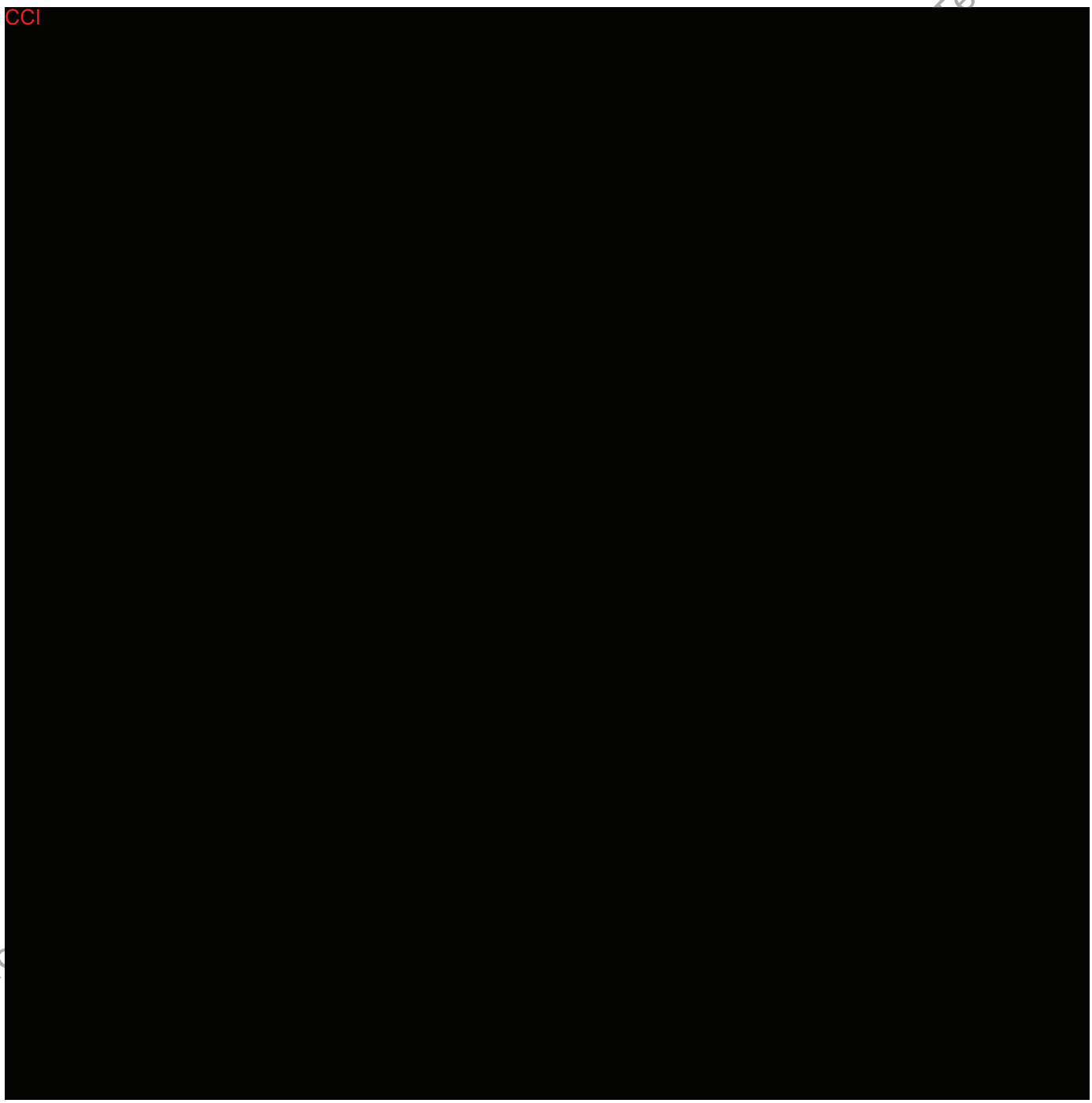

- A urine sample for illicit drug use and a blood alcohol level should be obtained as soon as possible after the convulsion has occurred.
- Document any electrolyte abnormalities or other signs of systemic illness not otherwise evident. Other pertinent laboratory values that should be recorded include the subject's electrolyte panel results, blood urea nitrogen, creatinine, and complete blood count with differential.

AEs of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

All AEs spontaneously reported by the subject or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.2.1 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal Liver Tests

If a subject had ALT or AST elevations >3 × ULN on 2 consecutive occasions, as specified in Section 9.1.11, the abnormality should be recorded as an AE. In addition, a relevant eCRF(s) must be completed providing additional information on relevant recent history, risk factors, clinical signs, symptoms, and results of any additional diagnostic tests performed.

If a subject has elevated ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.11 must also be performed. The relevant eCRF(s) must be completed and transmitted with the SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available later, then the investigator will transmit a follow-up electronic data capture SAE report (or paper-based SAE form if an electronic data capture SAE report is not feasible) or provide other written documentation and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities, including investigators and IRBs, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, suspected unexpected serious adverse reactions will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After submission of the CRFs to the sponsor, any change of, modification of or addition to the data on eCRFs should be made by the investigator with use of change and modification records of eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign and date the form.

After the lock of the study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with the approval from the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source

worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized prior to unblinding of subject's treatment assignment in Part A. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The randomized set will include all subjects who were randomly assigned to treatment through the IWRS.

The full analysis set (FAS) for Parts A and B will include all subjects who were randomized. In efficacy analyses, FAS subjects with both baseline and at least 1 valid postbaseline value will be used for appropriate analyses in Parts A and B. In FAS efficacy summaries, subjects will be analyzed according to the treatment to which they were randomized.

The safety analysis set for Parts A and B will include all subjects who received at least 1 dose of study drug. In safety summaries, subjects will be analyzed according to the treatment they received.

The PK analysis sets for Parts A and B will include all subjects who received at least 1 dose of study drug and have at least 1 measurable TAK-935 or M-1 plasma concentration.

The PD analysis set for Parts A and B will include all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma 24HC concentration.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized and listed for enrolled subjects by treatment group and overall. Descriptive statistics will be used to summarize data for continuous variables such as age and weight (eg, number of subjects, mean, median, standard deviation, and range) and for categorical variables such as sex, ethnicity, and race (number and percentage of subjects within each category). Medical history and medication history will be listed by subject.

13.1.3 Efficacy Analysis

For the primary efficacy endpoint, only subjects with a baseline and at least 1 postdose value will be included in the summary and analyses. The data from the last 7 days prior to the visits on Day 21 (Week 3), Day 105 (Week 15) (or the last dose in Part A, whichever is earlier), Day 147 (Week 21), and Day 203 (Week 29) (or the last dose in Part B, whichever is earlier) will be used to derive the mean 24-hour pain intensity for the corresponding visits.

For Part A, summary statistics will be provided for the observed values of the efficacy measures at baseline and each of the postdose visits by treatment group. Change from baseline and percent change from baseline will also be summarized with descriptive statistics by treatment group.

For Part B, summary statistics will be provided for the observed values of the efficacy measures at each of the postdose visits for all subjects, as well as by treatment group in Part A. Change from baseline and percent change from baseline will also be summarized with descriptive statistics. Baseline will be the baseline for Part A.

For the mean 24-hour pain intensity in Part A derived above, linear mixed models for repeated measurements will be used to evaluate the effect of TAK-935 on the primary and secondary endpoints. The change from baseline in the 24-hour mean pain intensity to the scheduled visits (Day 21, Week 3, Day 105, Week 15) will be the response in the model; baseline, site, visit (Day 21, Week 3, or Day 105, Week 15), treatment, and treatment by visit interaction will be the fixed effects; and a completely unstructured covariance matrix will be assumed. The treatment effect at each visit will be evaluated using the difference in the least-square means of the change from baseline between TAK-935 and placebo; 95% confidence intervals for the differences and p-values will also be provided. Percent of responders will be summarized and compared between treatment arms in Part A.

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13.1.5 Safety Analysis

Descriptive statistics will be used to summarize all safety endpoints, by treatment group as appropriate. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight and BMI, and ECG parameters.

Safety data summaries will be using the safety analysis set.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

13.2 Interim Analysis and Criteria for Early Termination

An unblinded interim analysis will be conducted after all subjects have completed Part A. Subject treatment will be unblinded for this interim analysis. The interim analysis will include the primary and secondary efficacy analysis as well as safety and PK/PD summaries for the data collected during Part A. Because this analysis will be conducted at the end of the double-blind period, this analysis will be considered as the primary efficacy assessment of TAK-935 on CRPS relative to placebo. No alpha spending or adjustment to sample size will be needed based on the results of this analysis.

13.3 Determination of Sample Size

Assuming a standard deviation of 2 and a 12% drop-out rate, a sample size of 24 subjects in total with randomization ratio of 2:1 is sufficient to achieve at least 65% power to detect a difference of 2 between TAK-935 and placebo by a 2-sample t-test on the change from baseline to Week 15 in mean 24-hour pain intensity NPS score at 0.10 2-sided significance level. A difference of 2 is within the accepted range of minimally clinically important difference for the 11-point NPS [1,2].

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the sponsor or its designee and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (if blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] Food and Drug Administration [FDA], the United Kingdom [UK] MHRA, the Pharmaceuticals and Medical Devices Agency [PMDA] of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

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

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.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

Study Period	Screening	Part A, Double-Blind Treatment									Part B, Optional Open-Label Extension								
Day	-28 to -1	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)	218 (±7) Final Follow-up (Part B) [c]
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	13 (ET)	PC
Informed consent	X																		
Inclusion/ Exclusion criteria	X	X (pre dose)																	
Demographics and medical history	X																		
Medication history	X																		
Physical examination	X	X (pre dose)				X		X	X		X		X					X	
Neurological examination, including fundoscopy and visual acuity (if possible)	X	X (pre dose)				X		X	X		X		X					X	
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Vital signs	X	X (pre dose)	X		X		X	X	X	X	X		X		X	X	X	X	
Height [e], weight, and BMI	X	X (pre dose)									X							X	

Study Period	Screening	Part A, Double-Blind Treatment									Part B, Optional Open-Label Extension								
Day	-28 to -1	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)	218 (±7) Final Follow-up (Part B) [c]
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	13 (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	
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.

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 (~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

CCI

[redacted]

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that local requirements or regulations for informed consent, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including (e)CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for subjects, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study, and for 30 days after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use a highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 90 days after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

CCI

CCI

[redacted]

CCI

[redacted]

In summary, the selected dose up-titration over time and the fractionated dosing

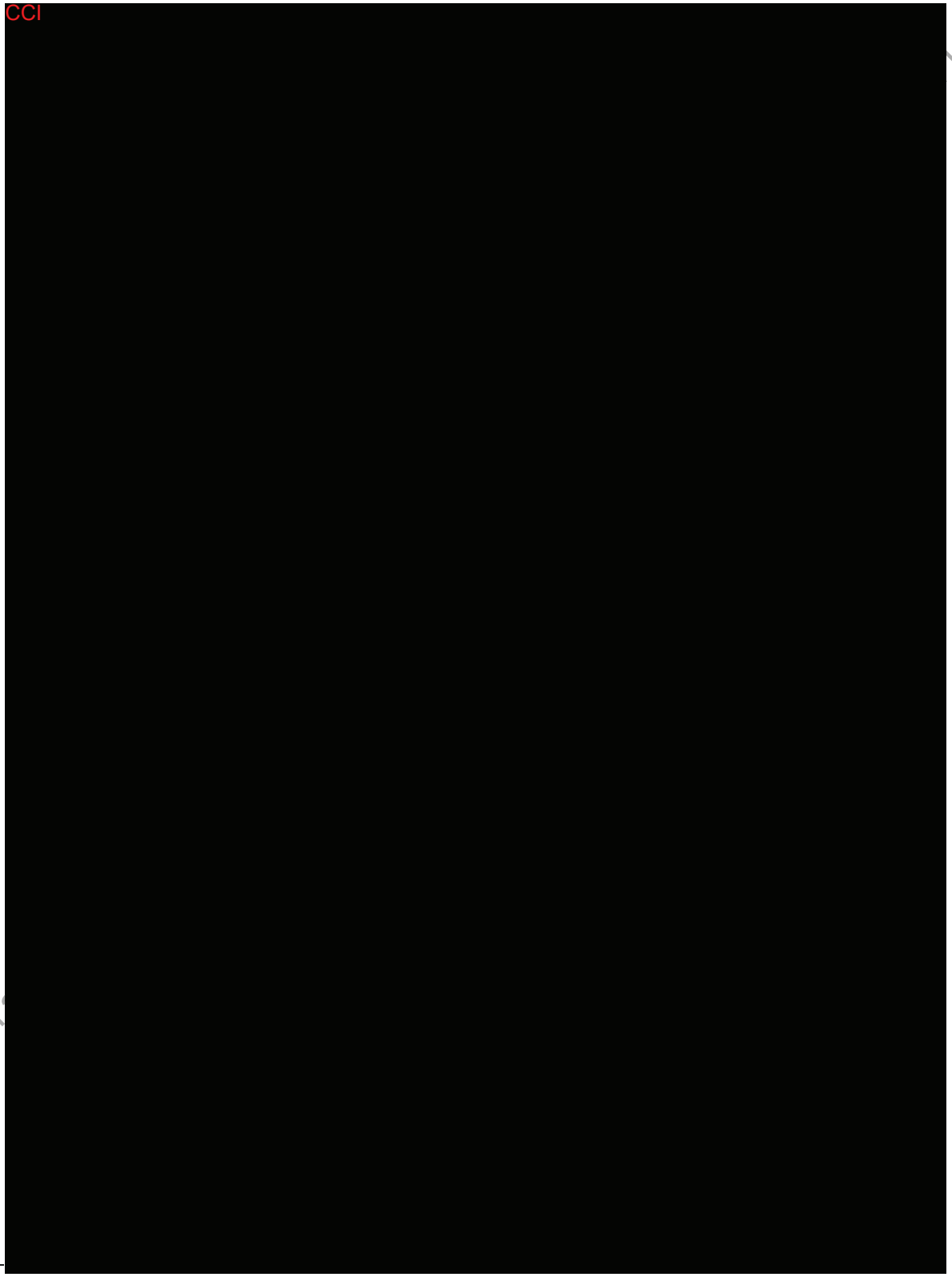
CCI

[redacted]

CCI

[redacted]

CCI



CCI

[redacted]

trough; T(EO>65%): time above EO threshold of at least 65%; $P(EO_{trough}<65\%)$: percentage of

CCI

[redacted]

wording:

- To investigate the effect of TAK-935 on overall function using the Patient Global Impression of Change (PGIC) and the Patient-Reported Outcomes Measurement Information System (PROMIS-29) scale.

CCI [redacted]

- To investigate the effect of TAK-935 on the CRPS Severity Score (CSS).
- To investigate the effect of TAK-935 on responder rate (responder is defined as ≥30% improvement in the 24-hour pain intensity).

Exploratory Objectives

CCI [redacted]

Amended or new wording:

Secondary Objectives

- To investigate the effect of TAK-935 on overall function using the Patient Global Impression of Change (PGIC) and the Patient-Reported Outcomes Measurement Information System (PROMIS-29) scale.

CCI [redacted]

- To investigate the effect of TAK-935 on the CRPS Severity Score (CSS).
- To investigate the effect of TAK-935 on responder rate (responder is defined as ≥30% improvement in the 24-hour pain intensity).

Exploratory Objectives

CCI [redacted]

Rationale for Change: Align bulleting/numbering of objectives for consistency with the numbers/bulleting in the endpoints section.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 5: Modified Figure 4.a.

The change occurs in Section 4.1 Background Figure 4.a:

Description of change: The horizontal axis Day 0 timepoint was changed from 'Day 0' to '6hr post ischemia (Day 0)'.

Rationale for Change: Update information on the CPIP model for better representation of study design.

Change 6: Clarified the rationale for the study.

The primary change occurs in Section 4.2 Rationale for the Proposed Study:

Added text: This study will be the first phase 2a study to test the efficacy, safety, and tolerability of TAK-935 in adults with CRPS. **Based on the mechanism of action, preclinical data on a pertinent model to CRPS and the safety characteristics of the completed and ongoing studies, we propose this phase 2a study that will test the efficacy, safety and tolerability of TAK-935 in adults with CRPS, a highly impacted population with great unmet need.**

Rationale for Change: Update the study rationale with a summary of available preclinical and clinical data.

Change 9: Moved the detail on pharmacogenomic analysis.

The primary change occurs in Section 6.2.3 Endpoints:

Added text: **Pharmacogenomic analysis may be conducted to investigate the contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study subjects in pharmacogenomic sample collection is optional.**

As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

Rationale for Change: Move pharmacogenomic analysis paragraphs from Rationale for the Proposed Study to the Endpoint section.

The following sections also contain this change:

- Section 4.2 Rationale for the Proposed Study

Change 8: Revised contraceptive requirements.

The primary change occurs in Section 9.1.16 Contraception and Pregnancy Avoidance Procedure:

Initial wording:

From signing of informed consent, throughout the duration of the study, and for up to 30 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below. From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list below). In addition, they must be advised not to donate ova during this period.

…

- Sexual abstinence, if it is the preferred and usual lifestyle of the subject, will be considered an acceptable method of contraception on a case-by-case basis upon prior approval by the medical monitor. Subjects practicing abstinence as a method of contraception must refrain from heterosexual intercourse throughout the duration of the study and for 30 days after last dose of study drug.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study and for 30 days after the last dose of study drug.

Amended or new wording:

From signing of informed consent, throughout the duration of the study, and for up to ~~30~~ **90** days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during th~~is period~~**e course of the study and for 90 days after the last dose of study drug**. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective~~/effective~~ contraception below. From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective~~/effective~~ method of contraception (from the list below). In addition, they must be advised not to donate ova during this period.

…

- Sexual abstinence, if it is the preferred and usual lifestyle of the subject, will be considered an acceptable method of contraception on a case-by-case basis upon prior approval by the medical monitor. Subjects practicing abstinence as a method of

contraception must refrain from heterosexual intercourse throughout the duration of the study **(for female and male subjects)** and for 30 **(female subjects) or 90 (male subjects)** days after last dose of study drug.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for**:**

- avoidance of pregnancy **(during the course of the study and for 30 (female subjects) or 90 (male subjects) days after the last dose of study drug),**
- donation of ova **(during the course of the study and for 30 days after the last dose of study drug),**
- ~~and~~ sperm donation **(**during the course of the study and for ~~30~~**90** days after the last dose of study drug**)**.

Rationale for Change: Correct a typographical error.

The following sections also contain this change:

- Section 7.1 Inclusion Criteria
- Section 7.2 Exclusion Criteria
- Section 9.1.17 Pregnancy
- Appendix C Elements of the Subject Informed Consent

Change 9: Modified the detail regarding blood volumes collected during the study.

The primary change occurs in Section 9.1.11 Procedures for Clinical Laboratory Samples:

Initial wording:	All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 5 mL, and the approximate total volume of blood for the study is 15 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.
Amended or new wording:	All samples will be collected in accordance with acceptable laboratory procedures. ~~The maximum~~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 ~~is approximately 5 mL,~~ and the approximate total volume of blood ~~for the study is 15 mL. Details of these procedures and required safety monitoring will be given in the laboratory~~**collected in the study will be given in the laboratory and/or study** manual.

Rationale for Change: Update to reflect that all blood volumes are included in the laboratory and/or study manual (local lab is utilized in this study).

The following sections also contain this change:

- Appendix A Schedule of Study Procedures, footnote 'i'.

Change 10: Clarified the ECG procedures for specific visits.

The primary change occurs in Section 9.1.18 ECG Procedure:

Initial wording:	A standard 12-lead ECG will be recorded in triplicate at predose and between 30 to 45 min postdose (~T_{max}).
Amended or new wording:	**A standard 12-lead ECG will be recorded at Visit 1 (Screening) to evaluate subject's eligibility.** A standard 12-lead ECG will be recorded in triplicate at predose **at Visit 2, and at predose** and between 30 to 45 min postdose (~T_{max}). **at Visits 5, 8, and 13.**

Rationale for Change: Provide clarification on ECG procedures, as per study manual.

The following sections also contain this change:

- Appendix A Schedule of Study Procedures, footnote 'f'.

Change 11: Clarified the efficacy analysis.

The primary change occurs in Section 13.1.3 Efficacy Analysis:

Added text:	**Percent of responders will be summarized and compared between treatment arms in Part A.**

Rationale for Change: Provide additional detail regarding responder rate analysis.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 12: Clarified the exploratory analysis.

The primary change occurs in Section 13.1.4 Exploratory Analysis:

Initial wording:	CCI [redacted]
Amended or new wording:	CCI [redacted]

CCI

Rationale for Change: Correct a typographical error and provide additional detail regarding rescue medication analysis.

Change 13: Clarified the interim analysis.

The primary change occurs in Section 13.2 Interim Analysis and Criteria for Early Termination:

Initial wording:	An unblinded interim analysis will be conducted after all subjects have completed Part A. Subject treatment will be unblinded for this interim analysis. The interim analysis will include the primary efficacy analysis as well as safety summaries for the data collected during Part A.
Amended or new wording:	An unblinded interim analysis will be conducted after all subjects have completed Part A. Subject treatment will be unblinded for this interim analysis. The interim analysis will include the primary **and secondary** efficacy analysis as well as safety **and PK/PD** summaries for the data collected during Part A.

Rationale for Change: Clarify the analysis planned, including secondary and PK/PD summaries.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 14: Clarified when blood samples for plasma protein binding assessment will be collected.

The primary change occurs in Appendix A Schedule of Study Procedures:

Description of change:	Added a separate row for plasma protein binding assessment and added a footnote 'k' to clarify when these samples will be collected.

Rationale for Change: Update blood sample collection recommendations for better clarity to the investigators and site staff.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	16-Dec-2019 20:45 UTC
	Biostatistics Approval	16-Dec-2019 20:50 UTC
	Clinical Approval	16-Dec-2019 20:57 UTC