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

SAP Approve Date: 10 February 2021

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

- Named persons or organizations associated with the study.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-935-2008

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

PHASE 1b/2a

Version**:** 1.0

Date**:** 10 February 2021

Prepared by:

PPD

Based on:

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

Study Title: Study of TAK-935 as an Adjunctive Therapy in Subjects with Complex Regional Pain Syndrome

PPD

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

24HC	24S-hydroxycholesterol
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BA	bioavailability
BID	twice daily
BMI	body mass index
$C_{av,ss}$	average concentration during a dosing interval at steady-state
CFR	Code of Federal Regulations
CH24H	Cholesterol 24-hydroxylase
CNS	central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
M-I	metabolite of TAK-935
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPS	per-protocol set
PTZ	pentylenetetrazol

QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

4.0 OBJECTIVES

4.1 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.

4.2 Secondary Objectives

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

4.3 Exploratory Objectives

CCI [redacted]

4.4 Safety Objectives

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

4.5 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension period in adult subjects aged ≥18 and ≤75 years with chronic CRPS (symptoms ≥6 months, diagnosed using the Budapest criteria). The primary objective will be to evaluate the efficacy of TAK-935 as an adjunctive therapy in the treatment of chronic CRPS as measured by the reduction in the NPS (an 11-point scale by electronic pain diary (e-diary)). This study will also evaluate efficacy of TAK-935 as measured by PROMIS-29 version 2.1, PGIC, CSS version 2, responder rate and the use of rescue medications.

Approximately 24 subjects will be randomized to ensure 21 completers in the double-blind phase of the study. The randomization ratio 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.

- Part B: Open-Label Extension.
  - 2-week titration period.
  - 12-week open label.
  - Taper period (maximum 6 days)/Follow-up (15 days after last dose of study drug)

Part A: Double-Blind Treatment (19-22 weeks including screening, titration, maintenance, and, if the subject does not continue into the open-label extension period, taper if needed and follow-up periods):

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 meet all inclusion criteria and none of the exclusion criteria at the screening visit will be asked to enter pain score daily in an electronic pain diary. 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 in NPS; The average 24-hour pain intensity score for a given day will be calculated as the mean of the 3 measurements collected for the day.

The baseline pain intensity is defined as the mean of the average screening 24-hour pain intensity score for the last 7 days before the first dose. Missing pain score entries will not be imputed. 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. At the same visit, after randomization and all pre-dose 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. 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 the 3-week titration period, 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 daily pain intensity will be collected 3 times a day using the electronic pain diary throughout Part A. Dosing information will also be entered using the same device.

The average pain intensity score for Visit 5 (Day 21, Week 3) and Visit 8 (Day 105, Week 15) (or the last dose in Part A) will be calculated as the mean of the average 24-hour pain intensity score collected during the last 7 days before the corresponding visit. No imputation will be performed for missing pain score entries.

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.

Any change in dose will be documented in the subject's clinic chart and dosing card. 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.

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

Following the 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 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 (16-17 weeks, including titration, maintenance, taper if needed, and follow-up periods):

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 received in Part A at Visit 8 (Day 105, Week 15). Subjects will remain at 200 mg BID for 1 week. The site will contact the subject by telephone on Day 108 (3 days after initiation of this dose) 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 the assigned dose, 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.

Any change in dose will be documented in the subject's clinic chart and dosing card. 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.

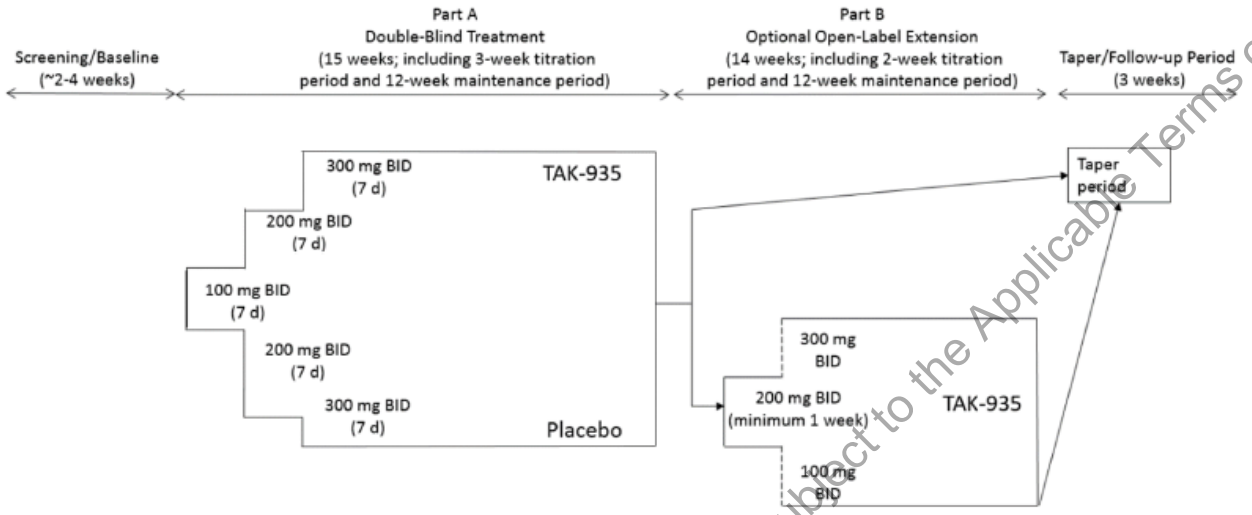
The average pain intensity score for Visit 11 (Day 147, Week 21) and Visit 13 (Day 203, Week 29) (or the last dose in Part B) will be calculated as the mean of the average 24-hour pain intensity score collected during the last 7 days before the corresponding visit. No imputation will be performed for missing pain score entries.

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 4.a. A schedule of study procedures is listed in Appendix A of the protocol.

Figure 4.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 (i.e., the subject still has pain), the dose will be increased to the next higher level. The maximum dose is 300 mg BID.

Following completion of Part A, subjects will have the option to continue into Part B, a 14-week open-label drug extension study 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.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

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

5.2 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 mean 24-hour pain intensity NPS) by the end of Part A (Week 15).

- Change and percent change of the PROMIS-29 version 2.1 total score from baseline to the end of Part A (Week 15).
- PGIC at the end of Part A (Week 15).
- Change and percent change of CSS from baseline to the end of Part A (Week 15).

5.3 Exploratory Endpoints

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5.4 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, and electrocardiogram parameter values after treatment in Part A and Part B.

6.0 DETERMINATION OF SAMPLE SIZE

Assuming a common standard deviation of 2 in the change of 7-day average pain score and a 12% drop-out rate, a sample size of 24 subjects in total with a randomization ratio of 2:1 is sufficient to achieve at least 65% power to detect a difference of 2 between TAK-935 and placebo using 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 in the 11-point NPS is within the accepted range of minimally clinically important difference in treating complex regional pain syndrome[1,2].

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

The Statistical Analysis Plan (SAP) should be read in conjunction with the study protocol and electronic case report forms (eCRFs).

All study-related raw data and derived data will be presented in data listings. Continuous variables will be summarized using the number of subjects with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values. Where indicated, coefficient of variation (CV%) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate. The denominator for the percentages will be based on the number of subjects who provide non-missing responses to the categorical variable.

Where applicable, variables will be summarized descriptively by study visit.

All confidence intervals (CI) and the *p*-values in statistical tests will be reported as 2-sided and the statistical significance will be assessed at a type-I error rate, α, of 0.10 significance level unless otherwise stated. The *p*-values will be rounded to 4 decimal places prior to assessment of statistical significance.

The means and medians will be presented in 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented in 2 more decimal places than the recorded data. The confidence interval of a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

7.1.1 Definition of Study Day and Baseline

Study day will be calculated relative to the date of the first dosing in Part A. Study day prior to the first dosing will be calculated as: date of assessment/event – date of first dosing; study day on or after the date of first dose of treatment will be calculated as: date of assessment/event – date of first dosing + 1.

In general, the baseline characteristics for the entire study will be defined as the last non-missing measurements prior to first dose of study drug in Part A. The baseline pain intensity for both Part A and Part B will be the screening average pain score, defined as the mean of the daily average screening 24-hour pain intensity score in the last 7 days before the first dose in Part A. The baseline reference values for clinical laboratory test results, vital sign measurements, C-SSRS, and ECG parameters in both Parts A and B will be the last non-missing measurements prior to the first dose of study drug in Part A. The baseline values in the exploratory endpoints for Part B will also be the corresponding values before the first dose of study drug in Part A.

Both date and time of the measurement and the dosing date and time should be used when determining the baseline if possible. In the case where the last non-missing measurement (except AE and concomitant medications) and the first dose in Part A coincide at the same time, or the same date if time of the measurement is not collected, that measurement will be considered as baseline value.

7.1.2 Conventions for Missing Data

There will be no imputation of incomplete or missing data other than the AE and concomitant medication dates mentioned in the two sections below.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summarization of concentration values. These values will be flagged in the data listings and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

7.1.3 Conventions for Missing Adverse Event Dates

Adverse events with completely or partially missing dates will be imputed as follows in order to determine the associated period. The listings will only display dates as entered.

7.1.3.1 Imputation of missing or partial dates of AE start dates

- Month/year available and day missing:
  - If the month and year are the same as those in the first dose date in Part A and the event is not indicated as a pre-treatment event, the first dose date in Part A is to be used to impute the start date.
  - If the month and year are the same as those in the first dose date in Part A and the event is indicated as a pre-treatment event, the date prior to the day of the first dose in Part A is to be used to impute the AE start date. If the date prior to the day of the first dose in Part A is in previous month/year, set the AE start month/year to the previous month/year.
  - If the month and year are after the first dose date in Part A and the same as or before the last dose date in Part A plus 15 days for patients who do not continue to Part B or before the first dose date in Part B, the first of the month will be used for the start date.
  - If the month and year are the same as the first dose date in Part B and the same as the last dose date in Part A, the first of the month will be used for the start date.
  - If the month and year are the same as the first dose date in Part B and after the last dose date in Part A, then the event is considered as a treatment emergent for Part B and the first dose date in Part B is to be used to impute the start date.
  - If the month and year are after the first dose date in Part B, the first day of the month will be used for the start date.
- Year available and month/day missing:
  - If the year is the same as the year of the first dose date in Part A and same as or before the first dose in Part B and the event is not indicated as a pre-treatment event, the first dose date in Part A is to be used to impute the AE start date.
  - If the year is the same as the year of the first dose date in Part A and same as or before the first dose in Part B and the event is indicated as a pre-treatment event, the date prior to the day of the first dose in Part A is to be used to impute the AE start date. If the date

prior to the day of the first dose in Part A is in previous month/year, set the start month/year to the previous month/year.

- If the year is the same as the year of the first dose in Part B and after the year of the last dose in Part A, the first dose date in Part B is to be used to impute the AE start date.
- If the year is not the same as the year of the first dose date in Part A or the year of first dose date in Part B, set the start date as January 1.

- Year/month/day all missing:
  - If the event is not indicated as a pre-treatment event, the first dose date in Part A is to be used to impute the AE start date.
  - If the event is indicated as a pre-treatment event, the date prior to the first dose date in Part A is to be used to impute the AE start date.

7.1.3.2 Imputation of missing or partial dates of AE end dates

If the event is indicated as ongoing at the end of the study, no imputation is needed.

If the event is not indicated as ongoing:

- Month/year available and day missing:
  - Use the last day of the month to impute the AE end date. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.
- Year available and month/day missing:
  - If the year is the same as or before the year of the last dose in Part B, set the end date as December 31.
  - If the year is after the year of the last dose in Part B, set the end date as January 1.
- Year/month/day all missing:
  - Impute the end date as December 31 of the Part B last dose year. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.

7.1.4 Conventions for Missing Concomitant Medication Dates

Concomitant medications with completely or partially missing dates will be imputed as follows. Note the imputed dates are used in determining the associated period. The listings will only display dates as entered.

7.1.4.1 Imputation of missing or partial dates of concomitant medication start dates

- Month/year available and day missing:
  - The first day of the month will be used for the start date.
- Year available and month/day missing:
  - Set the start date as January 1.
- Year/month/day all missing:
  - If date of birth is available, use the date of birth as the start date.
  - If date of birth is not available, estimate date of birth using the screening date and age, and use the estimated date of birth as the start date.

7.1.4.2 Imputation of missing or partial dates of concomitant medication end dates

If the concomitant medication is indicated as ongoing, no imputation is needed.

If the concomitant medication is not indicated as ongoing, use the same algorithm in Section 7.1.2.2 to impute.

7.2 Analysis Sets

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

The PK 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 post-dose measurable TAK-935 or M-I plasma concentration. PK analysis performed for Part B separately will include subjects who have received at least 1 dose of TAK-935 in Part B and have at least one post-dose measurable TAK-935 or M-I plasma concentration in Part B.

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. PD analysis performed for Part B separately will include subjects who have received at least 1 dose of TAK-935 in Part B and have at least one measurable plasma 24HC concentration.

The full analysis set (FAS) for Parts A and B will include all subjects who were randomized, received at least 1 dose of study drug, and have at least 1 valid post-baseline value for the assessment of average 24-hour pain score in Part A or Part B. Efficacy analyses performed for Part B separately will include subjects who have received at least 1 dose of TAK-935 in Part B and have at least one valid 7-day NPS assessment during Part B. In FAS efficacy summaries, subjects will be analyzed according to the treatment they received.

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 actual treatment they received. Safety analysis performed for Part B separately will include subjects who have received at least 1 dose of TAK-935 in Part B.

7.3 Disposition of Subjects

Study information will be presented, including date first subject signed the Informed Consent Form, date of first dose of study drug, date of last subject's last visit/contact in Part A and Part B, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Regulatory Activities (MedDRA) Version, World Health Organization Drug Dictionary Version (WHODRUG), and SAS Version.

Disposition of all screened subjects (denominator) will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

The number of randomized subjects in each study site will be summarized by treatment group (placebo or TAK-935) and overall.

Among randomized subjects, the number and percentage of subjects who complete study drug and all study visits in Part A of the study, prematurely discontinue study drug and study visits in Part A will be summarized by treatment group (placebo or TAK-935), final maintenance dose regimen (100, 200, or 300 mg BID), and overall for all randomized subjects in the double-blind period. For all the subjects who continue in Part B of the study, the number and percentage of subjects who complete study drug and all study visits in Part B, prematurely discontinue study drug and study visits in Part B will be summarized for Part B overall. The number of patients who prematurely discontinue study drug does not include those who have completed the study drug in the maintenance period but not the taper period. The number of patients who prematurely discontinue study visits does not include those who have completed visits in the maintenance period but not the safety follow-up phone call. For each study Part, the primary reason for discontinuation of study drug/visits, as entered on the electronic case report form (eCRF), will be tabulated. The date of first dose, date of last dose, duration of treatment and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings. Disposition of screen failure subjects in Part A will be summarized descriptively. Primary reasons for failure will be summarized and will be presented in a data listing.

The number and percentage of subjects who comprised each analysis set will be summarized by treatment group, final maintenance dose regimen, overall in Part A, and overall in Part B.

Details for important (significant) protocol deviations for subjects in Safety analysis set will be summarized in a table and provided in a data listing.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics (e.g., age, sex, ethnicity, race as described by the subject, smoking status at screening, disease characteristics and substance use) will be summarized and listed for subjects by treatment group (placebo or TAK-935) and overall using the safety analysis set in Part A. Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables (e.g., age, and weight), and the number and percentage of subjects within each category will be presented for categorical variables (e.g., sex, ethnicity, race). No inferential statistics will be presented. Individual subject demographic and baseline characteristic data will be listed.

Demographic variables of screen failure subjects and reasons for screen failure will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, any available safety data and reason for screen failure will also be presented in the data listing.

7.5 Medical History and Concurrent Medical Conditions

Medical history refers to the significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases present at signing of informed consent.

Medical history and concurrent medical conditions will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA, version 19.0) and will be summarized by treatment group and overall in Part A, using System Organ Class (SOC) and MedDRA preferred term. The table will include number and percentages of subjects and will be sorted in alphabetical order by system organ class and preferred term. A subject will only be counted once within a class even if he/she has multiple conditions/symptoms. Summaries will be based on the safety analysis set and presented for Part A only.

Part A period will begin with the signing of the informed consent. Part B period will begin with the first dose in Week 15 visit.

All medical history and concurrent medical condition data will also be presented in listings.

7.6 Medication History and Concomitant Medications

Medication history 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 informed consent. The timeframe for medication history for Part A will be within 6 months prior to signing the informed consent. Medications used anytime from the signing of the informed consent to right before the first dose in Part B if enrolled in Part B, or, if not enrolled in Part B, the last dose (including taper period if applicable) in Part A, will be considered concomitant medications for Part A. Medications used anytime from the first dose in Part B to the last dose (including taper period if applicable) will be considered concomitant medications for Part B.

Summaries of medication history and concomitant medications will be based on the safety analysis set. Summaries of medication history will be presented for Part A only. Concomitant medications that started and ended prior to the first dose will be summarized for Part A. Concomitant medications started prior to the first dose and ongoing on the day of the first dose, or started after the first dose will be summarized for Part A and Part B.

No inferential statistics will be presented. All prior and concomitant medications data will be summarized by treatment group and overall and presented in listings.

7.7 Study Drug Exposure and Compliance

The start and end dates and time of each dose for each subject in the safety analysis set will be reported in a data listing. Summaries of study drug exposure data will be provided by treatment

received (TAK-935 or placebo) and overall using the safety analysis set. No inferential statistics will be presented.

The duration of exposure (days) to the double-blind study medication in Part A is defined as (date of the last dose of double-blind study drug – date of first dose of double-blind study drug + 1). For patients who do not enter Part B, the date of last dose of study drug will be the date of last dose before tapering where applicable, and the overall duration of exposure to the TAK-935 will be the same as the duration of exposure in Part A. The duration of exposure to the open-label study medication in Part B is defined as (date of last dose of open-label study drug before tapering – date of first dose of open-label study drug + 1). For patients who are on placebo in Part A and dosed in Part B, the overall duration of exposure to the TAK-935 will be the same as the duration of exposure in Part B. For patients who have been treated in both Parts A and B with active drug (TAK-935), the overall duration of exposure to the TAK-935 is defined as (date of last dose of open-label study drug before tapering – date of first dose of double-blind study drug +1).

The date of last dose of study drug in Part A and Part B will be obtained from the e-diary and derived from drug accountability data where available. The date of the last dose of study drug in a study period will be the date of the last non-missing dose date before the tapering period in the corresponding study period. The date of the last dose of study drug based on drug accountability will be estimated as the last drug dispense date plus the number of days the drug was taken based on the last drug accountability form. When the two derived dates are different, the date based on drug accountability data, if available, will be used.

The duration of double-blind treatment in Part A will be summarized by treatment group as a continuous variable and, additionally, classified by the following categories: 1 to 21 days, 22 to 97, 98 to 119, 120-189, and 190 days or more. The intervals are calculated based on the actual recorded study days and the treatment termination date.

In Part A of the study, subjects are to take 100 mg/200 mg/300 mg of TAK-935 or matching placebo twice each day. In Part B, subjects are to take 100 mg/200 mg/300 mg TAK-935 twice daily. Overall percent study drug compliance for each period (Part A and Part B) will be calculated as:

$$\text{Drug compliance (\%) based on e-diary} = 100 \cdot \frac{\text{number of times the correct dose is taken}}{\text{number of times dosing information is recorded}}$$

$$\text{Drug compliance (\%) based on pill count} = 100 \ \frac{\text{number of tablets taken}}{\text{expected number of tablets to be taken}}$$

where expected number of tablets to be taken = [number of tablets to be taken daily*(date of last dose of medication – date of first dose of medication + 1)].

$$\text{e-diary pain score entry compliance (\%)} = 100 \cdot \frac{\text{number of times pain score is entered in the period}}{3 \times \text{number of days on the study in the period}}$$

$$\text{e-diary dosing entry compliance (\%)} = 100 \cdot \frac{\text{number of times dosing information is entered in the period}}{2 \times \text{number of days on the study in the period}}$$

All compliance measures will be presented to 1 decimal place in the derived dataset and Table, Figures, and Listings (TFLs) outputs.

All measures of study drug compliance and e-diary compliance in Part A and Part B will be summarized separately using descriptive statistics. and by the number of subjects in each of the following compliance categories: <70%, ≥70 to <85%, and ≥85 to ≤100%. For drug compliance by pill count, two additional categories, >100%, and missing, might be necessary.

All study drug administration (double-blind placebo in Part A, double-blind active (TAK-935) drug in Part A, and open-label study drug in Part B) and accountability data will be listed by subject number. The following variables will be listed for drug accountability: subject identifier, drug category, date and number of tablets dispensed and returned, and Drug compliance in Part A and Part B by pill count.

7.8 Efficacy Analysis

Efficacy analysis on numeric pain score, PROMIS-29, Patient Global Impression of Change (PGIC) and CPRS Severity Scale (CSS) will be performed based on FAS.

The weekly NPS for the visits on Weeks 3, 15, and 29 is the average of 24-hour pain scores in the last 7 days prior to the corresponding visit. The 24-hour pain score is the average of the pain scores recorded for the day. The 24-hour pain score is missing for a day when no pain score is recorded for the day. The 7-day average NPS is the average of the non-missing 24-hour pain score during the 7 days.

7.8.1 Primary Efficacy Endpoint

For the primary efficacy endpoint, only subjects with a screening baseline and at least 1 post-dose efficacy measurement will be included in the summary and analyses. The average 24-hour pain intensity score is defined as the mean of the recorded NPS (morning, afternoon and evening) of the day. The weekly NPS of a week is defined as the mean of the average 24-hour pain intensity score of the week. Summary statistics and plots of the mean and standard deviation of weekly average daily pain score for baseline and each subsequent week from Week 1 to Week 15 will be provided by treatment group. The baseline NPS is defined as the mean of the average screening 24-hour pain intensity score for the last 7 screening days before the first dose of study drug in Part A. The weekly NPS is defined as the mean of the average 24-hour pain intensity score in each week following the first dose, with Study Visit 2 (Day 1) as the first day in the first week. All subsequent weeks in Part A will be defined relative to Day 1. The change and percent change from baseline for each week from Week 1 to Week 15 will also be summarized and the change from baseline will be plotted. For subjects with no more than one day of NPS records for a week, the weekly NPS will be considered missing for the week.

For the mean 24-hour pain intensity in Part A, linear mixed models for repeated measurements will be used to evaluate the effect of TAK-935 on the primary endpoint. The change from baseline in the weekly average daily pain intensity to the scheduled visits (Day 21/Week 3, Day

105/Week 15) will be the response in the model; baseline NPS, site, visit (Day 21/Week 3, or Day 105/Week 15), treatment, and treatment by visit interaction will be the fixed effects, and subject the random effect. A completely unstructured covariance matrix will be assumed. In case a model does not converge, AR(1) or compound symmetry covariance matrix may be assumed. The week 3 NPS will be based on the records from the last 7 days prior to the visits on Day 21 (Week 3), or the last dose in Part A, whichever is earlier. The week 15 NPS will be based on the records from the last 7 days prior to the visits on Day 105 (Week 15), or the last dose in Part A if it is after 3 weeks, whichever is earlier, 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.

As a sensitivity analysis, a linear mixed model based on all weekly average daily pain intensity from Week 3 to Week 15, where available, will also be used to assess the efficacy of TAK-935 compared to Placebo. The baseline and weekly NPS are as defined as those used for weekly summary statistics. The model will be similar to the one used for primary analysis except all the available weekly mean 24-hour NPS scores from Week 3 to Week 15 will be included.

An additional sensitivity analysis will be performed using the same linear mixed model based on all weekly average NPS but including only subjects in the Placebo arm and subjects with at least 70% drug compliance in TAK-935 arm.

7.8.2 Secondary Efficacy Endpoints

Percentage change in mean 24-hour pain intensity will be analyzed similarly as in the primary analysis. Percentage change will be calculated based on the baseline and weekly NPS as defined in the summary statistics for the weekly NPS. Summary statistics of percentage change for each week will be summarized by treatment group from Week1 to Week 15.

Percent of responders will be summarized weekly from Week 1 to Week 29 by treatment group based on the baseline and weekly NPS as described in the summary statistics for weekly NPS. In a given week, a responder is defined as a subject with ≥30% improvement in the weekly average 24-hour pain intensity for the week compared to baseline. The proportion is calculated based on the number of subjects with average NPS for the week.

Summary statistics will be provided for other efficacy measures at baseline (PROMIS-29 and CSS) and the Week 15 and Week 29 visits (PROMIS-29, CSS and PGIC) by treatment received in Part A and overall. The PGIC scale at the end of Week 15 and Week 29 will be summarized as a categorical variable. Change from baseline and percent change from baseline for PROMIS-29 (T-score for each domain) and CSS total score will also be summarized with descriptive statistics by treatment received. CSS total score is the number of "Yes" answers to the questions on the 8 symptoms and 8 signs when all 16 questions are answered. The change in mean CSS total score from baseline to the end of Week 15 will be compared between treatment and placebo using a two-sample t-test. In addition to the overall CSS score, the number and proportion of subjects with a "Yes" answer to each of the 16 questions will be summarized for baseline and Weeks 15 and 29 by treatment received in Part A and overall.

The PROMIS-29 instrument consists of seven domains (short forms) related to physical, mental and social health with 4 questions in each domain as well as one 11-point rating scale (0-10) for pain intensity. The scoring of each of the seven domains (physical functioning, anxiety, depression, fatigue, pain interference, sleep disturbance, and satisfaction with social role participation) in PROMIS-29 will depend on whether a respondent has answered all items in the domain. If a respondent skips an item, the scoring will be based on the response pattern scoring provided by the Health Measures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice). For patients who have answered all questions, the scoring will be based on the score conversion table in Appendix D. First, find the total raw score for a short form with all questions answered by summing the scores of the response to each question. Then locate the applicable score conversion table in Appendix 1 and convert the total raw score into a T-score for the domain for each participant. The summary statistics will be provided for each of the seven domains separately.

7.8.3 Exploratory Endpoints

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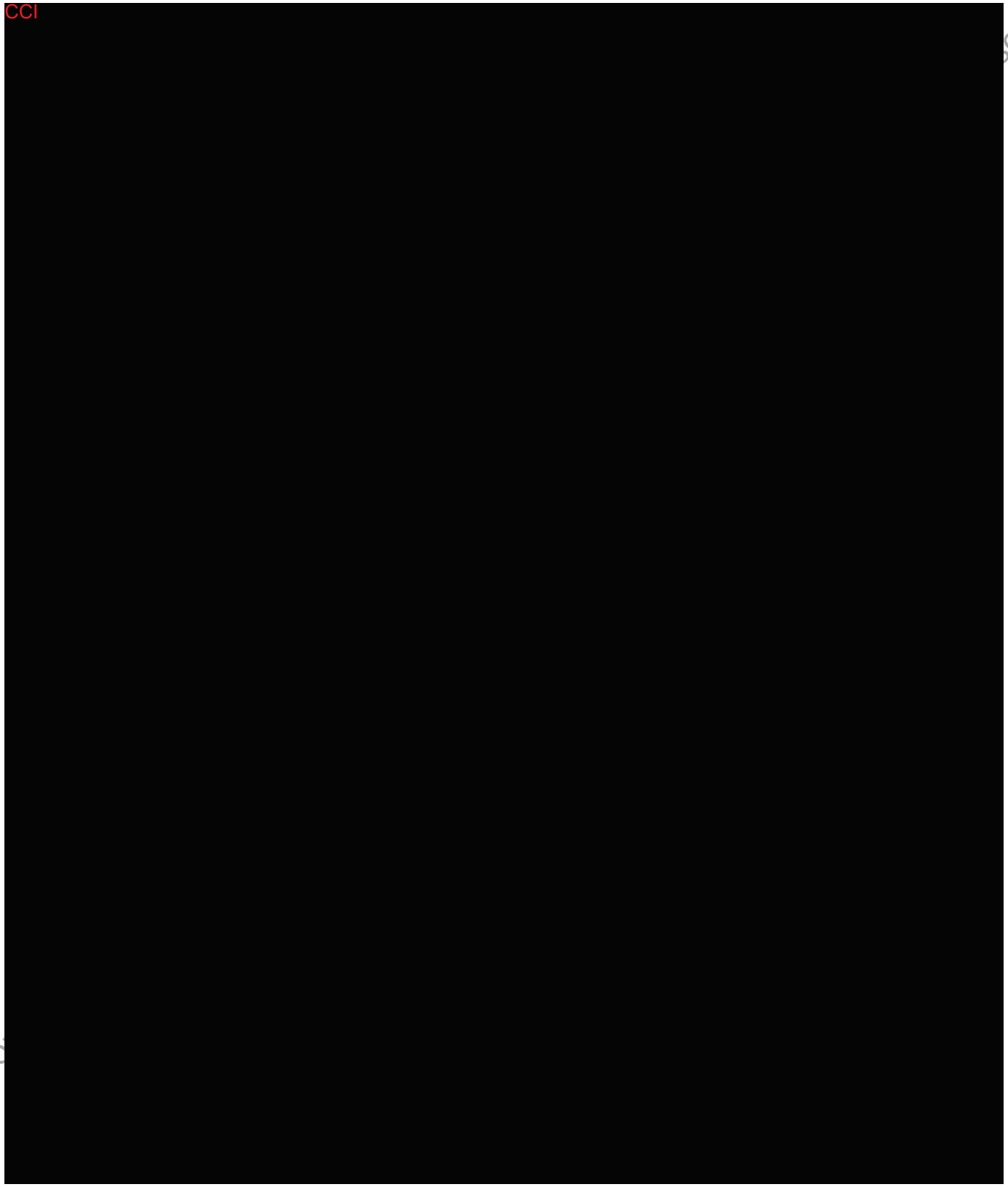

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7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

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7.9.2 Pharmacodynamic Analysis

7.9.2.1 Pharmacodynamic Concentrations

Blood samples for the measurement of 24HC levels in plasma will be collected according to the schedule shown in Appendix A of the protocol.

The PD measures of the plasma 24HC levels will be listed for each subject and summarized (N, mean, SD, median, minimum, and maximum) by each time point for each dose regimen and study period.

A population PK/PD analysis approach will be used to determine the population estimates for TAK-935. The PK and PD analysis will be described in a separate analysis plan, and the parameters for TAK-935 will be summarized in a separate population PK/PD report where data allow.

Correlation between 7-day average daily pain score and plasma 24HC levels during the double-blind and open-label treatment periods will also be evaluated. At each post-baseline visit where 24HC data are available, scatterplot of change in average weekly pain score from baseline against change in trough plasma 24HC levels will also be generated.

7.10 Other Outcomes

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7.11 Safety Analysis

Safety analyses include adverse events (AEs), clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters. The safety analysis set will be used for all summaries of safety parameters. The safety endpoints will be summarized by Part A and Part B separately, and additionally for Part A and B combined. For each period, summary statistics will be provided by treatment received at the start datetime of the AE (Placebo and TAK-935 for Part A and TAK-935 for Part B) and overall. The listings will include treatment and dose level at the start datetime of the corresponding AE.

For the analyses of AEs, for subjects who did not enter Part B, the Part A period will be from the first dose in Part A up to 15 days (onset date – last date of dose + 1 ≤15) after the last dose of study drug in Part A, including the taper period. For subjects who entered Part B, the Part A period is from the first dose in Part A up to right before the first dose in Part B, and the Part B period will be from the first dose in Part B up to 15 days (onset date –date of last dose + 1 ≤15) after the last dose of study drug in Part B including the taper period.

For the analyses of safety laboratory parameters, vital signs and ECG, week 15 will be summarized in part A. Otherwise, the data handling should be same as how it is described in the context of analyses of AEs above.

The safety endpoints include:

- 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, and electrocardiogram parameter values after treatment in Part A and Part B.

7.11.1 Adverse Events

A Pre-Treatment 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 medication; a causal relationship with study participation is not required.

A treatment-emergent adverse event (TEAE) is defined as any untoward medical occurrence in a clinical investigation subject after the administration of a study drug; it does not necessarily have to have a causal relationship with this treatment. PTE and TEAE verbatim terms will be coded by SOC and PT using MedDRA (version 19 or later).

TEAEs for Part A will be defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, that occurs after the first dose of study drug received in Part A and, for those not enrolled in Part B, up to 15 days (onset date – last date of dose + 1 ≤ 15) after the last dose of study drug in Part A, or for those enrolled in Part B, before the first dose of study drug in Part B. AEs that occur on the same day as the first dose of study drug in Part A but with missing time will be considered as TEAEs for Part A.

TEAEs for Part B will be defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, that occurs after the first dose of study drug received in Part B and up to 15 days (onset date –date of last dose + 1 ≤ 15) after the last dose of study drug in Part B. AEs that occur on the same day as the first dose of study drug in Part B but with missing time will be considered as TEAEs for Part B.

TEAEs for Part A and B combined will be defined as any sign, symptom, syndrome, or new illness, regardless of relationship to study drug, that occur after the first dose of study drug received in Part A and up to 15 days (onset date –date of last dose + 1 ≤ 15) after the last dose of study drug in Part B. AEs that occur on the same day as the first dose of study drug in Part A but with missing time will be considered as TEAEs for Part A and B.

TEAEs will be presented by severity (mild, moderate, and severe). Serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death will also be summarized using SOC and PT.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs under the same treatment or TAK-935 dose level in the same study period are coded to the same SOC or PT. For the intensity

or relatedness summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE with maximum intensity or strongest relationship will be included in the summary.

AEs with missing severity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. Similarly, if the relationship of an event is missing, the event will be considered as related but in listings it will be presented as missing.

In general, TEAEs will be tabulated at the following levels: overall summary (subjects with at least 1 AE in any dose or treatment), the MedDRA SOC, and the MedDRA PT. The tables will include the number and percentage (N (%)) of subjects. The following summary tables will be generated for each study part (Part A, Part B, and Parts A and B combined) and summarized by treatment received Part A and overall:

- Overview of Treatment-Emergent Adverse Events.
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Most Frequent (>5%) Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Pretreatment Adverse Events by System Organ Class and Preferred Term (Part A only).

In addition, subject mappings for the TEAEs by SOC and PT will be generated.

Data listings will be provided for PTEs, TEAEs, TEAEs leading to study drug discontinuation, SAEs, CCI [redacted], and AEs that resulted in death.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory tests (hematology, serum chemistry and urinalysis) will be analyzed using the safety analysis set and will be evaluated and presented using International System of Units (SI) unless otherwise stated. Table 9.a in the protocol shows a list of all clinical laboratory tests.

All laboratory test parameters will be displayed in individual subject data listings in both SI units and conventional (CV) units. For test results not in SI units, the conversion to SI units will be done in derived analysis data sets using the known conversion factors. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived dataset. All summaries and analyses will be based on the values using these preferred SI units.

Only observations within 15 days of the last dose of study drug will be included in the tables. No inferential statistics will be presented unless otherwise stated.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for the observed and change from baseline values will be presented for Parts A and B. Study baseline defined in Section 7.1.1 will be used for change from baseline in each part of the study. Note that character urinalysis tests will only be listed.

Laboratory Markedly Abnormal Values (MAVs), identified by the criteria defined in Appendix A, will be tabulated. If a subject has a MAV for a particular laboratory test, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal laboratory test result will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries if MAV criteria are satisfied.

All clinical laboratory data will be presented in both SI and conventional units in data listings.

7.11.3 Vital Signs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to summarize vital sign parameters (body temperature, respiratory rate, systolic BP, diastolic BP, and pulse) at baseline, each post-baseline visit, and change from baseline to each post-baseline visit for both Parts A and B. Study baseline defined in Section 7.1.1 will be used. Only observations within 7 days of the study drug will be included in the tables.

Vital sign MAVs, identified by the criteria defined in Appendix B, will be tabulated. If a subject has a MAV for a particular vital sign parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal vital signs measurement will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries if MAV criteria are satisfied.

All vital signs will be listed in a data listing.

7.11.4 12-Lead ECGs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of ECG parameters, including heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (Fridericia's corrections), will be presented for baseline, each post-baseline visit, and change from baseline to each post-baseline visit for both Parts A and B. Study baseline defined in Section 7.1.1 will be used. All measurements, including those during unscheduled visits, will be provided in data listings, but only the scheduled measurements will be included in the summary. Only observations within 7 days of the study drug will be included in the tables. No inferential statistics will be presented.

ECG MAVs, identified by the criteria defined in Appendix C, will be tabulated. If a subject has a MAV for a particular 12-lead ECG parameter, all visits for that subject for that parameter will be

listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal 12-lead ECG measurement will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

Overall ECG interpretation category (normal, abnormal not clinically significant, abnormal clinically significant, not evaluable) is collected by eCRF at baseline and at each scheduled post-baseline visit. Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations, not evaluable, with missing, if applicable, and total categories by each treatment (placebo, TAK-935).

All ECG parameters will be listed in a data listing.

7.12 Interim Analysis

An unblinded interim analysis will be conducted after all subjects have completed Part A but prior to the completion of Part B of the study. An unblinded team not involved in the study conduct or the program will perform the unblinded analysis in order not to introduce bias to the conduct or analysis of the study. No modification of sample size will be made based on the analysis. The investigators and study sites will not have access to the results of the interim analysis until the final unblinding of the study.

The interim analysis will include the primary and secondary efficacy analysis, safety summaries, as well as descriptive summary statistics of TAK-935 plasma concentration and 24HC for each dose regimen based on the data collected during Part A. If the preparation and analysis of PK and PD data takes significantly longer than the clinical and safety data, the results can be delivered separately. 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 will be needed.

8.0 REFERENCES

1. Goebel A, Bisla J, Carganillo R, Frank B, Gupta R, Kelly J, et al. Low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome: a randomized trial. Ann Intern Med 2017;167(7):476-83.
2. Maughan EF, Lewis JS. Outcome measures in chronic low back pain. Eur Spine J 2010;19(9):1484-94.

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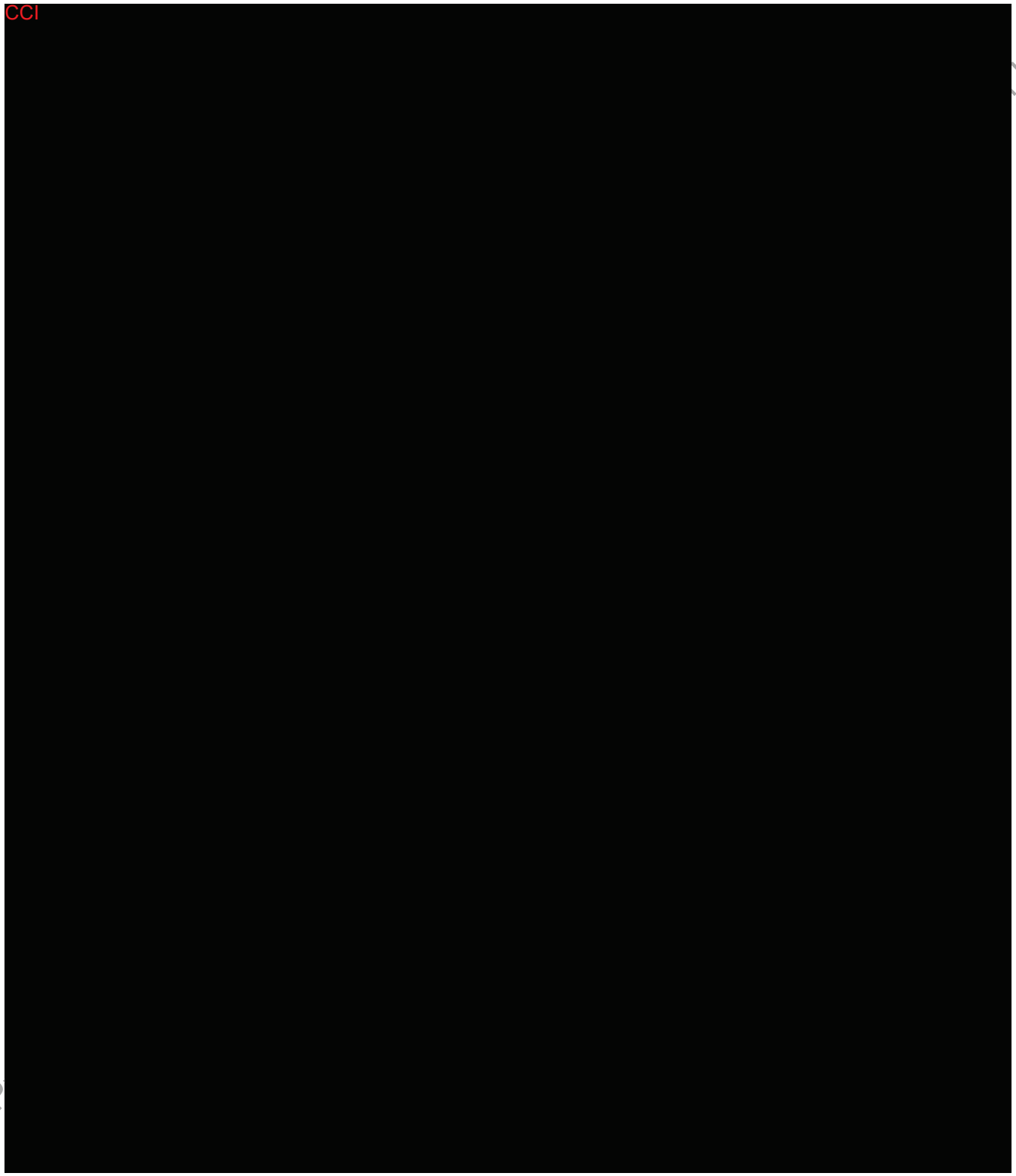

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Appendix D PROMIS 29 – PROFILE V2.1 Scoring Tables

Adult v2.0 - Physical Function 4a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
4	22.5	4.0
5	26.6	2.8
6	28.9	2.5
7	30.5	2.4
8	31.9	2.3
9	33.2	2.3
10	34.4	2.3
11	35.6	2.3
12	36.7	2.3
13	37.9	2.3
14	39.2	2.4
15	40.5	2.4
16	41.9	2.5
17	43.5	2.6
18	45.5	2.8
19	48.3	3.3
20	57.0	6.6
*SE = Standard Error on T-score metric		

Adult v1.0 - Anxiety 4a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
4	40.3	6.1
5	48.0	3.6
6	51.2	3.1
7	53.7	2.8
8	55.8	2.7
9	57.7	2.6
10	59.5	2.6
11	61.4	2.6
12	63.4	2.6
13	65.3	2.7
14	67.3	2.7
15	69.3	2.7
16	71.2	2.7
17	73.3	2.7
18	75.4	2.7
19	77.9	2.9
20	81.6	3.7
*SE = Standard Error on T-score metric		

Adult v1.0 - Depression 4a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
4	41.0	6.2
5	49.0	3.2
6	51.8	2.7
7	53.9	2.4
8	55.7	2.3
9	57.3	2.3
10	58.9	2.3
11	60.5	2.3
12	62.2	2.3
13	63.9	2.3
14	65.7	2.3
15	67.5	2.3
16	69.4	2.3
17	71.2	2.4
18	73.3	2.4
19	75.7	2.6
20	79.4	3.6
*SE = Standard Error on T-score metric		

Adult v1.0 - Fatigue 4a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
4	33.7	4.9
5	39.7	3.1
6	43.1	2.7
7	46.0	2.6
8	48.6	2.5
9	51.0	2.5
10	53.1	2.4
11	55.1	2.4
12	57.0	2.3
13	58.8	2.3
14	60.7	2.3
15	62.7	2.4
16	64.6	2.4
17	66.7	2.4
18	69.0	2.5
19	71.6	2.7
20	75.8	3.9
*SE = Standard Error on T-score metric		

Adult v1.0 - Sleep Disturbance 4a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
4	32.0	5.2
5	37.5	4.0
6	41.1	3.7
7	43.8	3.5
8	46.2	3.5
9	48.4	3.4
10	50.5	3.4
11	52.4	3.4
12	54.3	3.4
13	56.1	3.4
14	57.9	3.3
15	59.8	3.3
16	61.7	3.3
17	63.8	3.4
18	66.0	3.4
19	68.8	3.7
20	73.3	4.6
*SE = Standard Error on T-score metric		

Adult v1.0 – Ability to Participate in Social Roles and Activities 4a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
4	27.5	4.1
5	31.8	2.5
6	34.0	2.3
7	35.7	2.2
8	37.3	2.1
9	38.8	2.2
10	40.5	2.3
11	42.3	2.3
12	44.2	2.3
13	46.2	2.3
14	48.1	2.2
15	50.0	2.2
16	51.9	2.2
17	53.7	2.3
18	55.8	2.3
19	58.3	2.7
20	64.2	5.1
*SE = Standard Error on T-score metric		

Adult v1.0 - Pain Interference 4a		
Short Form Conversion Table		
Raw Summed Score	T-score	SE*
4	41.6	6.1
5	49.6	2.5
6	52.0	2.0
7	53.9	1.9
8	55.6	1.9
9	57.1	1.9
10	58.5	1.8
11	59.9	1.8
12	61.2	1.8
13	62.5	1.8
14	63.8	1.8
15	65.2	1.8
16	66.6	1.8
17	68.0	1.8
18	69.7	1.9
19	71.6	2.1
20	75.6	3.7
*SE = Standard Error on T-score metric		

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	11-Feb-2021 17:26 UTC