Title: A Phase 1b Randomized, Double-Blind, Placebo-Controlled, Crossover Study of a Single Intravenous Infusion Dose of TAK-925 in Patients With Idiopathic Hypersomnia

NCT Number: NCT04091438

Protocol Approve Date: 04 March 2020

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 1b Randomized, Double-Blind, Placebo-Controlled, Crossover Study of a Single Intravenous Infusion Dose of TAK-925 in Patients With Idiopathic Hypersomnia

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge, MA 02319		
Study Number:	TAK-925-2002		
IND Number:	144843	**EudraCT Number:**	Not applicable
Compound:	TAK-925		
Date:	04 March 2020	**Version/Amendment Number:**	02

Amendment History:

Date	Amendment Number	Amendment Type	Region
01 August 2019	Initial Protocol	Not applicable	Global
07 November 2019	01	Substantial	Global
04 March 2020	02	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda 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.

Contact Type/Role	North America Contact	Japan Contact
Serious adverse event and pregnancy reporting	PPD	
Medical Monitor (medical advice on protocol and study drug)		
Responsible Medical Officer (carries overall responsibility for the conduct of the study)		

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 study 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

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert 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 study site agreement.
- Responsibilities of the Investigator (Appendix C)

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix E 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)

1.3 Protocol Amendment 02 Summary of Changes

This document describes the changes to the protocol incorporating Amendment 02.

In addition to the overview of changes provided below, in this amendment minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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

Changes in amendment

The following is a summary of changes made in the amendment:

1. The number of participating sites was updated.
2. The description of the evaluation period in the study summary section was clarified.
3. The document referred to in the section on study-related responsibilities was corrected to "Transfer of Regulatory Obligations".
4. It was clarified in the primary objective that the population consisted of adult subjects with idiopathic hypersomnia (IH).
5. The wording of the secondary objective was made consistent with the primary objective.
6. CCI [redacted]
7. It was clarified in the study design that the maintenance of wakefulness sessions will be terminated at approximately 1700.
8. It was clarified that subjects with an Epworth Sleepiness Scale (ESS) score <11 who are taking stimulants at screening may continue the screening process and repeat the ESS at Study Day -2 following washout.
9. It was clarified in the study design that sodium oxybate must be discontinued at least 4 weeks prior to screening.
10. The subject's normal bedtime was clarified to be between 2200 and 2300.
11. CCI [redacted]
12. The overview of inpatient unit study schedule was corrected and clarified.
13. CCI [redacted]
14. CCI [redacted]

15. The safety risk related to heart rate in the criteria for premature discontinuation was changed from 115 to 100 bpm.
16. The safety risk related to mood changes in the criteria for premature discontinuation was limited to only severe changes in mood.
17. A safety risk for treatment-emergent serious adverse events (AEs) or severe AEs that are considered related to treatment was added to the criteria for premature discontinuation.
18. Text was added to clarify that, if a subject with a history of IH has a diagnostic nocturnal polysomnography (nPSG) or multiple sleep latency test (MSLT) older than 10 years (or the test results are not available), the investigator will obtain a current nPSG/MSLT.
19. The apnea-hypopnea index (AHI) for subject selection was changed from ≤15 to ≤10/hour. Also, it was added to the selection criteria that subjects should have a periodic limb movement arousal index (PLMAI) ≤15/hour.
20. Redundant and/or duplicate selection criteria were removed from the protocol.
21. Selection criteria related to contraception were reworded and clarified.
22. It was added to the selection criteria that subjects with an average nightly sleep duration ≤8 hours (480 minutes) will be excluded.
23. It was clarified in the selection criteria that the alcohol test used during the study will be a breathalyzer.
24. It was clarified that subjects with a resting heart rate (HR) outside of the range 40-90 bpm (rather than 45-100 bpm) will not be eligible for selection.
25. It was clarified that subjects with a usual bedtime later than 2400 (midnight) rather than 0100 are not eligible to participate.
26. The exclusion criterion on nicotine dependence that is likely to have an effect on sleep was expanded to include smoking ≥10 cigarettes per day.
27. It was added to the exclusion criteria that subjects unwilling to discontinue all caffeine during the confinement period of the study will not be eligible for selection.
28. Major depression was added as an example of psychiatric disorders for which subjects will be excluded from participation.
29. The period for refraining from certain food products was corrected to be through Study Day 4 (including washout intervals between treatment periods) rather than until the follow-up visit.
30. It was clarified that known in vivo cytochrome P-450 (CYP)3A (not only CYP3A4) inhibitors or inducers were prohibited drug classes.
31. It was clarified that subjects will receive 3 standardized meals per day during confinement.
32. Food, drink, and other product restrictions were clarified.

33. It was added to the protocol that subjects will be allowed to go on short supervised walks on washout days.
34. It was clarified that lack of efficacy should not be recorded in the voluntary withdrawal category of discontinuation criteria. It was also clarified that the criterion is applicable to subjects or their legally acceptable representative.
35. It was corrected that details of the randomization schedule are provided in the pharmacy manual rather than the interactive voice response (IVRS) manual.
36. It was clarified that informed consent must be obtained before beginning withdrawal of excluded medications.
37. The time subjects should rest in a bed following dosing was corrected from 4 to 2 hours.
38. The actigraphy procedure was clarified.
39. The duration of the nPSG was clarified.
40. CCI [redacted]
41. International normalized ratio (INR) measurement was added to the overview of laboratory tests for subjects with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >3 times the upper limit of normal (ULN).
42. CCI [redacted]
43. The procedure on collecting and reporting of serious adverse events (SAEs) was clarified.
44. CCI [redacted]
45. The term "adverse events of special interest" was removed from the description of the safety analyses.
46. A footnote was added to the Schedule of Study Procedures table to allow optional pre-screening on a case-by-case basis.
47. The measurement of O_2 saturation was added to the Schedule of Study Procedures table.
48. CCI [redacted]
49. It was added to the Schedule of Study Procedures that urine drug screen and pregnancy test results should be available before dosing on Day 1 of Treatment Period 1.
50. CCI [redacted]
51. The urine pregnancy test was moved from Study Day-1 to Study Day -2 in the Schedule of Study Procedures table.
52. A footnote was added to the Schedule of Study Procedures table to clarify that glycosylated hemoglobin will be assessed only in diabetic subjects.

53. Footnotes were added to the Schedule of Study Procedures table to clarify site staff will make every effort to keep subjects awake following completion of clinical testing procedures on Study Day -2 and during the day from 0700 until between 2200-2300 on Study Days 2 and 4.
54. Appendix G (Pregnancy and Contraception) was reorganized and completed where needed.

TABLE OF CONTENTS

1.0 ADMINISTRATIVE INFORMATION 2
1.1 Contacts 2
1.2 Approval 3
1.3 Protocol Amendment 02 Summary of Changes 5
2.0 STUDY SUMMARY 14
3.0 STUDY REFERENCE INFORMATION 19
3.1 Study-Related Responsibilities 19
3.2 Principal Investigator/Coordinating Investigator 19
3.3 List of Abbreviations 20
3.4 Corporate Identification 22
4.0 INTRODUCTION 23
4.1 Background 23
4.1.1 Orexin and Idiopathic Hypersomnia 23
4.1.2 TAK-925 24
4.2 Rationale for the Proposed Study 25
4.3 Benefit/Risk Profile 26
5.0 STUDY OBJECTIVES AND ENDPOINTS 27
5.1 Objectives 27
5.1.1 Primary Objective 27
5.1.2 Secondary Objective 27
5.1.3 Exploratory Objectives 27
5.2 Endpoints 27
5.2.1 Primary Endpoints 27
5.2.2 Secondary Endpoint 27
5.2.3 Exploratory Endpoints 28
6.0 STUDY DESIGN AND DESCRIPTION 29
6.1 Study Design 29
6.2 Justification for Study Design, Dose, and Endpoints 31
6.2.1 Rationale for Study Design 31
6.2.2 Rationale for Dose 31
6.2.3 Rationale for Endpoints 32
6.3 Premature Termination or Suspension of Study or Study Site 34
6.3.1 Criteria for Premature Termination or Suspension of the Study 34
6.3.2 Criteria for Premature Termination or Suspension of Study Sites 35

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites 35
7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS 36
7.1 Inclusion Criteria 36
7.2 Exclusion Criteria 37
7.3 Excluded Medications 39
7.4 Diet, Fluid, and Activity Control 41
7.4.1 Diet and Fluids 41
7.4.2 Activity 41
7.5 Criteria for Discontinuation or Withdrawal of a Subject 42
7.6 Procedures for Discontinuation or Withdrawal of a Subject 43
7.7 Subject Replacement 43
8.0 CLINICAL STUDY MATERIAL MANAGEMENT 44
8.1 Study Drug and Materials 44
8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling 44
8.1.1.1 Ancillary Supplies 44
8.1.1.2 Sponsor-Supplied Drug 44
8.1.2 Storage 44
8.1.3 Dose and Regimen 44
8.1.4 Overdose 45
8.2 Study Drug Assignment and Dispensing Procedures 45
8.3 Randomization Code Creation and Storage 45
8.4 Study Drug Blind Maintenance 45
8.5 Unblinding Procedure 45
8.6 Accountability and Destruction of Sponsor-Supplied Drugs 46
9.0 STUDY PLAN 47
9.1 Administrative Procedures 47
9.1.1 Informed Consent Procedure 47
9.1.2 Inclusion and Exclusion 47
9.1.3 Medical and Social History and Demographics 47
9.1.4 Prior and Concomitant Medication 47
9.1.5 Washout of Prohibited Concomitant Medications 48
9.1.6 Actigraphy and Sleep Diary 48
9.2 CCI
9.2.
9.2.

9.2.3 CCI
9.2.4
9.2.5
9.2.6
9.2.7
9.2.8
9.3 PD Evaluation/Assessments 50
9.3.1 nPSG 50
9.3.2 CCI
9.3.3 ESS 50
9.3.4 CCI
9.3.5
9.4 Laboratory Assessments/Procedures 51
9.5 PK CCI Samples 53
9.5.1 PK CCI Evaluations 53
9.5.2 PK Measurements 53
9.5.2.1 Blood for PK Measurements 53
9.5.2.2 PK Sample Analysis 54
CCI
9.6 Blood Volume 55
9.7 Confinement 56
9.8 Documentation of Screen Failure 56
9.9 Documentation of Study Entrance/Randomization 57
9.10 Monitoring Subject Treatment Compliance 57
10.0 PRETREATMENT EVENTS AND AES 58
10.1 Definitions 58
10.1.1 PTEs 58
10.1.2 AEs 58
10.1.3 Additional Points to Consider for PTEs and AEs 58
10.1.4 SAEs 60
10.1.5 AEs of Special Interest 61
10.1.6 Intensity of PTEs and AEs 61
10.1.7 Causality of AEs 61

10.1.8 Relationship to Study Procedures 62
10.1.9 Start Date 62
10.1.10 Stop Date 62
10.1.11 Frequency 62
10.1.12 Action Concerning Study Drug 62
10.1.13 Outcome 62
10.2 Procedures 63
10.2.1 Collection and Reporting of AEs 63
10.2.1.1 PTE and AE Collection Period 63
10.2.1.2 PTE and AE Reporting 63
10.2.2 Collection and Reporting of SAEs 64
10.2.3 Reporting of Abnormal LFTs 65
10.3 Follow-up of SAEs 65
10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities 65
11.0 STUDY-SPECIFIC COMMITTEES 66
12.0 DATA HANDLING AND RECORDKEEPING 67
12.1 eCRFs 67
12.2 Record Retention 67
13.0 STATISTICAL METHODS 69
13.1 Statistical and Analytical Plans 69
13.1.1 Analysis Sets 69
13.1.1.1 Safety Set 69
13.1.1.2 PK Set 69
13.1.1.3 PD Set 69
13.1.2 Analysis of Demographics and Other Baseline Characteristics 69
13.1.3 PK Analysis 69
13.1.4 PD Analysis 69
13.1.5 Safety Analysis 70
13.2 Interim Analysis and Criteria for Early Termination 70
13.3 Determination of Sample Size 70
14.0 QUALITY CONTROL AND QUALITY ASSURANCE 72
14.1 Study Site Monitoring Visits 72
14.2 Protocol Deviations 72
14.3 Quality Assurance Audits and Regulatory Agency Inspections 72
15.0 ETHICAL ASPECTS OF THE STUDY 73

15.1 IRB and/or IEC Approval 73
15.2 Subject Information, Informed Consent, and Subject Authorization 74
15.3 Subject Confidentiality 75
15.4 Publication, Disclosure, and Clinical Trial Registration Policy 75
15.4.1 Publication and Disclosure 75
15.4.2 Clinical Study Registration 75
15.4.3 Clinical Study Results Disclosure 76
15.5 Insurance and Compensation for Injury 76
16.0 REFERENCES 77

LIST OF IN-TEXT TABLES

Table 6.a Summary of Treatment Assignment for Each Sequence 29
Table 6.b Overview of the Inpatient Unit Study Schedule 31
Table 7.a Prohibited Drug Classes 40
Table 7.b List of Restricted Food, Drinks and Other Products 41
Table 9.a Clinical Laboratory Tests 52
Table 9.b Primary Specimen Collection for [redacted] PK Samples 53
Table 9.c Blood Volume 56
Table 10.a Takeda Medically Significant AE List 61

LIST OF APPENDICES

Appendix A Schedule of Study Procedures 78
Appendix B Treatment Day 1 Hourly Schedule of Procedures (Approximate Times) for Treatment Periods 1 and 2 82
Appendix C Responsibilities of the Investigator 83
Appendix D Elements of the Subject Informed Consent 85
Appendix E Investigator Consent to Use of Personal Information 88
Appendix F ICSD-3 Diagnostic Criteria for IH 89
Appendix G Contraception and Pregnancy 90
Appendix H Detailed Description of Amendments to Text 94

2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc. (MPI)* 40 Landsdowne Street Cambridge MA 02139, USA * Millennium Pharmaceuticals is a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited and thereafter, any reference to the sponsor will use Takeda's name	**Compound:** TAK-925	
Title of Protocol: A Phase 1b Randomized, Double-Blind, Placebo-Controlled, Crossover Study of a Single Intravenous Infusion Dose of TAK-925 in Patients With Idiopathic Hypersomnia	**IND No.:** 144843	**EudraCT No.:** Not applicable
Study Number: TAK-925-2002	**Phase:** 1b	

Study Design:

This is a randomized, double-blind, placebo-controlled, 2-period, 2-treatment crossover study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of a single intravenous (IV) infusion dose of TAK-925 in subjects with idiopathic hypersomnia (IH). Subjects will be males and females aged 18 through 75 years, inclusive, with IH diagnosed according to the International Classification of Sleep Disorders-3 (ICSD-3) criteria as verified by a previous nocturnal polysomnogram (nPSG) and multiple sleep latency test (MSLT) study performed within the last 10 years.

The treatment periods begin on Day 1 of Treatment Period 1 (Study Day 1) with Treatment Period 2 commencing on Study Day 3. In the morning of Day 1 of Treatment Period 1, eligible subjects will be randomized to 1 of 2 sequence groups as listed in the table below. After randomization, the subject will be dosed in 2 treatment periods according to the order defined by the sequence group to which he/she is randomized. On Day 1 of each treatment period, TAK-925 (or placebo) will be administered as a single 9-hour IV infusion commencing at approximately 0800. The infusion will be terminated at approximately 1700. CCI [redacted] summary of study drug assignment for each sequence follows:

Sequence	N	Treatment Period 1	Treatment Period 2
1	20	TAK-925 112 mg	Placebo
2	20	Placebo	TAK-925 112 mg

CCI [redacted] A total of 40 subjects will be randomized so that at least 36 subjects will complete the study. To avoid enrollment of short sleepers with chronic sleep deprivation, prospective participants will complete approximately 7 consecutive days of actigraphy supported by a sleep diary beginning on Study Day -9 and ending on Study Day -3 (ie, the day before their Study Day -2 admission to the clinical unit), to ensure an average nightly sleep duration of ≥420 minutes (7 hours) during the subject's normal nocturnal sleep period and also, that if the subject's average nightly sleep duration is ≤480 minutes (8 hours), that the subject does not have insufficient sleep syndrome (sleeping >2 hours/night more on "off days" than on "work days"). After screening, eligible subjects must discontinue their stimulant medications used for treatment of IH. Medications must be discontinued for a minimum of 7 days or at least 5 half-lives of each medication, whichever is longer, before the first day of dosing (Day 1 of Treatment Period 1). Sodium oxybate must be discontinued at least 4weeks prior to

screening.

The screening period is up to 28 days. Following screening, subjects who meet all screening entry criteria will be admitted to the clinical unit on Study Day -2Semi-recumbent vital signs will be obtained following admission; the ESS will be recorded in the late afternoon. An overnight 8-hour nocturnal polysomnography (nPSG) will be performed, commencing at the subject's usual bedtime (eg, between 2200 and 2300) to confirm that the subject does not have other comorbid sleep disorders or clinically significant nocturnal hypoxemia (O_2 saturation ≤80% for ≥5% of total sleep time), and to confirm the apnea-hypopnea index (AHI) is ≤10/hour and the periodic limb movement index associated with arousals (PLMAI) is ≤15/hour.

Study Day -1 is the designated baseline assessment day and is also intended for accommodation to sleeping in the clinical unit without nPSG hookups. CCI [redacted] CCI [redacted] There will be a minimum 24-hour washout interval between the end of TAK-925 infusion and the commencement of treatment in the subsequent treatment period to allow for complete elimination of the preceding treatment effect. Study Days 2 and 4 are washout days. CCI [redacted] CCI [redacted] During the study, adverse events (AEs) will be recorded, and clinical labs, vital signs, and ECGs will be obtained. Subjects will be discharged from the unit following completion of study exit procedures in the afternoon of Study Day 4 (Day 2 of Treatment Period 2).

Subjects will be contacted by telephone approximately 7 days (±2 days) following unit discharge for a safety check and all women of childbearing potential will be asked to return to the clinic to complete a urine pregnancy test. If needed, subjects may be seen in the clinic for any safety issues or concerns.

An overview of the inpatient unit study schedule follows:

Screening Period	**Check-in and Baseline**	**Treatment Periods 1 and 2**		**End-of-Study Visit**
		Dosing	**Washout**	
Study Days -28 to -3	Study Days -2 (nPSG [a]) and -1 (Baseline)	**Study Days 1 and 3** Study drug administration/PD, PK, and safety assessments	**Study Days 2 and 4** [b] PK and safety assessments	Study Day 11 (±2 days) Follow-up (in clinic or by phone call)
	←———— Confinement Study Day -2 to Study Day 4 ————→			

nPSG: nocturnal polysomnography; PD: pharmacodynamic; PK: pharmacokinetic.
[a] nPSG only on Study Day-2.
[b] Discharge from unit on Study Day 4.

Primary Objective:

To evaluate the safety and tolerability of administering a single IV infusion of TAK-925 to adult subjects with IH.

Secondary Objective:

To investigate the PK of a single IV infusion of TAK-925 in adult subjects with IH.

Exploratory Objectives:

CCI [redacted]

Subject Population: Male and female subjects aged 18 through 75 years, inclusive, with IH diagnosed according to the ICSD-3 criteria as verified by a previous nPSG and MSLT study performed within the last 10 years.

Number of Subjects: Up to 40 randomized subjects	**Number of Sites:** Approximately 21 sites in the United States and 3 sites in Japan.
Dose Levels: TAK-925 112 mg Placebo	**Route of Administration:** TAK-925 or placebo IV infusion
Duration of Treatment: Single 9-hour IV infusion in each treatment period, with a washout period of 24 hours between the end of infusion and the start of the next treatment	**Period of Evaluation:** Up to 41 days (including screening up to 28 days, confinement for 6 days [Treatment Periods 1 to 2 with a minimum 24-hour washout between periods]), and end of study follow-up telephone call on Study Day 11 (±2 days)

Main Criteria for Inclusion:

- A diagnosis of IH, as defined by the ICSD-3, as verified by a previous nPSG and MSLT study performed within the last 10 years.
- Onset of hypersomnia between 10 and 30 years of age.
- Body mass index (BMI) of 18 through 33 kg/m^2 inclusive.
- Seven consecutive days of actigraphy supported by a sleep diary (recorded while the subject was wearing the actigraph) obtained prior to the nPSG (Study Day -2) shows an average nightly sleep duration of ≥420 minutes during the subject's normal nocturnal sleep period.
- nPSG (Study Day -2) demonstrates that subject does not have other comorbid sleep disorders or clinically significant nocturnal hypoxemia (O_2 saturation ≤80% for ≥5% of total sleep time) and that their AHI is ≤10/hour, their periodic limb movement arousal index (PLMAI) is ≤15/hour, and total sleep time is ≥6.5 hours.
- CCI [redacted]
- Subjects taking medication for treatment of excessive daytime sleepiness must be willing to discontinue medication prior to randomization into the study.
- ESS score ≥11 at screening and on Day -2. Subjects with an ESS score of <11 who are taking stimulants at screening may continue the screening process and repeat the ESS at Study Day -2 following washout.
- Blood pressure (BP) must be <140 mmHg (systolic) and <90 mmHg (diastolic) at screening and Study Day -2. BP measures should be obtained after the subject has been resting for a minimum of 10 minutes and may be repeated 3 times if the BP is elevated above these parameters. The median BP reading will be used.

Main Criteria for Exclusion:

- Average nightly sleep duration is ≤8 hours (480 minutes) and the subject has insufficient sleep syndrome as evidenced by sleeping >2 hours/night more on "off-days" relative to "work days" as determined by actigraphy and sleep diary obtained prior to the nPSG (Study Day -2).
- Resting heart rate (HR) outside of the range of 40 to 90 beats per minute, off stimulants.
- Screening ECG reveals a QT interval with Fridericia correction method >450 ms (men) or >470 ms (women).
- Usual bedtime later than 2400 (midnight) or an occupation requiring nighttime shift work or variable shift work within the past 6 months, or travel with significant jet lag within 14 days before Study Day -2.
- History of sleep disorder other than IH, based on interviews at the screening visit, such as obstructive sleep apnea (OSA), restless legs syndrome, or periodic limb movements of sleep (PLMS) associated with arousals.
- Use of any over the counter or prescription medications with stimulating properties within 7 days prior to dosing or 5 half-lives (whichever is longer) that could affect the evaluation of excessive daytime sleepiness, or any use of sodium oxybate within 4 weeks of screening.
- Nicotine dependence that is likely to have an effect on sleep (eg, a subject who routinely awakens at night to smoke) or challenge the conduct of this study (smokes ≥10 cigarettes/day) and/or an unwillingness to discontinue all smoking and nicotine use during the confinement portion of the study (Day -2 to Day 4).
- Caffeine consumption of more than 600 mg/day for 7 days before Study Day 1 (1 serving of coffee is approximately equivalent to 120 mg of caffeine) and/or unwilling to discontinue all caffeine during the confinement portion of the study (Day -2 to Day 4).
- Alcohol use that is likely to have an effect on sleep and/or an unwillingness to discontinue all alcohol use from 72 hours before check-in through discharge on Study Day 4.
- History or presence of any unstable medical condition, behavioral or psychiatric disorder (including major depression or active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the study per the judgment of the investigator.

Main Criteria for Evaluation and Analyses:

The primary endpoints for this study are:

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who meet the markedly abnormal criteria for clinical safety laboratory tests at least once post a regimen.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once post a regimen.
- Percentage of subjects who meet the markedly abnormal criteria for 12-lead safety ECG parameters at least once post a regimen.

The secondary endpoints for this study are:

- TAK-925 PK parameters:
  - Observed plasma concentration at the end of infusion (C_{eoi}).
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).

The exploratory endpoints for this study are:

CCI [redacted]

Statistical Considerations:

Standard summaries of TEAEs, adverse events of special interest (AESIs), clinical safety labs, vital signs, and ECGs will be performed. Where appropriate, BP and QT parameters will be summarized (N, mean, SD, median, minimum and maximum) for baseline, post-dose, change from baseline, and change from time-matched baseline to post-dose by treatment.

The observed HR and BP will be analyzed using linear mixed effect model for repeated measures in crossover studies. The model will include sequence, period, treatment, time points, and treatment by time point interaction as fixed effects and a random effect for subject. The estimated mean HR and BP for each treatment and the associated standard error and 95% CI will be extracted from the model at each time, along with all pairwise differences from placebo and associated standard errors, 95% CIs, and p-values. The same quantities, averaged over all timepoints during the infusion and post the end of the infusion, will also be extracted from the model using appropriate contrasts.

Individual plasma concentrations of TAK-925 CCI [redacted] and PK parameter estimates will be listed for each subject and summarized using descriptive statistics, as appropriate.

Sample Size Justification:

Up to 40 subjects are planned to be randomized equally to each treatment sequence to ensure 36 subjects complete the study. This number of subjects is typical for phase 1 crossover study designs and is considered sufficient for assessment of safety. CCI [redacted] In addition, when the true difference between TAK-925 and placebo is minimal, the chance to observe the same event is no more than 10%. Non-informative prior distributions were used in the above probability calculation. Allowing for 4 dropouts (10%), 40 subjects are planned to be randomized.

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 Transfer of Regulatory Obligations. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Not applicable.

3.3 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AHI	Apnea-Hypopnea Index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
CCI	[redacted]
bpm	beats per minute
BMI	body mass index
BP	blood pressure
C_{eoi}	observed plasma concentration at the end of infusion
CHO	Chinese hamster ovary
CI	confidence interval
CL	total clearance after IV administration
C_{max}	maximum observed plasma concentration
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Edition 5
ECG	electrocardiogram
eCRF	electronic case report form
EDS	excessive daytime sleepiness
EEG	electroencephalogram
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HR	heart rate
ICH	International Council for Harmonisation
ICSD-3	International Classification of Sleep Disorders-3
IEC	independent ethics committee
IH	idiopathic hypersomnia
IRB	institutional review board
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
CCI	[redacted]

LFT	liver function test
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MSLT	multiple sleep latency test
MWT	Maintenance of Wakefulness Test
nPSG	nocturnal polysomnography
NT1	narcolepsy type 1
NT2	narcolepsy type 2
OSA	obstructive sleep apnea
OTC	over the counter
OX	orexin
OX1R	orexin type-1 receptor
OX2R	orexin type-2 receptor
CCI	[redacted]
CCI	[redacted]
PK	pharmacokinetic(s)
PLMAI	Periodic Limb Movement Arousal Index
PLMS	Periodic Limb Movements of Sleep
PTE	pretreatment event
CCI	[redacted]
PSG	polysomnogram
REM	rapid eye movement
RLS	restless legs syndrome
RT	reaction time
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous(ly)
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state after IV administration
V_z	volume of distribution during the terminal disposition phase after IV administration
WHO	World Health Organization

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
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

4.1.1 Orexin and Idiopathic Hypersomnia

Orexin (OX) is a neuropeptide and the orexinergic system is a major wake-promoting system of the brain. Two orexinergic neuropeptides, OX-A and OX-B, have been identified to date. These neuropeptides exert effects via 2 types of receptors: orexin type-1 receptor (OX1R) and orexin type-2 receptor (OX2R). OX-A has a high affinity to OX1R and OX2R, and OX-B has a high affinity to OX2R. The 2 types of OX receptors have a distinct distribution in the arousal network: the locus coeruleus contains only OX1Rs, the tuberomammillary nucleus contains only OX2Rs, and both receptor types occur in the dorsal raphe nucleus and ventral tegmental area. The 2 types of OX receptors also make distinct contributions to the regulation of arousal. OX2Rs in the tuberomammillary nucleus are essential for the maintenance of wakefulness, whereas both receptor types are required for the inhibition of rapid eye movement (REM) sleep [1].

The pathological loss of orexinergic neurons is associated with the development of narcolepsy type 1 (NT1) [2]. Narcolepsy with cataplexy, or NT1, has been defined by International Classification of Sleep Disorders, Edition 3 (ICSD-3) criteria as having low levels of orexin in cerebrospinal fluid (<110 pg/mL; <30% of normal levels), coming from the nearly complete loss of orexin producing neurons [3].

Idiopathic hypersomnia (IH), defined by ICSD-3, is a chronic neurological disorder that results in excessive daytime sleepiness and is frequently accompanied by long nocturnal or daytime sleep, unrefreshing sleep, difficulty in awakening, cognitive dysfunction, and autonomic symptoms [4]. The etiology of the condition is unknown. Orexin levels in patients with IH are within normal limits. IH is thought to be a relatively rare disease with the prevalence rate of 0.02% to 0.010% [5]. However, the lack of clear distinguishing symptoms, the unknown mechanism of disease, and lack of a diagnostic biomarker result in difficulties in discriminating IH from other types of hypersomnia, and thus the prevalence remains unclearly established.

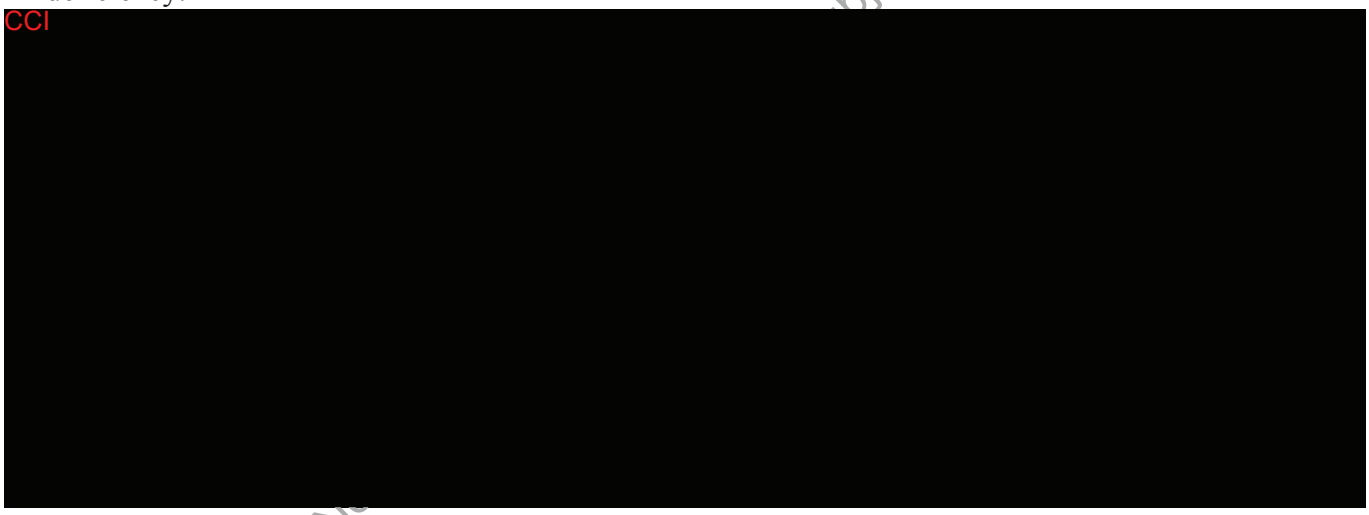
Very few clinical studies have been conducted for the treatment of IH. A double-blind placebo-controlled crossover study with a treatment period of 3 weeks each with 200 mg of modafinil vs placebo in 33 drug-free adult IH patients without long sleep according to ICSD-2 criteria found that modafinil significantly decreased the Epworth Sleepiness Scale (ESS) by 4.5 points. Change in sleep latency on the Maintenance of Wakefulness Test (MWT) versus placebo was not significant. The clinical global impression improved significantly on modafinil from baseline to the last visit on treatment [6]. Medications used for the treatment of IH include stimulants such as modafinil, armodafinil methylphenidate, dextroamphetamine, and pemoline as well as in some patients, sodium oxybate, clarithromycin, and flumazenil. Antidepressants with activating effects such a bupropion and venlafaxine may also be used. Modafinil is the only drug that had a marketing authorization in some European countries for the treatment of patients with IH. However, the European Medicines Agency withdrew the indication of modafinil for the treatment of IH because the risk for development of skin or hypersensitivity reactions and neuropsychiatric disorders outweighed the evidence for clinically important efficacy. There is no

gold standard treatment for IH. As such, there is a huge unmet medical need for an effective treatment of the excessive daytime sleepiness (EDS) in this condition.

4.1.2 TAK-925

TAK-925 is a first-in-class OX2R-selective agonist. TAK-925 has a half-maximal effective concentration of 5.5 nM in OX2R– Chinese hamster ovary (CHO) cells, versus >30 μM in OX1R–CHO cells, indicating over 5,000-fold selectivity for OX2R. In vivo pharmacology studies demonstrated significant effects of TAK-925 on increasing wakefulness and decreasing cataplexy-like events in the OX/ataxin-3 transgenic mouse model of narcolepsy. In contrast, TAK-925 did not show an arousal effect in OX2R knock-out mice, consistent with selectivity for OX2R. In addition, the arousal effect of TAK-925 after single dosing was demonstrated in 3 different species of wild-type animals without orexin deficiency, including mice, cynomolgus monkeys, and marmosets during their normal sleep phase. These preclinical studies suggest that TAK-925 should show arousal effects in hypersomnolent states, whether or not due to orexin deficiency.

CCI



The first-in-human phase 1 study (TAK-925-1001), was conducted in Japan. This study was designed to assess the safety, tolerability, pharmacokinetics (PK), and PD of single, ascending doses of TAK-925 when administered via a 9-hour IV infusion to healthy adult and healthy elderly subjects (aged ≥65 years old) and subjects with NT1. Single doses ranging from 7 to 240 mg in healthy subjects, and single doses of 5, 11.2, and 44.8 mg tested in subjects with NT1, were safe and well-tolerated with no severe adverse events (AEs) or serious adverse events (SAEs). All AEs except influenza (considered as moderate) were mild in severity. A single event of euphoric mood was reported for a subject receiving 44.8 mg TAK-925, the event was considered related to study drug and resolved the same day. All cardiovascular-related AEs (increased blood pressure [BP], pulse rate increased) were considered mild by the investigator. The incidence of increased BP was increased in a dose-dependent manner starting from 134 mg (2 of 6 healthy adult subjects [33.3%]) and was most evident in the 240-mg group (4 of 6 healthy adult subjects [66.7%]). At the same dose of 112 mg, the incidence of increased BP was higher in Cohort 3 healthy elderly subjects (3 of 6 subjects [50.0%]), compared with Cohort 1 and 2 healthy adult subjects (2 of 6 subjects

[33.3%]). Dose-related increases in BP and pulse after single dosing were observed in healthy cohorts. CCI [redacted].

Following a single IV infusion, mean plasma systemic exposure of TAK-925 increased approximately dose proportionally across cohorts. On average, time to reach plateau was approximately 3 hours and the plasma terminal elimination $t_{1/2}$ ranged from approximately 3 to 5 hours across all doses. TAK-925 exposure was increased by <30% in elderly subjects (aged 65 to 80 years) possibly due to decreased hepatic clearance. Furthermore, a proof-of-mechanism (POM) study in sleep-deprived healthy subjects was conducted in the United States (TAK-925-1002). CCI [redacted] CCI [redacted] All regimens were well-tolerated with no severe or SAEs, and most AEs were mild. A single event of euphoric mood was reported for a subject during treatment with 112 mg TAK-925; the event was considered mild in intensity, related to study drug, and resolved the following day. Changes in DBP appeared to increase with increasing concentration of TAK-925 but there were no apparent trends in the change from time-matched baseline in heart rate (HR) or SBP when compared to TAK-925 plasma concentration. Lastly, another study, TAK-925-1003, is evaluating both NT1 subjects (orexin deficient) as well as narcolepsy type 2 (NT2) subjects (orexin levels though to be within normal) with TAK-925 administered as a 9-hour IV infusion for 7 days.

For more detailed background on TAK-925 nonclinical and clinical studies, please refer to the Investigator's Brochure.

The purpose of this study is to evaluate the safety, tolerability, PK, and PD of a single IV infusion of TAK-925 in subjects with IH to support further development of TAK-925 as a potential treatment for this condition.

4.2 Rationale for the Proposed Study

Results from Study TAK-925-1002 in sleep-deprived subjects suggest that there may be potential benefit of TAK-925 in other patient populations who have EDS associated with primary sleep disorders that are not associated with orexin deficiency, including patients with NT2, IH, and EDS associated with obstructive sleep apnea (OSA). Hence in this proposed phase 1b study, adult patients diagnosed with IH according to the ICSD-3 criteria will be evaluated.

4.3 Benefit/Risk Profile

TAK-925 is a first-in-class OX2R-selective agonist. Nonclinical pharmacology studies demonstrated that TAK-925 had arousal effects in hypersomnolent states both in animals with orexin deficiency (mice) and animals without orexin deficiency (mice, cynomolgus monkeys and marmosets). To explore potential effects in humans, the TAK-925-1001 (first-in-human) and TAK-925-1002 studies included healthy adult subjects, healthy elderly subjects, narcolepsy subjects with orexin deficiency (NT1), and sleep-deprived healthy subjects. In this proposed phase 1b study, subjects with IH will be evaluated. The results may provide an early indication of whether TAK-925 has PD effects in subjects with IH and is safe and well-tolerated.

CCI

[redacted]

Increased SBP was noted in the safety pharmacology study in monkeys. This is considered a potentially on-mechanism effect based on published literature [7]. In the completed clinical studies of TAK-925, mild treatment-emergent adverse events (TEAEs) of increased BP and HR have been observed, which resolved after treatment discontinuation. The 112 mg dose level proposed in this study was found to be safe and tolerable in these studies in which healthy subjects received single IV doses of TAK-925 up to 240 mg (Study TAK-925-1001). In sleep-deprived healthy subjects, administration of the 112 mg dose level resulted in some elevation of placebo-adjusted mean DBP of approximately 6 to 9 mmHg throughout much of the nocturnal infusion time although not reported as TEAEs (Study TAK-925-1002). In this study, BP will be frequently monitored for all subjects. As TAK-925 has been shown to have a short elimination half-life, discontinuation of infusion, if needed, would be expected to result in rapid resolution of increased BP. Stopping criteria for effects on BP are provided (see Section 6.3).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of administering a single IV infusion of TAK-925 to adult subjects with IH.

5.1.2 Secondary Objective

The secondary objective of this study is to investigate the PK of a single IV infusion of TAK-925 in adult subjects with IH.

5.1.3 Exploratory Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

- Percentage of subjects who experience at least 1 TEAE.
- Percentage of subjects who meet the markedly abnormal criteria for clinical safety laboratory tests at least once post a regimen.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once post a regimen.
- Percentage of subjects who meet the markedly abnormal criteria for 12-lead safety electrocardiogram (ECG) parameters at least once post a regimen.

5.2.2 Secondary Endpoint

- TAK-925 PK parameters:
  - Observed plasma concentration at the end of infusion (C_{eoi}).
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).

CCI

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1b, randomized, double-blind, placebo-controlled, 2-period, 2-treatment crossover study to evaluate the PK, CCI safety, and tolerability of a single IV infusion dose of TAK-925 in subjects with IH. Subjects will be males and females aged 18 through 75 years, inclusive, with IH diagnosed according to the ICSD-3 criteria (Appendix F) as verified by a previous nocturnal polysomnography (nPSG) and multiple sleep latency test (MSLT) study performed within the last 10 years.

The treatment periods begin on Day 1 of Treatment Period 1 (Study Day 1) with Treatment Period 2 commencing on Study Day 3. In the morning of Day 1 of Treatment Period 1, eligible subjects will be randomized to 1 of 2 sequence groups as listed in Table 6.a. After randomization, the subject will be dosed in 2 treatment periods according to the order defined by the sequence group to which he/she is randomized. On Day 1 of each treatment period, TAK-925 (or placebo) will be administered as a single 9-hour IV infusion commencing at approximately 0800. The infusion will be terminated at approximately 1700. CCI [redacted].

A summary of the treatment assignment and sequence is presented in Table 6.a. The Schedule of Study Procedures is included in Appendix A and Treatment Day 1 Hourly Schedule is in Appendix B.

Table 6.a Summary of Treatment Assignment for Each Sequence

Sequence	N	Treatment Period 1	Treatment Period 2
1	20	TAK-925 112 mg	Placebo
2	20	Placebo	TAK-925 112 mg

At the screening visit, eligible subjects who have an ESS score of ≥11 will complete medical histories and physical examinations, semi-recumbent vital signs assessment, a 12-lead ECG, Beck Depression Inventory II (BDI-II), Columbia Suicide Severity Rating Scale (C-SSRS), and clinical safety laboratory tests. Subjects with an ESS score of <11 who are taking stimulants at screening may continue the screening process and repeat the ESS at Study Day -2 following washout. A total of 40 subjects will be randomized so that at least 36 subjects will complete the study. To avoid enrollment of short sleepers with chronic sleep deprivation, prospective participants will complete approximately 7 consecutive days of actigraphy supported by a sleep diary beginning on Study Day -9 and ending on Study Day -3 (ie, the day before their Study Day -2 admission to the clinical unit), to ensure an average nightly sleep duration of ≥420 minutes (7 hours) during the subject's normal nocturnal sleep period, and, if the subject's average nightly sleep duration is ≤480 minutes

(8 hours), that the subject does not have insufficient sleep syndrome (sleeping >2 hours/night more on "off days" than on "work days"). During screening, eligible subjects must discontinue their stimulant medications used for treatment of IH. Medications must be discontinued for a minimum of 7 days or at least 5 half-lives of each medication, whichever is longer, before the first day of dosing (Day 1 of Treatment Period 1). Sodium oxybate must be discontinued at least 4weeks before screening.

The screening period is up to 28 days. Following screening, subjects who meet all screening entry criteria will be admitted to the clinical unit (Study Day -2). Semi-recumbent vital signs will be obtained following admission, and the ESS will be recorded in the late afternoon. An overnight 8-hour nPSG will be performed commencing at approximately the subject's normal bedtime (eg, between 2200 and 2300) to confirm that the subject does not have other comorbid sleep disorders or clinically significant nocturnal hypoxemia (O_2 saturation ≤80% for ≥5% of total sleep time), and to confirm the apnea hypopnea index (AHI) is ≤10/hour and the periodic limb movement index associated with arousals (PLMAI) is ≤15/hour.

CCI [redacted] Safety assessments including BP, pulse, respiration rate, and ECG will be collected per the Schedule of Study Procedures (Appendix A).

On Day 1 of Treatment Period 1 (Study Day 1), all eligible subjects will be randomized and receive the first dose of study drug. TAK-925 or placebo will be administered as a single 9-hour IV infusion commencing at approximately 08:00. CCI [redacted] tudy Days 2 and 4 are washout days. CCI [redacted] Safety assessments including AEs, vital signs, and ECGs will be recorded. During the study, AEs will be recorded, and clinical labs, vital signs, and safety ECGs will be obtained. Subjects will be discharged from the unit following completion of study exit procedures in the afternoon of Study Day 4 (Day 2 of Treatment Period 2).

Subjects will return to the study site or be contacted by telephone approximately 7 days (±2 days) following unit discharge for a safety check and all women of childbearing potential must return to the study site to complete a urine pregnancy test at the end-of-study visit.

An overview of the inpatient unit study schedule is presented in Table 6.b.

Table 6.b Overview of the Inpatient Unit Study Schedule

Screening Period	Check-in and Baseline	Treatment Periods 1 and 2		End-of-Study Visit
		Dosing	Washout	
Study Days -28 to -3	Study Days -2 (nPSG [a]) and -1 (Baseline)	**Study Days 1 and 3** Study drug administration/CC PK, and safety assessments	**Study Days 2 and 4** [b] PK and safety assessments	Study Day 11 (±2 days) Follow-up (in clinic or by phone call)
	← Confinement Study Day -2 to Study Day 4 →			

nPSG: nocturnal polysomnography; CCI PK: pharmacokinetic.
[a] nPSG only on Study Day -2.
[b] Discharge from unit on Study Day 4.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Rationale for Study Design

This is a study with a 2-period Williams crossover design to evaluate the safety, tolerability, PK, CCI of TAK-925. The endpoints in such studies have smaller variability than those in the parallel design as the subjects are used as their own control. Such design has been previously used in other studies of drugs that have been evaluated for effects on wakefulness [8]. As previously shown, mean TAK-925 concentrations decline rapidly after the end of infusion with levels quantifiable up to 18 hours post-dose at a dose of 112 mg; hence, a greater than 24-hour period from the end of dosing of TAK-925 to the start of the next dosing is deemed sufficient to ensure adequate drug washout. The short washout interval also enables full confinement from Treatment Period 1 to Treatment Period 2, which will potentially reduce the dropout rates and increase study compliance. Some subjects with IH have severe daytime sleepiness despite their best efforts to stay awake. CCI

6.2.2 Rationale for Dose

Based on the currently available information, this study will evaluate a single-dose of TAK-925 at 112 mg.

Single-dose administration of TAK-925 in a slow infusion over 9 hours up to 240 mg in healthy adult subjects, up to 112 mg in healthy elderly subjects, and up to 44.8 mg in subjects with NT1, was well-tolerated with no major safety concerns. BP and HR increases were the most frequently reported TEAEs. While these increases were consistently observed with TAK-925 doses ≥134.4 mg/day in healthy adult subjects (or 112 mg/day in healthy elderly subjects) with a greater incidence of these AEs at the maximum dose of 240 mg, no BP or HR increase AEs were reported with lower TAK-925 doses.

A single dose of 112 mg is selected to evaluate a dose of TAK-925 that is expected to produce wake-promoting effects, while maintaining an acceptable clinical safety profile in this IH subject population. CCI [redacted]

6.2.3 Rationale for Endpoints

As this is a single-dose study, the standard safety endpoints for early clinical development will be included. In a safety pharmacology study of TAK-925 as well as in the first-in-human study (TAK-925-1001), cardiovascular-related adverse findings including PR prolongation and elevation of BP and HR were reported. Based on these observations, the following assessments will be included:

- TEAEs; subjects will be monitored closely throughout the study for any AEs.
- Physical examinations.
- Vital signs, including frequent monitoring of BP, pulse, and respiratory rate.
- 12-lead ECGs.
- Clinical laboratory safety evaluations (standard hematology, serum chemistry, and urinalysis).

To characterize the PK of TAK-925 CCI [redacted] administered as a single IV infusion dose to subjects with IH, the following PK parameters will be estimated as data permit.

- AUC_{∞}.
- AUC_{last}.
- C_{max}.
- C_{eoi}.
- Time of first occurrence of C_{max} (t_{max}).
- Terminal disposition phase half-life ($t_{1/2z}$).
- Volume of distribution at steady state after IV administration (V_{ss}) (only for TAK-925).
- Volume of distribution during the terminal disposition phase after IV administration (V_z) (only for TAK-925).
- Total clearance after IV administration (CL) (only for TAK-925).
- CCI [redacted]

CCI

[redacted]

CCI

[redacted]

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 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 compound 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.
- If the interim analysis results meet the stopping criteria (see Section 13.2).

Other Safety Monitoring and Specific Stopping Criteria for Individual Subjects

CCI

[redacted]

- Any subject who experiences a treatment-emergent serious AE or a severe AE that is considered related to treatment.

6.3.2 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.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) 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 randomization.

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 and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is male or female, aged 18 to 75 years, inclusive, at the time of informed consent.
4. A diagnosis of IH, as defined by the ICSD-3 (Appendix F), as verified by a previous nPSG and MSLT study performed within the last 10 years.

   Note: If there is a potential subject with a history of IH whose diagnostic nPSG/MSLT was performed more than 10 years ago or is not available and the subject continues to experience symptoms consistent with IH, the PI will obtain a current nPSG/MSLT.
5. Onset of hypersomnia between 10 and 30 years of age.
6. Seven consecutive days of actigraphy supported by a sleep diary (recorded while the subject was wearing the actigraph) obtained prior to the nPSG (Study Day -2) shows an average nightly sleep duration of ≥420 minutes during the subject's normal nocturnal sleep period.
7. nPSG (Study Day -2) demonstrates that subject does not have other comorbid sleep disorders or clinically significant nocturnal hypoxemia (O_2 saturation ≤80% for ≥5% of total sleep time) and that their AHI is ≤10/hour, their PLMAI is ≤15/hour, and that their total sleep time is ≥6.5 hours.
8. CCI [redacted]
9. Subjects taking medication for treatment of EDS must be willing to discontinue medication prior to randomization into the study.
10. Body mass index (BMI) of 18 through 33 kg/m^2 inclusive.
11. ESS score ≥11 at screening and on Day -2. Subjects with an ESS score of <11 who are taking stimulants at screening may continue the screening process and repeat the ESS at Study Day -2 following washout (see Table 7.a).
12. Male subjects who are non-sterilized and their female sexual partners of childbearing potential must follow the contraception methods described in Appendix G. In addition, male subjects must agree to not donate sperm from the first dose of study drug until 5 half-lives plus 90 days after the last dose of study drug.

13. Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must agree to use a highly effective method of contraception as described in Appendix G from signing of informed consent until 5 half-lives of TAK-925 plus 30 days.
14. Female subjects who are post-menopausal or permanently sterile according to the definitions in Appendix G.
15. Female subjects of childbearing potential must have a negative urine pregnancy test at screening and Study Day -1.
16. BP must be <140 mmHg (systolic) and <90 mmHg (diastolic) at screening and Study Day -2. BP measures should be obtained after the subject has been resting for a minimum of 10 minutes and may be repeated 3 times if the BP is elevated above these parameters. The median BP reading will be used.

7.2 Exclusion Criteria

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

1. Average nightly sleep duration is ≤8 hours (480 minutes) and the subject has insufficient sleep syndrome as evidenced by sleeping >2 hours/night more on "off-days" relative to "work days" as determined by actigraphy and sleep diary obtained prior to the nPSG (Study Day -2).
2. Positive urine screen for drugs of abuse and/or positive alcohol breathalyzer test at screening and/or Study Day -2. An exception at screening is made for stimulants or other drugs that the subject has been prescribed, but the drug screen must be negative at Study Day -2.
3. History of drug or alcohol abuse within the 12 months prior to screening (Diagnostic and Statistical Manual of Mental Disorders, Edition 5 [DSM-5 criteria]).
4. Women who are pregnant or breastfeeding.
5. Resting HR outside of the range of 40 to 90 bpm off stimulants.
6. Screening ECG reveals a QT interval with Fridericia correction method >450 ms (men) or >470 ms (women).
7. Usual bedtime later than 24:00 (midnight) or an occupation requiring nighttime shift work or variable shift work within the past 6 months, or travel with significant jet lag within 14 days before Study Day -2.
8. History of a sleep disorder other than IH, based on interviews at the screening visit, such as OSA, restless legs syndrome, or periodic limb movements of sleep (PLMS) associated with arousals.
9. Used of any over-the-counter (OTC) or prescription medications with stimulating properties within 7 days prior to dosing or 5 half-lives (whichever is longer) that could affect the evaluation of EDS, or any use of sodium oxybate within 4 weeks of screening (see Table 7.a).
10. Nicotine dependence that is likely to have an effect on sleep (eg, a subject who routinely awakens at night to smoke) or challenge the conduct of this study (smokes ≥10 cigarettes/day)

and/or an unwillingness to discontinue all smoking and nicotine use during the confinement portion of the study (Day -2 to Day 4).

11. Caffeine consumption of more than 600 mg/day for 7 days before Study Day 1 (1 serving of coffee is approximately equivalent to 120 mg of caffeine) and/or unwilling to discontinue all caffeine during the confinement portion of the study (Day -2 to Day 4).
12. Alcohol use that is likely to have an effect on sleep and/or an unwillingness to discontinue all alcohol use from 72 hours before check-in through discharge on Study Day 4.
13. History or presence of any unstable medical condition, behavioral or psychiatric disorder (including major depression or active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the study per the judgment of the investigator.
14. Employee or family member of the investigator, study site, contract research organization (CRO), or sponsor.
15. Previously participated in a TAK-925 study or has participated in another investigational study within 4 weeks prior to the screening visit.
16. In the opinion of the clinical investigator, should not participate in the study.
17. Allergic to any excipient in the study drug.
18. History of epilepsy or seizures, including having had a single seizure or a history of childhood febrile seizures or has a clinically significant history of head trauma.
19. Positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency antibody/antigen, at the screening visit. Note: Subjects with positive hepatitis B virus or hepatitis C virus serology may be enrolled if quantitative polymerase chain reaction for hepatitis B virus or hepatitis C virus RNA is negative.
20. Donated blood or plasma within 6 weeks prior to Study Day 1 or planning to donate blood or plasma within 12 weeks after study exit.
21. Answered "YES" on Questions 4 or 5 on the Suicidal Ideation subscale of the C-SSRS at screening (defined period as 3 months prior to screening) or evidence of suicidal behavior within 6 months of screening as measured by the Suicidal Behavior subscale of the C-SSRS.
22. Diagnosis of major depressive disorder (DSM-5) within the past 6 months or BDI-II total score of >16 at the screening visit.
23. Renal creatinine clearance ≤60 mL/min at the time of screening and Study Day -2.
24. History of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation.
25. Known coronary artery disease, a history of myocardial infarction, angina, cardiac rhythm abnormality, or heart failure.

26. Abnormal laboratory test values that suggest a clinically significant underlying disease or any subject with transaminase (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) >2.0 ×upper limit of normal (ULN) at the screening visit or Study Day -2.
27. Unable to refrain from or anticipates using food products listed in Table 7.b, beginning approximately 7 days prior to administration of the first dose of study drug, through Study Day 4 inclusive.

7.3 Excluded Medications

Subjects must be instructed not to take any medications during the study, including OTC products, without first consulting with the investigator. Occasional use of acetaminophen and aspirin is allowed.

Subjects who require treatment with 1 or more of prohibited medications should be excluded or discontinued (as appropriate) from the study. If a subject is prescribed treatment with a prohibited medication during the conduct of the study, the investigator should contact the sponsor or designee to review the relevant clinical information and medication treatment to determine subject disposition.

Additional detailed guidance on excluded/allowed medications may be provided in separate reference documentation provided to study sites.

Table 7.a provides a list of medications/drug classes that are prohibited for 7 days or 5 half-lives, before the first day of dosing (Day 1 of Treatment Period 1).

Table 7.a Prohibited Drug Classes

Prohibited Drug Classes	**Starting from 7 days or 5- half-lives, whichever period is longer for the drug classes listed below, before administration of study drug**
Psychostimulants	Including methylphenidate hydrochloride, modafinil, armodafinil, solriamfetol, pitolisant, methamphetamine hydrochloride, pemoline, venlafaxine, duloxetine, atomoxetine, reboxetine, esreboxetine, decongestants, diet aids
Antipsychotic drugs	
Benzodiazepines (minor tranquilizers)	
Mood stabilizers	
Sedating anticonvulsants	
Sedative hypnotics	
Parkinson's disease/RLS drugs	
Adrenocorticosteroids	
Interferon, interleukin-formulation	
Muscle-relaxants (eg, baclofen)	
Sedating antihistamines and decongestants	Non-sedating antihistamines are allowed
Sodium oxybate	Requires no use for 4 weeks prior to screening
Sedating antitussives	
Sedating antiemetics	
Sedating analgesics	
Sedating antihypertensives	
St. John's wort, kava-kava, gingko biloba, health foods containing melatonin.	
Known in vivo CYP3A inhibitors or inducers: 1. Potent CYP3A inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir, ritonavir, elvitegravir, indinavir, saquinavir, idelalisib, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, telaprevir, tipranavir, troleandomycin, voriconazole. 2. Moderate CYP3A inhibitors: amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporin, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, fluvoxamine, miconazole, imatinib, istradefylline, tofisopam, verapamil. 3. Potent CYP3A inducers: carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin. 4. Moderate CYP3A inducers: bosentan, efavirenz, etravirine.	

CYP3A4: cytochrome P450 3A4; RLS: restless legs syndrome.

7.4 Diet, Fluid, and Activity Control

7.4.1 Diet and Fluids

Subjects will receive 3 standardized meals per day each including approximately 30% fat (relative to the total calories) during confinement in the unit. Breakfast will be served at approximately 0700 each morning; lunch and dinner will be served at standardized times so as not to coincide or interfere with clinical testing [redacted].

Subjects will follow the restrictions of food, drinks, and other products listed in Table 7.b.

Table 7.b List of Restricted Food, Drinks and Other Products

Category	Screening Period (Days -28 to -3)	Inpatient Day -2 to Discharge on Day 4
Tobacco- and nicotine-containing products	Restricted to less than 10 cigarettes per day	Completely restricted
Alcohol	Restricted for 72 hours prior to check-in	Completely restricted
Xanthine and/or caffeine	No more than 600 mg/day 7 days before dosing	Completely restricted
Food Products		
Grapefruit/grapefruit juice and Seville oranges	Completely restricted 7 days before dosing	Completely restricted
Other fruit juices		Restricted for 12 hours before and after administration of each dose of study drug on pharmacokinetic sampling days (Days 1 and 3 of each treatment period). Consumption of all fruits other than grapefruit and Seville oranges is allowed on all days of the study.
Mustard greens (ie, kale, broccoli, watercress, collard greens, kohlrabi, Brussel sprouts, and mustard)	Completely restricted 7 days before dosing	Completely restricted
Charbroiled meat	Completely restricted 7 days before dosing	Completely restricted

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling) from the screening visit until administration of the initial dose of study drug, throughout the study (including the washout interval between treatment periods), and until the follow-up visit. Short supervised walks outside the unit are permitted on washout days.

7.5 Criteria for Discontinuation or 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 9.8.

1. Pretreatment event (PTE) or AE: The subject has experienced a PTE or 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 PTE or AE.

   - Liver function test (LFT) 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 9.4), if the following circumstances occur at any time during study drug treatment:

     – ALT or AST >8 × ULN, or

     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio >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%).

   - Suicidality:

     – Study drug should be discontinued immediately for subjects at imminent risk of suicide per the investigator's clinical judgment.

   - BP and HR increase: Criteria for stopping an infusion due to elevated BP or HR are defined as follows ("sustained" is defined as 2 readings separated by approximately 15 minutes):

     – Sustained SBP ≥160 mmHg or sustained post-dose change from pre-dose baseline of ≥30 mmHg.

     – Sustained DBP ≥100 mmHg or sustained post-dose change from pre-dose baseline of ≥30 mmHg

     – Sustained HR >100 bpm or sustained post-dose change from pre-dose baseline of ≥30 bpm.

   - Seizures
   - Severe changes in mood.
   - Any subject who experiences a treatment-emergent serious AE or a severe AE that is considered related to treatment.

   Note: The reasons above should be recorded on the eCRF if the PTE or AE is chosen as the primary reason of discontinuation.

2. 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.
3. 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.
4. Voluntary withdrawal: The subject (or subject's legally acceptable representative) 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.
5. Study termination: The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. 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 Appendix G.
7. Other:

   Note: The primary reason 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 without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit.

7.7 Subject Replacement

If deemed appropriate by the investigator or sponsor, additional subjects may be randomized due to subject discontinuation from the study to achieve the targeted number of completers.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

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.

1. TAK-925 solution for IV infusion.
2. Matched placebo solution for IV infusion.

Takeda will supply all clinical drug supplies for this study. Each United States Pharmacopeia Type I glass vial nominally contains 10 mL of compounded sterile solution, sealed with a fluoropolymer-coated butyl rubber stopper and over-sealed with an aluminum seal and a plastic cap. Study drug containers will be affixed with clinical labels in accordance with local regulatory requirements.

8.1.1.1 Ancillary Supplies

All ancillary supplies will be provided by either the study site or the sponsor or designee, based upon availability. The list of ancillary supplies and source information can be found in the pharmacy manual or in the referenced compounding manual when applicable. If provided by the sponsor, unused ancillary supplies will be accounted for and disposed of as directed by the sponsor or designee.

8.1.1.2 Sponsor-Supplied Drug

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

1. TAK-925 solution for IV infusion.
2. Matched placebo solution for IV infusion.

8.1.2 Storage

Study drug at the sites must be stored in a secure, limited-access location under the storage conditions specified on the label and remain in the original container until dispensed. The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the study site.

The study drug will be stored at 20°C to 25°C (68°F -77°F); excursions permitted to 15°C to 30°C (59°F -86°F).

A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

Doses and regimens are provided in Table 6.a.

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 in order to capture this important safety information consistently in the database. 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

Subjects will be randomized using an interactive voice response (IVRS)/(interactive web response system [IWRS]). On Day 1 of Treatment Period 1, subjects will be assigned a randomization number in ascending numerical order at the clinical site. The randomization number encodes the sequence which describes the order in which each subject will receive TAK-925 112 mg or placebo. Each subject will be administered blinded study drug, labeled with his/her unique randomization number, throughout the study.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule for the IVRS/IWRS system. Details are in the pharmacy manual. In addition, the pharmacy manual includes instructions for emergency unblinding. Storage conditions are also specified in the pharmacy manual.

8.4 Study Drug Blind Maintenance

The study drug blind will be maintained through a randomization schedule held by the IVRS/IWRS system and by the site pharmacists.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. If possible, the medical monitor/monitor should be contacted before the blind is broken. Unblinding will be performed per the standard operating procedures of the study site.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator is responsible for keeping accurate records of the study drug received from the sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the end of the study. For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction.

9.0 STUDY PLAN

The following sections describe the study procedures and data to be collected as indicated in the Schedule of Study Procedures (Appendix A). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Assessments should be completed at the designated visit/time points. An hourly schedule of procedures for Day 1 of each treatment period is listed in Appendix B

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters the study, and before any protocol-directed procedures are performed, including withdrawal of prohibited medications. The requirements of the informed consent are described in Section 15.2.

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

CCI

[redacted]

9.1.2 Inclusion and Exclusion

Each subject will be assessed through randomization according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical and Social History and Demographics

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

Medical and social history, including use of tobacco and alcohol, 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.

9.1.4 Prior and Concomitant Medication

Qualified site personnel will review subject's prior and concomitant medication use. Medications are defined as prescription and OTC drugs, vaccines, supplements, nutraceuticals, and oral herbal preparations.

Medication history information to be obtained includes any medication relevant to eligibility criteria and safety evaluation prior to randomization.

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject OTC.

9.1.5 Washout of Prohibited Concomitant Medications

The use of concomitant medications is prohibited starting from 7 days or 5 half-lives, whichever period is longer for the drug classes listed in Table 7.a before administration of the first dose of study drug.

9.1.6 Actigraphy and Sleep Diary

Approximately 7 consecutive days of actigraphy supported by a sleep diary will be recorded beginning on Study Day -9 and ending on Study Day -3 (ie, the day before their Study Day -2 admission to the clinical unit). Data from the actigraphy device will be downloaded by the site to ensure that a subject sleeps on average 420 min (7 hours)/night and does not have insufficient sleep syndrome, as specified in the exclusion criteria.

9.2 Clinical Procedures/Assessments

9.2.1 Physical Examination Procedure

A full physical examination will be performed at the times specified in the Schedule of Study Procedures (Appendix A) and will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

All postbaseline physical examinations should assess clinically significant changes from the baseline assessment.

9.2.2 Height, Weight, and BMI

Body weight and height will be obtained with the subject's shoes off, and jacket or coat removed.

BMI equals a subject's weight in kilograms divided by height in meters squared (BMI = kg/m^2). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4, round down, and 0.5 to 0.9, round up.

9.2.3 BDI-II

The Beck Depression Inventory is a widely used psychometric test for measuring the intensity, severity, and depth of depression in patients with psychiatric diagnoses. This study will use the most updated version of the Beck Depression Inventory (1996, BDI-II).

The test is composed of 21 questions, each designed to assess a specific symptom common among people with depression. Each answer is scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. The standardized cutoffs used are:

- 0–13: minimal depression.

- 14–19: mild depression.
- 20–28: moderate depression.
- 29–63: severe depression.

The BDI-II is positively correlated with the Hamilton Depression Rating Scale with a Pearson r of 0.71, showing good agreement. The test was also shown to have a high one-week test-retest reliability (Pearson r = 0.93), suggesting that it was not overly sensitive to daily variations in mood [12]. The test also has high internal consistency (α = .91) [13].

9.2.4 C-SSRS

Suicidal ideation will be assessed using the C-SSRS at the times stipulated in the Schedule of Study Procedures (see Appendix A). 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. Any suicidal ideation or suicidal behavior during study periods detected by C-SSRS will be recorded as AEs. The investigator will ensure that any suicidal ideation or behavior is medically addressed, including assessment and treatment by qualified medical personnel.

9.2.5 Study Drug Administration

On Day 1 of each treatment period, study drug (TAK-925 112 mg or placebo) will be administered as described in Section 6.1.

9.2.6 Vital Sign Procedure

Vital signs will include SBP and DBP, HR, body temperature, and respiratory rate. The same method (eg, same size cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

Body temperature will be measured with an oral (temperature taken at floor of the mouth) or tympanic thermometer. O_2 saturation index will be measured at screening (finger monitor).

Subjects should rest in a bed with the head of the bed at 30 degrees for at least 5 minutes before vital signs are measured. Vital signs will include HR, respiratory rate, SBP, and DBP. The same method (eg, same size cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

Subjects should continue to rest in a bed with the head of the bed at 30 degrees from the time of dosing until 2 hours post-dose except to stand if necessary for study-related procedures.

9.2.7 12-Lead ECG

A standard 12-lead ECG will be recorded. The following parameters will be recorded electronically by a central reader from the subject's ECG trace: HR, RR interval, PR interval, QT interval, QRS interval.

9.2.8 AE Monitoring

AE monitoring begins after signing of the informed consent form. Changes in subject health status from the baseline assessment until study drug administration should be captured as pre-treatment events. A complete description of AE collection and reporting procedure is provided in Section 10.0.

CCI

CCI

[redacted]

9.4 Laboratory Assessments/Procedures

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.

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

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry		Urinalysis
Hematocrit	Albumin	Chloride	Blood
Hemoglobin	Alkaline phosphatase	Creatinine	Glucose
Platelets	ALT	GGT	Nitrite
RBC	AST	Glucose	Protein
WBC	Bilirubin (total); if above ULN, total bilirubin will be fractionated	HDL	Specific gravity
		LDL	
		Phosphate	
	Blood urea nitrogen	Potassium	
	Calcium	Protein (total)	
	Carbon dioxide	Sodium	
		Total cholesterol	
		Triglycerides	

Other	
Serum	**Urine**
HIV HBsAg and anti-HCV HbA1C [a] FSH [b] INR [c]	Drug screen including amphetamines, barbiturates, benzodiazepines, buprenorphine/metabolite, cannabinoids, cocaine/metabolites, MDMA, methadone/metabolite, opiates, oxycodone/oxymorphone, and phencyclidine; hCG (for pregnancy) [c]

ALT: alanine aminotransferase; anti-HCV: antibody to hepatitis C virus; AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; GGT: γ-glutamyl transferase; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HDL: high-density lipoprotein; HIV: human immunodeficiency virus; INR: international normalized ratio; LDL: low-density lipoprotein; MDMA, 3,4-methylenedioxy-methamphetamine; RBC: red blood cells; ULN: upper limit of normal; WBC: white blood cells.
[a] Diabetic subjects only.
[b] Postmenopausal women only.
[c] If ALT or AST >3 times the ULN.
[d] Women of childbearing potential only.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase, and international normalized ratio) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.3 for the appropriate guidance on reporting abnormal LFTs.)

If ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the medical monitor/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).

9.5 PK [CCI] Samples

9.5.1 PK [CCI] Evaluations

Primary specimen collection for PK [CCI] are provided in Table 9.b. Samples for PK [CCI] analysis will be collected as specified in the schedule in **Appendix A**.

Table 9.b Primary Specimen Collection for [CCI] PK Samples

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-925 [CCI]	Blood	Plasma	PK measurements	Mandatory

[CCI]

[CCI] PK: pharmacokinetic(s).

9.5.2 PK Measurements

The PK parameters of TAK-925 [CCI] will be determined from plasma concentrations from all evaluable subjects using noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following PK parameters will be calculated from plasma concentrations of TAK-925 [CCI] as data permit:

AUC_{∞}	$t_{1/2z}$
AUC_{last}	V_{ss} (TAK-925 only)
C_{max}	V_z (TAK-925 only)
C_{eoi}	CL (TAK-925 only)
t_{max}	[CCI]

Additional PK parameters may be calculated as appropriate. A detailed PK analysis plan will be prepared before PK parameter computation.

9.5.2.1 Blood for PK Measurements

Blood samples (one 3-mL sample per scheduled time) for determination of plasma concentrations of TAK-925 [CCI] will be collected into chilled blood collection tubes (vacutainer) containing the anticoagulant K2EDTA (dipotassium ethylenediaminetetraacetic acid) according to the Schedule of Study Procedures in Appendix A. An hourly schedule of sampling on Day 1 of each treatment period is provided in Appendix B.

To reflect the plasma exposure more precisely, blood samples will be collected from the arm opposite to the one on which IV infusion is performed. If the opposite arm in not available, blood

samples should be collected at a site that is as distant to the infusion site as possible, and the site of the blood sampling should be documented. The blood sampling times and times of the start and end of infusions should be recorded accurately on the source document and eCRF; particular care should be given when recording the blood sampling times during the infusion and around the time close to the infusion. Sampling time points may be adjusted based on the preliminary emerging concentration data collected from prior subjects, but the total number of samples collected per subjects should not exceed the planned number.

Instructions for collecting, processing, and shipping of PK samples are provided in the laboratory manual.

9.5.2.2 PK Sample Analysis

Plasma concentration of TAK-925 CCI [redacted] will be measured by a validated high-performance liquid chromatography with tandem mass spectrometry assay. Part of the archival plasma samples may be used for potential analysis of unknown CCI [redacted] characterization, if appropriate.

CCI [redacted]

CCI

9.6 Blood Volume

It is anticipated that the total blood volume drawn for each subject will be approximately 107 mL. The amount of blood for each type of sample is summarized in Table 9.c.

Table 9.c Blood Volume

		Number of Samples					
	Sample Volume (mL)	Screening	Study Day -2	Study Day -1	Treatment Periods 1-2 Day 1-2	Follow-up	Total Volume (mL)
Laboratory safety tests	10	1	1	0	1	0	30
FSH [a]	5	1					5
HIV/hepatitis screen	6	1	0	0	0	0	6
CCI							
Blood for PK	3	0	0	0	20	0	60
Total blood volume per subject							107

FSH: follicle-stimulating hormone; HIV: human immunodeficiency virus; CCI
PK: pharmacokinetics.
[a] Postmenopausal women only.

9.7 Confinement

Subjects will report to the clinical site on Study Day -2 and will leave after completion of all study-related procedures on Study Day 4.

At the discretion of the investigator, subjects may be requested to remain in the clinical site longer to further assess safety.

9.8 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 IVRS/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:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.

Subject identification numbers assigned to subjects who fail screening should not be reused.

9.9 Documentation of Study Entrance/Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance/randomization into the treatment phase.

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

9.10 Monitoring Subject Treatment Compliance

Study drug (TAK-925 and matching placebo) will be administered as a continuous IV infusion at the clinical site by authorized personal. Interruptions of the IV infusion and reason(s) for such interruptions will be recorded on the eCRF.

10.0 PRETREATMENT EVENTS AND AEs

10.1 Definitions

10.1.1 PTEs

A 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.

10.1.3 Additional Points to Consider for PTEs and 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 PTEs or 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.

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

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 a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest and/or continued monitoring of an abnormal value or finding are

not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious, or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs/serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, 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 PTEs or 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 a PTE or 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 PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- 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 PTEs or AEs, but instead will be documented in the eCRF. Any manifested side effects will be considered PTEs or 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 fulfills 1 or more of the serious criteria below:

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 inpatient 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).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

PTEs 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

CCI [redacted] AESIs will be collected and reported as AEs or SAEs, as defined in Section 10.1.2 and 10.1.4, according to the procedures in Section 10.2.1 and 10.2.2, respectively.

10.1.6 Intensity of PTEs and 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.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as not related.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.10Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose interrupted – the dose was interrupted due to the particular AE.
- Dose delayed – the dose was delayed due to the particular AE.

10.1.13Outcome

- Recovered/resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the

subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".

- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Study Day 1) or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Study Day 1). Routine collection of AEs will continue until the follow-up/early termination visit.

10.2.1.2 PTE and 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 a serious PTE 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. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

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 PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.

5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

SAEs should be reported via SAE eCRF in Rave EDC, which is the preferred method of reporting SAEs. A Takeda SAE eCRF must be completed in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but should contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

If access to Rave EDC is not feasible within 24 hours of receiving the event, the paper SAE forms should be submitted via fax. The SAE form should be completed within 24 hours of first onset or notification of the event, signed by the investigator, and transmitted via fax or email to the attention of the contact listed in Section 1.1. In case of fax, site personnel need to confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day.

Email submission of SAE forms (to the appropriate e-mail address listed below) with a portable document format (PDF) attachment should only be used in the case where fax is not possible and access to Rave EDC is not feasible within 24 hours of receiving the event. In case of e mail, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via e mail within 1 business day.

- United States and Canada: PVSafetyAmericas@tpna.com
- Rest of World: eupv@tgrd.com

If SAEs are reported via fax or by email, Rave EDC must be updated as soon as possible with the appropriate information.

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 LFTs

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have 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 9.4 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda 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, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately. 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 or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports 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 study. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

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, PTEs, 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 (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

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.

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.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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 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 use of change and modification records of the eCRFs. 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 informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), 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.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. 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

13.1.1.1 Safety Set

The safety set will consist of all subjects who were randomized and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

13.1.1.2 PK Set

The PK analysis set will consist of all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma concentration.

CCI [redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized and listed by treatment sequence and overall. Descriptive statistics will be used to summarize data for continuous variables such as age and weight (number of subjects [N], mean, median, SD, minimum, and maximum) and for categorical variables such as sex, ethnicity, and race (number and percentage of subjects within each category). Tobacco and alcohol use will also be summarized. Medical history and medication history will be listed by subject.

13.1.3 PK Analysis

Individual plasma concentrations of TAK-925 CCI [redacted] and PK parameter estimates will be listed for each subject and summarized using descriptive statistics as appropriate.

CCI [redacted]

CCI

[redacted]

13.1.5 Safety Analysis

AEs will be summarized using the safety analysis set.

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

Standard summaries of TEAEs, clinical safety labs, vital signs and ECGs will be performed. Where appropriate, BP and QT parameters will be summarized (N, mean, SD, median, minimum and maximum) for baseline, post-dose, change from baseline and change from time-matched baseline to post-dose by treatment.

The observed HR and BP will be analyzed using linear mixed effect model for repeated measures in crossover studies. The model will include sequence, period, treatment, time points, and treatment by time point interaction as fixed effects and a random effect for subject within sequence. The estimated mean HR and BP for each treatment and the associated standard error and 95% CI will be extracted from the model at each time, along with all pairwise differences from placebo and associated standard errors, 95% CIs, and p-values. The same quantities, averaged over all timepoints during the infusion and post the end of the infusion, will also be extracted from the model using appropriate contrasts.

13.2 Interim Analysis and Criteria for Early Termination

When at least 12 subjects completed both treatment periods, an interim analysis may be performed for futility, superiority, and/or sample size re-estimation. The criteria for futility and superiority will be described in the SAP.

13.3 Determination of Sample Size

Up to 40 subjects are planned to be randomized equally to each treatment sequence to ensure 36 subjects complete the study. This number of subjects is typical for phase 1 crossover study designs and is considered sufficient for assessment of safety. CCI [redacted]

CCI [redacted] In addition, when the true difference between TAK-925 and placebo is minimal, the chance to observe the same event is no more than 10%.
Non-informative prior distributions were used in the above probability calculation. Allowing for 4 dropouts (10%), 40 subjects are planned to be randomized.

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 (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, 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 or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

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.

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 Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency 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 Harmonised 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 C. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local 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 or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American 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 or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, 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 or IEC for approval. The IRB's or IEC'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 (ie, before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/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. Until the site receives drug/notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, 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 or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC 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 or IEC 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 informed consent form, 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 informed consent form 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 informed consent form will detail the requirements of the subject 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 informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, 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 informed consent form, 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 or IEC. If the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, 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 informed consent form 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 or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering 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 informed consent form, 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 informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative 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 informed consent form.

CCI

[redacted]

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 study database or documentation via a subject identification 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 identification 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, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs 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.

15.4.2 Clinical Study Registration

In order to ensure that information on clinical studies 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 studies 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 study information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study 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 Study Results Disclosure

Takeda will post the results of clinical studies 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.

16.0 REFERENCES

1. Ohno K, Sakurai T. Orexin neuronal circuitry: role in the regulation of sleep and wakefulness. Front Neuroendocrinol 2008;29(1):70-87.
2. Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities. Annu Rev Pharmacol Toxicol 2011;51:243-66.
3. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. (ICSD-3). Rochester, MN: American Academy of Sleep Medicine; 2014.
4. Trotti LM. Idiopathic hypersomnia. Sleep Med Clin 2017;12(3):331-44.
5. Sowa NA. Idiopathic hypersomnia and hypersomnolence disorder: A systematic review of the literature. Psychosomatics 2016;57(2):152-64.
6. Mayer G, Benes H, Young P, Bitterlich M, Rodenbeck A. Modafinil in the treatment of idiopathic hypersomnia without long sleep time--a randomized, double-blind, placebo-controlled study. J Sleep Res 2015;24(1):74-81.
7. Huang SC, Dai YW, Lee YH, Chiou LC, Hwang LL. Orexins depolarize rostral ventrolateral medulla neurons and increase arterial pressure and heart rate in rats mainly via orexin 2 receptors. J Pharmacol Exp Ther 2010;334(2):522-9.
8. Gasior M, Freeman J, Zammit G, Donnelly P, Gao J, Ferreira-Cornwell MC, et al. Maintenance of wakefulness with lisdexamfetamine dimesylate, compared with placebo and armodafinil in healthy adult males undergoing acute sleep loss. J Clin Psychopharmacol 2014;34(6):690-6.
9. Kaida K, Takahashi M, Akerstedt T, Nakata A, Otsuka Y, Haratani T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. Clin Neurophysiol 2006;117(7):1574-81.
10. Reyner LA, Horne JA. Falling asleep whilst driving: are drivers aware of prior sleepiness? Int J Legal Med 1998;111(3):120-3.
11. Thomann J, Baumann CR, Landolt H-P, Werth E. Psychomotor vigilance task demonstrates impaired vigilance in disorders with excessive daytime sleepiness. Journal of Clinical Sleep Medicine 2014;10(09):1019-24.
12. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio 1996;78(2):490-8.
13. Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck Depression Inventories-IA and-II in psychiatric outpatients. Journal of personality assessment 1996;67(3):588-97.

Appendix A Schedule of Study Procedures

Period Day	**Screening** [a]	**nPSG**	**Baseline**	**Treatment Period 1**		**Treatment Period 2**		**Follow-up Period** [n]	**Early Termination**
	Study Day -28 to Study Day -3		Day -1	Day 1	Day 2	Day 1	Day 2		
Study Day		Study Day -2	Study Day -1	**Study Day 1**	Study Day 2	**Study Day 3**	Study Day 4	**Study Day 11 (±2 days)**	-
Administrative procedures									
Informed consent [b]	X								
Inclusion/exclusion criteria	X	X	X						
Medical history/demographics	X								
Prior and concomitant medication review – Continuous review	X	X	X	X	X	X	X	X	X
Washout of prohibited concomitant medications	X	X							
Clinical procedures/assessments									
Full physical examination	X		X		X		X		X
Height	X								
Weight	X						X		X
BMI	X								
C-SSRS	X	X					X		X
BDI-II	X								
Actigraphy [c]	X								
TAK-925/placebo administration [d]				X		X			
Vital signs (HR, pulse, BP) [e]	X	X	X	X	X	X	X		X

Period Day	**Screening** [a]	**nPSG**	**Baseline**	**Treatment Period 1**		**Treatment Period 2**		**Follow-up Period** [n]	**Early Termination**
			Day -1	Day 1	Day 2	Day 1	Day 2		
Study Day	Study Day -28 to Study Day -3	Study Day -2	Study Day -1	**Study Day 1**	Study Day 2	**Study Day 3**	Study Day 4	**Study Day 11 (±2 days)**	-
CCI [redacted]									
O_2 saturation index (finger monitor)	X								
CCI [redacted]									
Continuous monitoring of AEs	X	X	X	X	X	X	X	X	X
Pharmacodynamic evaluation/assessments									
nPSG		X							
CCI [redacted]									
Laboratory procedures/assessments									
Hematology [l]	X	X					X		X
Urinalysis	X	X					X		X
Serum chemistry	X	X					X		X
Urine drug screen and breathalyzer screen for alcohol [j]	X	X [k]							
Hepatitis screen	X								
HIV screen	X								
Urine pregnancy test [l]	X	X [k]					X	X	X
FSH (for postmenopausal women only)	X								

Period Day	**Screening** [a]	**nPSG**	**Baseline**	**Treatment Period 1**		**Treatment Period 2**		**Follow-up Period** [n]	**Early Termination**
			Day -1	Day 1	Day 2	Day 1	Day 2		
Study Day	Study Day -28 to Study Day -3	Study Day -2	Study Day -1	**Study Day 1**	Study Day 2	**Study Day 3**	Study Day 4	**Study Day 11 (±2 days)**	-
CCI [redacted]									
CCI [redacted]									
PK evaluations									
Blood sample for PK TAK-925 CCI [redacted]				X	X	X	X		X
Other									
Confinement		X [o]	X	X	X [p]	X	X [p]		

AE: adverse event; BDI-II: Beck Depression Inventory II; BMI: body mass index; C-SSRS: Columbia Suicide Severity Rating Scale; DBP: diastolic blood pressure; ECG: electrocardiogram; ESS: Epworth Sleepiness Scale; ET: early termination; FSH: follicle-stimulating hormone; HIV: human immunodeficiency virus; HR: heart rate; CCI [redacted]; nPSG: nocturnal polysomnography; CCI [redacted]; CCI [redacted]; PK: pharmacokinetic; CCI [redacted]; SBP: systolic blood pressure.

[a] Optional pre-screening testing on a case-by-case basis as approved by Takeda. PI is responsible for performance and interpretation of nPSG/MSLT.

[b] Must be signed prior to any study-related procedures.

[c] Nocturnal actigraphy testing, supported by a sleep diary, will be collected for 7 consecutive days (beginning on Study Day -9 and ending on Study Day -3, ie, the day before their Study Day-2 admission to the clinical unit for the nPSG) to document the subject does not have "insufficient sleep syndrome".

[d] On Day 1 of each period, TAK-925 or placebo will be administered as a single 9-hour IV infusion commencing at approximately 0800.

[e] Semi-recumbent BP and HR will be recorded during screening and Study Day -2; On Study Day -1, BP and HR will be recorded at the approximate times matched to Study Day 1 assessment times indicated in Appendix B: on Day 1 of each treatment period, BP and HR will be recorded immediately prior to the start of infusion, and approximately 1, 3, 5, 7, 9, 10, and 13 hours post-start of infusion. On Day 2 of each treatment period, BP and HR will be recorded 24 hours post-start of infusion.

[f] Respiratory rate and body temperature will be recorded at screening and Study Day -2. On Study Day -1, and on Study Days 2 and 4. On Day 1 of each treatment period, respiratory rate and body temperature will be recorded immediately prior to the start of infusion and at approximately 3, 5, 7, and 13 hours after the start of infusion.

CCI [redacted]

[i] Glycosylated hemoglobin only in diabetic subjects.

[j] A urine screen for drugs of abuse and breathalyzer screen for alcohol will be conducted at screening and Study Day -2. An exception at screening is made for stimulants or other drugs that the subject has been prescribed, but the drug screen must be negative at Study Day -2.

[k] Urine drug screen and pregnancy test results should be available before dosing on Day 1 of Treatment Period 1.

[l] Female subjects of childbearing potential only. Women of childbearing potential must return to the study site to complete a urine pregnancy test at the end-of-study visit.

[m] During each treatment period, blood for PK analysis of TAK-925 CCI will be obtained: pre-dose, 1, 3, 5, 7 and 9 hours after start of infusion, and at 0.17, 1, 4, and 15 hours after end of the infusion.

[n] Safety follow-up assessments will be conducted. The follow-up assessments can either be conducted as a visit to the site or as a telephone contact.

[o] Following completion of clinical testing procedures, site staff will make every effort to keep subjects awake until between 2200-2300.

[p] On Study Days 2 and 4, site staff will make every effort to keep subjects from sleeping during the day from 0700 until between 2200-2300.

Appendix B Treatment Day 1 Hourly Schedule of Procedures (Approximate Times) for Treatment Periods 1 and 2

Procedure	24-Hour Clock Time															
	Day 1 Pre-dose	08:00	09:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00	19:00	20:00	21:00	23:00
Awaken	X															
TAK-925 or placebo IV administration		START	X	X	X	X	X	X	X	X	STOP					
CCI																
CCI																
PK sampling [b]	X		X		X		X		X		X	X			X	

CCI; IV: intravenous; CCI; PK: pharmacokinetic; CCI Vigilance Task.

[a] These assessments will be obtained immediately prior to the start of study drug infusion.

[b] Blood for PK analysis of TAK-925 (CCI) will be obtained predose, 1, 3, 5, 7 and 9 hours after start of infusion, and at 0.17, 1, 4, and 15 hours after end of the infusion on Day 1. The 0.17 time point does not fall on the hour and the 15-hour postdose assessment falls on Day 2; therefore, these assessments are not indicated in the table.

CCI

[redacted]

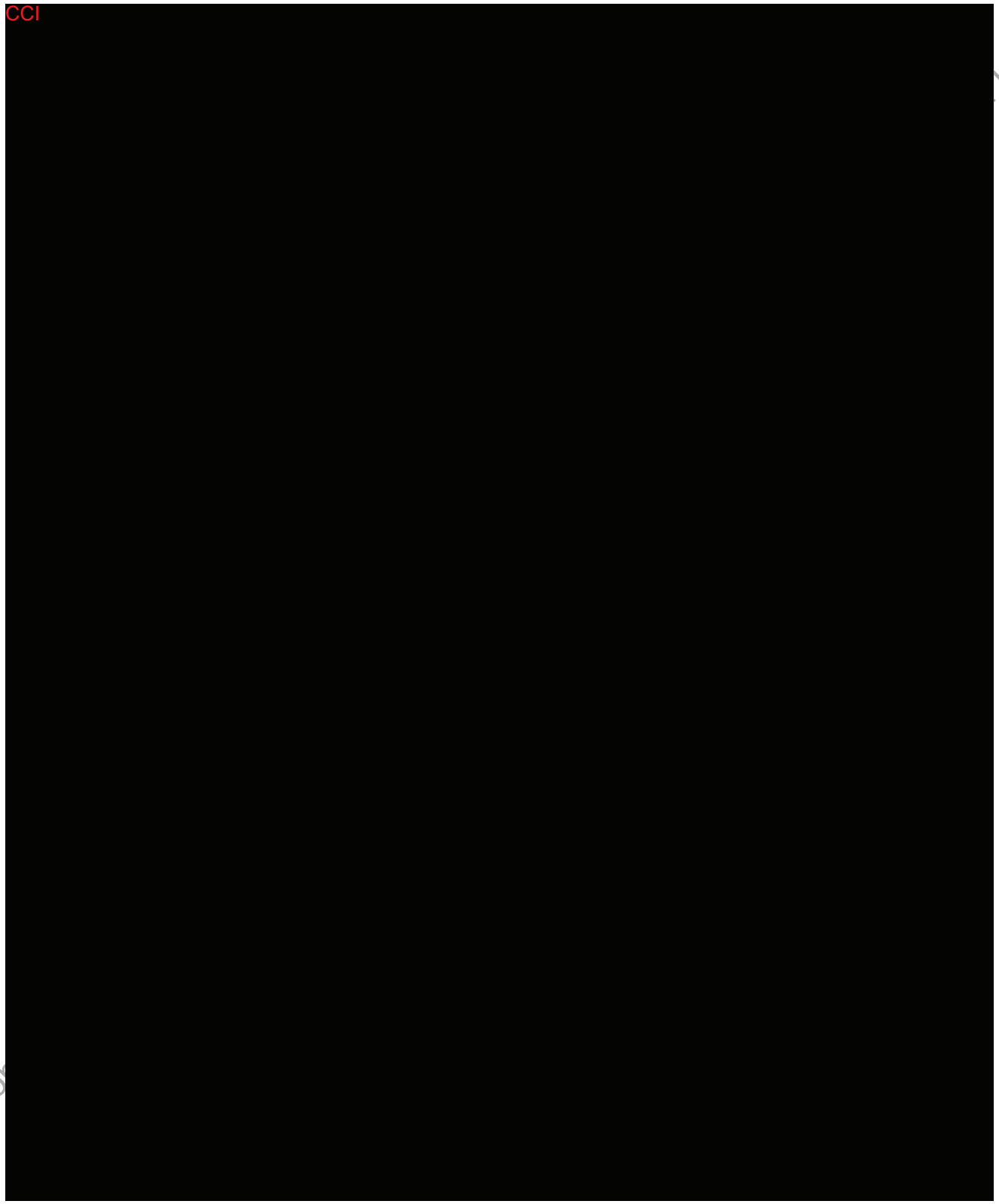
CCI

[redacted]

CCI

[redacted]

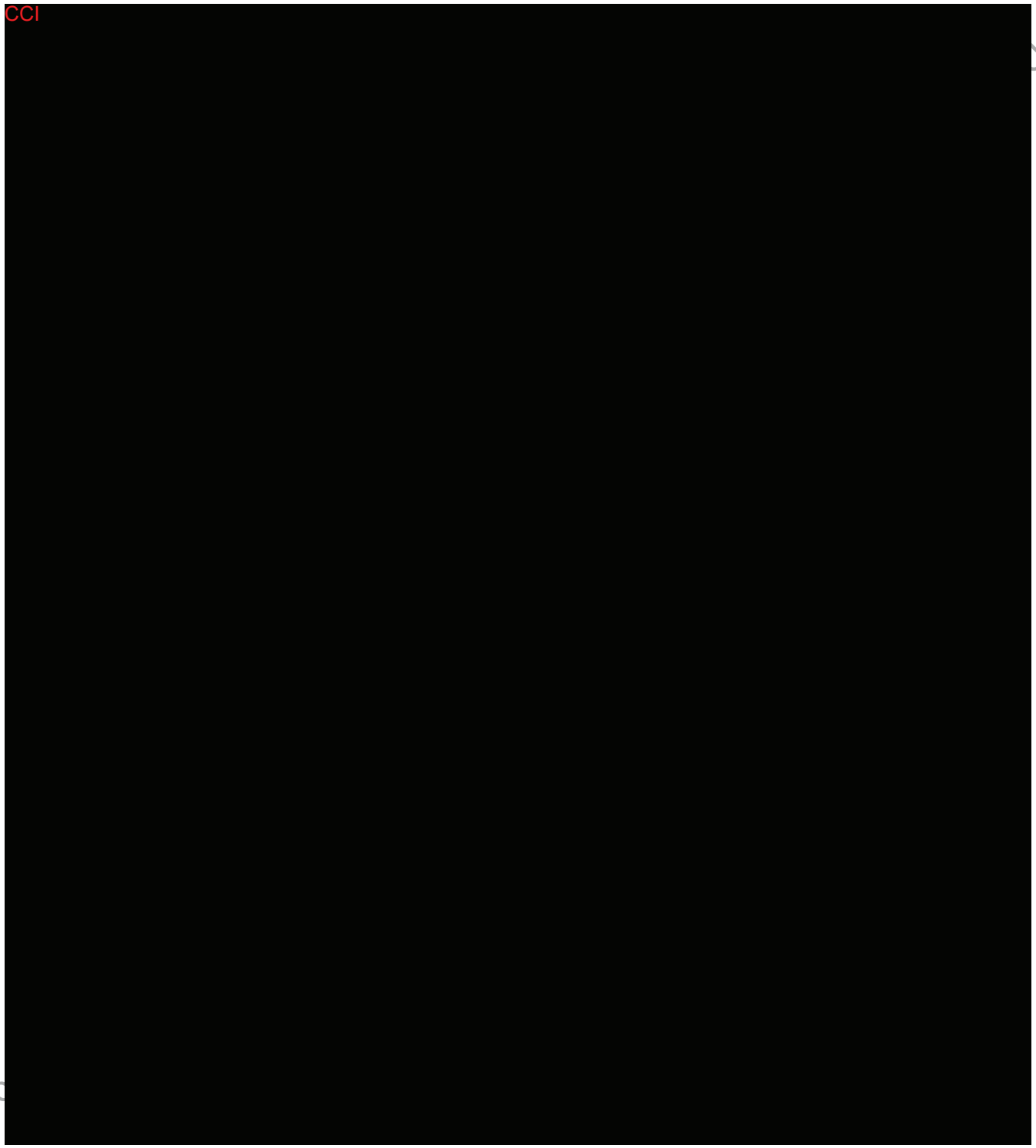
CCI



CCI

[redacted]

CCI



CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix H Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment 02 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: The number of participating sites was updated.

The primary change occurs in Section 2.0:STUDY SUMMARY.

Initial Wording: Approximately 15 in the United States and 2 sites in Japan.

New or Amended Wording: Approximately ~~15~~**21** sites in the United States and ~~2~~**3** sites in Japan.

Rationale for Change: The expected number of participating sites was updated.

Change 2: The description of the evaluation period in the study summary section was clarified.

The primary change occurs in Section 2.0:STUDY SUMMARY.

Initial Wording: Up to 43 days: including up to a 28-day screening period, 6-day confinement (including polysomnogram [PSG] and baseline assessments, and Treatment Periods 1 and 2 with a minimum 24 hour washout between periods), and an outpatient site visit or telephone follow-up after 7 (±2) days.

New or Amended Wording: Up to ~~43~~**41** days~~:~~ **(**including ~~up to a 28-day~~ screening ~~period~~ **up to 28 days**, ~~6-day~~ confinement **for 6 days** ~~(including polysomnogram [PSG] and baseline assessments, and~~ **[**Treatment Periods 1 ~~and~~**to** 2 with a minimum 24-hour washout between periods**]**), and **end of study** ~~an outpatient site visit or~~ **follow-up** telephone **call** ~~follow-up after 7~~ **on Study Day 11** (±2) days.

Rationale for Change: Clarification of study duration.

Change 3: The document referred to in the section on study-related responsibilities was corrected to "Transfer of Regulatory Obligations".

The primary change occurs in Section 3.1: Study-Related Responsibilities.

Initial Wording: The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template.

New or Amended Wording: The sponsor will perform all study-related activities with the exception of those identified in the ~~Study-Related Responsibilities template~~**Transfer of Regulatory Obligations.**

Rationale for Change: Correction of document name.

Change 4: It was clarified in the primary objective that the population consisted of adult subjects with idiopathic hypersomnia (IH).

The primary change occurs in Section 5.1.1: Primary Objective.

Initial Wording: The primary objective of this study is to evaluate the safety and tolerability of administering a single IV infusion dose of TAK-925 to patients with IH.

New or Amended Wording: The primary objective of this study is to evaluate the safety and tolerability of administering a single IV infusion ~~dose~~ of TAK-925 to ~~patients~~ **adult subjects** with IH.

Rationale for Change: Consistency.

Section 2.0:STUDY SUMMARY also contains this change.

Change 5: The wording of the secondary objective was made consistent with the primary objective.

The primary change occurs in Section 5.1.2: Secondary Objective.

Initial Wording: The secondary objective of this study is to investigate the PK of TAK-925 when administered via infusion to patients with IH.

New or Amended Wording: The secondary objective of this study is to investigate the PK of ~~TAK-925 when administered via~~ **a single IV** infusion **of TAK-925** ~~to patients~~ **in adult subjects** with IH.

Rationale for Change: Consistency.

Section 2.0:STUDY SUMMARY also contains this change.

CCI

[redacted]

Rationale for Change: Consistency.

Section 2.0:STUDY SUMMARY also contains this change.

Change 7: It was clarified in the study design that the maintenance of wakefulness sessions will be terminated at approximately 1700.

The primary change occurs in Section 6.1: Study Design.

Added text: ... On Day 1 of each treatment period, TAK-925 (or placebo) will be administered as a single 9-hour IV infusion commencing at approximately 0800. **The infusion will be terminated at approximately 1700**.

Rationale for Change: clarification of study procedures.

Section 2.0:STUDY SUMMARY also contains this change.

Change 8: It was clarified that subjects with an Epworth Sleepiness Scale (ESS) score <11 who are taking stimulants at screening may continue the screening process and repeat the ESS at Study Day -2 following washout.

The primary change occurs in Section 6.1: Study Design.

Added text: **Subjects with an ESS score of <11 who are taking stimulants at screening may continue the screening process and repeat the ESS at Study Day -2 following washout.**

Rationale for Change: Clarification of study procedures.

The following sections also contain this change:

- Section 2.0: STUDY SUMMARY.
- Section 7.1: Inclusion Criteria.

Change 9: It was clarified in the study design that sodium oxybate must be discontinued at least 4 weeks prior to screening.

The primary change occurs in Section 6.1: Study Design.

Added text: **Sodium oxybate must be discontinued at least 4 weeks before screening.**

Rationale for Change: Clarification.

Section 2.0:STUDY SUMMARY also contains this change.

Section 7.3: Excluded Medications, Table 7.a: Prohibited Drug Classes also contains this change

Change 10: The subject's normal bedtime was clarified to be between 2200 and 2300.

The primary change occurs in Section 6.1: Study Design.

Added text: An **overnight 8-hour** nPSG will be performed commencing at approximately the subject's normal bedtime **(eg, between 2200 and 2300)** to confirm that the subject does not have other comorbid sleep disorders…

Rationale for Change: Clarification.

Section 2.0:STUDY SUMMARY also contains this change.

Change 11: CCI [redacted]

The primary change occurs in Section 6.1: Study Design.

CCI [redacted]

Rationale for Change: Clarification.

Section 2.0:STUDY SUMMARY also contains this change.

Change 12: The overview of inpatient unit study schedule was corrected and clarified.

The primary change occurs in Section 6.1: Study Design as revisions to Table 6.b: Overview of the Inpatient Unit Study Schedule

Description of Changes: It was clarified that on Study Days 1 and 3, CCI assessment would be performed in addition to study drug administration and PK and safety assessments.

Rationale for Change: Clarification of study procedures.

Section 2.0:STUDY SUMMARY also contains this change.

CCI [redacted]

The primary change occurs in Section 6.2.3: Rationale for Endpoints CCI [redacted]

CCI [redacted]

Rationale for Change: Clarification.

Change 15: The safety risk related to heart rate in the criteria for premature discontinuation was changed from 115 to 100 bpm.

The primary change occurs in Section 6.3.1: Criteria for Premature Termination or Suspension of the Study

Initial Wording: Sustained HR >115 beats per minute (bpm) or sustained post-dose change from pre-dose baseline of ≥30 bpm.

New or Amended Wording: Sustained HR >~~115~~**100** beats per minute (bpm) or sustained post-dose change from pre-dose baseline of ≥30 bpm.

Rationale for Change: Update of discontinuation criteria.

Section 7.5: Criteria for Discontinuation or Withdrawal of a Subject also contains this change.

Change 16: The safety risk related to mood changes in the criteria for premature discontinuation was limited to only severe changes in mood.

The primary change occurs in Section 6.3.1: Criteria for Premature Termination or Suspension of the Study

Initial Wording: Changes in subject mood, including feeling high, talkativeness, irritability, and hyperactivity.

New or Amended Wording: **Severe c**~~C~~hanges in subject mood, including feeling high, talkativeness, irritability, and hyperactivity.

Rationale for Change: Update of discontinuation criteria.

Change 17: A safety risk for treatment-emergent serious adverse events (AEs) or severe AEs that are considered related to treatment was added to the criteria for premature discontinuation.

The primary change occurs in Section 6.3.1: Criteria for Premature Termination or Suspension of the Study

Added text: **Any subject who experiences a treatment-emergent serious AE or a severe AE that is considered related to treatment.**

Rationale for Change: Update of discontinuation criteria.

Section 7.5: Criteria for Discontinuation or Withdrawal of a Subject also contains this change.

Change 18: Text was added to clarify that, if a subject with a history of IH has a diagnostic nocturnal polysomnography (nPSG) or multiple sleep latency test (MSLT) older than 10 years (or the test results are not available), the investigator will obtain a current nPSG/MSLT.

The primary change occurs in Section 7.1: Inclusion Criteria, criterion #4.

Added text: **Note: If there is a potential subject with a history of IH whose diagnostic nPSG/MSLT was performed more than 10 years ago or is not available and the subject continues to experience symptoms consistent with IH, the PI will obtain a current nPSG/MSLT.**

Rationale for Change: Clarification of selection criteria.

Change 19: The apnea-hypopnea index (AHI) for subject selection was changed from ≤15 to ≤10/hour. Also, it was added to the selection criteria that subjects should have a periodic limb movement arousal index (PLMAI) ≤15/hour.

The primary change occurs in Section 7.1: Inclusion Criteria.

Initial wording: nPSG (Study Day -2) demonstrates that subject does not have other comorbid sleep disorders (periodic limb movement index associated with arousals ≥15/hour) or clinically

significant nocturnal hypoxemia (oxygen saturation ≤80% for ≥5% of total sleep time) and that their AHI is ≤15 and total sleep time is ≥6.5 hours.

New or amended wording: nPSG (Study Day -2) demonstrates that subject does not have other comorbid sleep disorders ~~(periodic limb movement index associated with arousals ≥15/hour)~~ or clinically significant nocturnal hypoxemia (~~oxygen~~ **O_2** saturation ≤80% for ≥5% of total sleep time) and that their AHI is ≤~~15~~**10/hour, their PLMAI is ≤15/hour,** and **that their** total sleep time is ≥6.5 hours.

Rationale for Change: Clarification of selection criteria.

The following sections also contain this change:

- Section 2.0:STUDY SUMMARY.
- Section 7.2: Exclusion Criteria.

Change 20: Redundant and/or duplicate selection criteria were removed from the protocol.

The primary change occurs in Section 7.1: Inclusion Criteria, formerly criterion #9.

Deleted text: ~~Understand and be willing and able to comply with all study procedures and restrictions and agree to participate by providing written informed consent.~~

Rationale for Change: Clarification of selection criteria.

Change 21: Selection criteria related to contraception were reworded and clarified.

The primary change occurs in Section 7.1: Inclusion Criteria, criterion #12, #13 and #14.

Initial wording: For a male subject who is nonsterilized and sexually active with a female partner of childbearing potential, the subject must meet the following birth control requirements:

- Agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from the first dose of study drug until 5 half-lives (1 day) plus 90 days after the last dose of study drug. No restrictions are required for a vasectomized male subject, provided the subject is at least 1-year post-bilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a non-vasectomized man. Appropriate documentation of surgical procedure should be provided.
- Agrees to not donate sperm from the first dose of study drug until 5 half-lives plus 90 days after the last dose of study drug.

For a female subject of childbearing potential who is sexually active with a nonsterilized male partner, the subject must agree to use highly effective methods of contraception from signing of informed consent until 5 half-lives of TAK-925 (1 day) plus 30 days. Definitions and procedures for adequate contraception, pregnancy avoidance, and reporting responsibilities are defined in Appendix G.

For female subjects to be classified as "not of childbearing potential", the subject must meet 1 of the following requirements:

- Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or 6 months of spontaneous amenorrhea in females aged >45 years, with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL).

Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.

- Had a tubal ligation with appropriate documentation of surgical procedure.
- Has a congenital condition resulting in no uterus.

New or amended wording: ~~For a male subject who is nonsterilized and sexually active with a female partner of childbearing potential, the subject must meet the following birth control requirements:~~

- ~~Agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from the first dose of study drug until 5 half-lives (1 day) plus 90 days after the last dose of study drug. No restrictions are required for a vasectomized male subject, provided the subject is at least 1 year post-bilateral vasectomy procedure prior to the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year prior to the first dose of study drug must follow the same restrictions as a non-vasectomized man. Appropriate documentation of surgical procedure should be provided.~~
- ~~Agrees to not donate sperm from the first dose of study drug until 5 half-lives plus 90 days after the last dose of study drug.~~

~~For a female subject of childbearing potential who is sexually active with a nonsterilized male partner, the subject must agree to use highly effective methods of contraception from signing of informed consent until 5 half-lives of TAK-925 (1 day) plus 30 days. Definitions and procedures for adequate contraception, pregnancy avoidance, and reporting responsibilities are defined in Appendix G.~~

~~For female subjects to be classified as "not of childbearing potential", the subject must meet 1 of the following requirements:~~

- ~~Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or 6 months of spontaneous amenorrhea in females aged >45 years, with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL).~~

~~Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.~~

- ~~Had a tubal ligation with appropriate documentation of surgical procedure.~~

~~Has a congenital condition resulting in no uterus.~~

12. Male subjects who are non-sterilized and their female sexual partners of childbearing potential must follow the contraception methods described in Appendix G. In addition, male subjects must agree to not donate sperm from the first dose of study drug until 5 half-lives plus 90 days after the last dose of study drug.

13. Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must agree to use a highly effective method of contraception as described in Appendix G from signing of informed consent until 5 half-lives of TAK-925 plus 30 days.

14. Female subjects who are post-menopausal or permanently sterile according to the definitions in Appendix G.

Rationale for Change: Clarification of selection criteria.

Change 22: It was added to the selection criteria that subjects with an average nightly sleep duration ≤8 hours (480 minutes) will be excluded.

The primary change occurs in Section 7.2: Exclusion Criteria, criterion #1.

Initial wording: Insufficient sleep syndrome as evidenced by sleeping >2 hours/night more on "off-days" relative to "work days" as determined by actigraphy and sleep diary obtained prior to the nPSG (Study Day -2).

New or amended wording: ~~Insufficient~~ **Average nightly sleep duration is ≤8 hours (480 minutes) and the subject has insufficient** sleep syndrome as evidenced by sleeping >2 hours/night more on "off-days" relative to "work days" as determined by actigraphy and sleep diary obtained prior to the nPSG (Study Day -2).

Rationale for Change: Clarification of study procedures.

Section 2.0: STUDY SUMMARY also contains this change.

Change 23: It was clarified in the selection criteria that the alcohol test used during the study will be a breathalyzer.

The primary change occurs in Section 7.2: Exclusion Criteria, criterion #2.

Initial wording: Positive urine screen for drugs of abuse and/or positive alcohol test at screening and Study Day -2. An exception at screening is made for stimulants or other drugs that the subject has been prescribed, but the drug screen must be negative at Study Day -2.

New or amended wording: Positive urine screen for drugs of abuse and/or positive alcohol **breathalyzer** test at screening and Study Day -2. An exception at screening is made for stimulants or other drugs that the subject has been prescribed, but the drug screen must be negative at Study Day -2.

Rationale for Change: Clarification of study procedures.

Change 24: It was clarified that subjects with a resting heart rate (HR) outside of the range 40-90 bpm (rather than 45-100 bpm) will not be eligible for selection.

The primary change occurs in Section 7.2: Exclusion Criteria, criterion #5.

Initial wording: During screening, the subject has a resting HR outside of the range of 45 to 100 bpm, confirmed on repeat testing within a maximum of 30 minutes.

New or amended wording: ~~During screening, the subject has a r~~**R**esting HR outside of the range of ~~45~~**40** to ~~100~~**90** bpm~~, confirmed on repeat testing within a maximum of 30 minutes~~ **off stimulants**.

Rationale for Change: Clarification of study procedures.

Section 2.0: STUDY SUMMARY also contains this change.

Change 25: It was clarified that subjects with a usual bedtime later than 2400 (midnight) rather than 0100 are not eligible to participate.

The primary change occurs in Section 7.2: Exclusion Criteria, criterion #7.

Initial wording: Usual bedtime later than 01:00 or an occupation requiring nighttime shift work or variable shift work within the past 6 months, or travel with significant jet lag within 14 days before Study Day -2

New or amended wording: Usual bedtime later than ~~01~~**24**:00 **(midnight)** or an occupation requiring nighttime shift work or variable shift work within the past 6 months, or travel with significant jet lag within 14 days before Study Day -2

Rationale for Change: Clarification of study procedures.

Section 2.0: STUDY SUMMARY also contains this change.

Change 26: The exclusion criterion on nicotine dependence that is likely to have an effect on sleep was expanded to include smoking ≥10 cigarettes per day.

The primary change occurs in Section 7.2: Exclusion Criteria, criterion #10.

Initial wording: Nicotine dependence that is likely to have an effect on sleep (eg, a subject who routinely awakens at night to smoke) and/or an unwillingness to discontinue all smoking and nicotine use during the confinement portion of the study (Day -2 to Day 4).

New or amended wording: Nicotine dependence that is likely to have an effect on sleep (eg, a subject who routinely awakens at night to smoke) **or challenge the conduct of this study (smokes ≥10 cigarettes/day)** and/or an unwillingness to discontinue all smoking and nicotine use during the confinement portion of the study (Day -2 to Day 4).

Rationale for Change: Clarification of study procedures.

Section 2.0: STUDY SUMMARY also contains this change.

Change 27: It was added to the exclusion criteria that subjects unwilling to discontinue all caffeine during the confinement period of the study will not be eligible for selection.

The primary change occurs in Section 7.2: Exclusion Criteria, criterion #11.

Initial wording: Caffeine consumption of more than 600 mg/day for 7 days before Study Day 1 (1 serving of coffee is approximately equivalent to 120 mg of caffeine).

New or amended wording: Caffeine consumption of more than 600 mg/day for 7 days before Study Day 1 (1 serving of coffee is approximately equivalent to 120 mg of caffeine) **and/or unwilling to discontinue all caffeine during the confinement portion of the study (Day -2 to Day 4).**

Rationale for Change: Clarification of study procedures.

Section 2.0: STUDY SUMMARY also contains this change.

Change 28: Major depression was added as an example of psychiatric disorders for which subjects will be excluded from participation.

The primary change occurs in Section 7.2: Exclusion Criteria, criterion #13.

Initial wording: History or presence of any unstable medical condition (eg, fibromyalgia, chronic fatigue syndrome, Lyme disease, chronic pain syndromes), behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the trial per the judgment of the investigator.

New or amended wording: History or presence of any unstable medical condition ~~(eg, fibromyalgia, chronic fatigue syndrome, Lyme disease, chronic pain syndromes),~~ behavioral or psychiatric disorder (including **major depression or** active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the ~~trial~~**study** per the judgment of the investigator.

Rationale for Change: Clarification of study procedures.

Section 2.0: STUDY SUMMARY also contains this change.

Change 29: The period for refraining from certain food products was corrected to be through Study Day 4 (including washout intervals between treatment periods) rather than until the follow-up visit.

The primary change occurs in Section 7.2: Exclusion Criteria, criterion #27.

Initial wording: The subject is unable to refrain from or anticipates using food products (Table 7.b), including grapefruit juice, beginning approximately 7 days prior to administration of the first dose of study drug, throughout the study (including the washout interval between treatment periods), and until the follow-up visit.

New or amended wording: ~~The subject is u~~**U**nable to refrain from or anticipates using food products ~~(~~**listed in** Table 7.b~~), including grapefruit juice~~, beginning approximately 7 days prior to

administration of the first dose of study drug, ~~throughout the study~~**through Study Day 4 inclusive** ~~(including the washout interval between treatment periods), and until the follow-up visit.~~

Rationale for Change: Clarification of study procedures.

Change 30: It was clarified that known in vivo cytochrome P-450 (CYP)3A (not only CYP3A4) inhibitors or inducers were prohibited drug classes.

The primary change occurs in Section 7.3: Excluded Medications within Table 7.aProhibited Drug Classes

Description of Changes: CYP3A4 was changed to CYP3A across the table.

Rationale for Change: Correction of prohibited drug classes.

Change 31: It was clarified that subjects will receive 3 standardized meals per day during confinement.

The primary change occurs in Section 7.4.1: Diet and Fluids.

Initial wording: Subjects will receive 3 standardized meals each day including approximately 30% fat (relative to the total calories) during confinement in the unit.

Amended or new wording: Subjects will receive 3 standardized meals **per day** each ~~day~~ including approximately 30% fat (relative to the total calories) during confinement in the unit.

Rationale for Change: Clarification of study procedures.

Change 32: Food, drink, and other product restrictions were clarified.

The primary change occurs in Section 7.4.1: Diet and Fluids within Table 7.b List of Restricted Food, Drinks and Other Products

Description of Changes:

In the xanthine and/or caffeine category, it was clarified that these products are to be completely restricted from Inpatient Study Day -2 to Discharge on Study Day 4.

Seville oranges were added to the list of food products to be completely restricted from Inpatient Study Day -2 to Discharge on Study Day 4. Consumption of all fruits other than grapefruit and Seville oranges is allowed on all days of the study.

Rationale for Change: Clarification of study procedures.

Change 33: It was added to the protocol that subjects will be allowed to go on short supervised walks on washout days.

The change occurs in Section 7.4.2: Activity.

Added text: Subjects will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling) from the screening visit until administration of the initial dose of study drug, throughout the study (including the washout interval between treatment periods), and until the follow-up visit. **Short supervised walks outside the unit are permitted on washout days.**

Rationale for Change: Clarification of study procedures.

Change 34: It was clarified that lack of efficacy should not be recorded in the voluntary withdrawal category of discontinuation criteria. It was also clarified that the criterion is applicable to subjects or their legally acceptable representative.

The change occurs in Section 7.5: Criteria for Discontinuation or Withdrawal of a Subject, criterion #4.

Added text: 4. Voluntary withdrawal: The subject (**or subject's legally acceptable representative)** 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.**

Rationale for Change: Clarification of study procedures.

Change 35: It was corrected that details of the randomization schedule are provided in the pharmacy manual rather than the interactive voice response (IVRS) manual.

The change occurs in Section 8.3: Randomization Code Creation and Storage

Initial wording: Details are in the IVRS system manual.

New or amended wording: Details are in the ~~IVRS system~~ **pharmacy** manual.

Rationale for Change: Correction of study procedures.

Change 36: It was clarified that informed consent must be obtained before beginning withdrawal of excluded medications.

The change occurs in Section 9.1.1: Informed Consent Procedure

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

New or amended wording: Informed consent must be obtained ~~prior to~~**before** the subject ~~entering into~~**enters** the study, and before any protocol-directed procedures are performed, **including withdrawal of medications**.

Rationale for Change: Clarification of study procedures.

Change 37: The time subjects should rest in a bed following dosing was corrected from 4 to 2 hours.

The change occurs in Section 9.2.6: Vital Sign Procedure

Initial wording: Subjects should continue to rest in a bed with the head of the bed at 30 degrees from the time of dosing until 4 hours post-dose except to stand if necessary for trial-related procedures.

New or amended wording: Subjects should continue to rest in a bed with the head of the bed at 30 degrees from the time of dosing until 4 **2** hours post-dose except to stand if necessary for ~~trial~~ **study**-related procedures.

Rationale for Change: Clarification of study procedures.

Change 38: The actigraphy procedure was clarified.

The primary change occurs in Section 9.1.6: Actigraphy and Sleep Diary

Initial wording:

9.1.6 Actigraphy

Seven consecutive days of nocturnal actigraphy, supported by a sleep diary, will be obtained prior to the nPSG (Study Day 2) to ensure that a subject's average nightly sleep duration is ≥420 minutes during the subject's normal nocturnal sleep period and the subject does not have "insufficient sleep syndrome" as evidenced by sleeping >2 hours/night more on "off-days" relative to "work days".

New or amended wording:

9.1.6 Actigraphy **and Sleep Diary**

~~Seven~~ **Approximately 7** consecutive days of ~~nocturnal~~ actigraphy~~,~~ supported by a sleep diary~~,~~ will be ~~obtained prior to the nPSG (~~**recorded beginning on** Study Day -~~2~~**9 and ending on Study Day -3 (ie, the day before their Study Day -2 admission to the clinical unit). Data from the actigraphy device will be downloaded by the site** ~~)~~ to ensure that a ~~subject's average nightly sleep duration is~~ **subject sleeps on average 420 min/night and does not have insufficient sleep syndrome, as specified in the exclusion criteria** ≥420 ~~minutes during the subject's normal nocturnal sleep period and the subject does not have "insufficient sleep syndrome" as evidenced by sleeping >2 hours/night more on "off-days" relative to "work days".~~

Rationale for Change: Clarification of study procedures.

The following sections also contain this change:

- Section 2.0: STUDY SUMMARY.
- Section 6.1: Study Design.
- Section 7.1: Inclusion Criteria
- Appendix A Schedule of Study Procedures, footnote "b".

Change 39: The duration of the nPSG was clarified.

The primary change occurs in Section 9.3.1: nPSG

Initial wording: On Study Day -2, subjects will undergo an 8-hour nPSG, commencing at approximately the subject's usual bedtime, to exclude any significant comorbid sleep disorders other than IH.

New or amended wording: On Study Day -2, subjects will undergo an 8-hour nPSG, commencing at approximately the subject's usual bedtime, **but not after 2300,** to exclude any significant comorbid sleep disorders other than IH.

Rationale for Change: Clarification of study procedures.

CCI [redacted]

Rationale for Change: Clarification of study procedures.

Change 41: International normalized ratio (INR) measurement was added to the overview of laboratory tests for subjects with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >3 times the upper limit of normal (ULN).

The primary change occurs in Section 9.4: Laboratory Assessments/Procedures within Table 9.a Clinical Laboratory Tests

Description of changes: INR was added to the list of serum tests along with a footnote that it should only be tested if ALT or AST >3 times the ULN.

Rationale for Change: Correction of study procedures.

CCI [redacted]

Rationale for Change: Correction of study procedures.

Change 43: The procedure on collecting and reporting of serious adverse events (SAEs) was clarified.

The primary change occurs in Section 10.2.2: Collection and Reporting of SAEs

Initial wording:

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English or in Japanese, and signed by the investigator

immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

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

Reporting of serious PTEs will follow the procedure described for SAEs

New or amended text:

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

SAEs should be reported via SAE eCRF in Rave EDC, which is the preferred method of reporting SAEs. A Takeda SAE eCRF must be completed in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but should contain, at a minimum:

~~A Takeda SAE form must be completed, in English or in Japanese, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:~~

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

If access to Rave EDC is not feasible within 24 hours of receiving the event, the paper SAE forms should be submitted via fax. The SAE form should be completed within 24 hours of first onset or notification of the event, signed by the investigator, and transmitted via fax or email to the attention of the contact listed in Section 1.1. In case of fax, site personnel need to

confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day.

Email submission of SAE forms (to the appropriate e-mail address listed below) with a portable document format (PDF) attachment should only be used in the case where fax is not possible and access to Rave EDC is not feasible within 24 hours of receiving the event. In case of e mail, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via e mail within 1 business day.

- **United States and Canada: PVSafetyAmericas@tpna.com**
- **Rest of World: eupv@tgrd.com**

If SAEs are reported via fax or by email, Rave EDC must be updated as soon as possible with the appropriate information.

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

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

~~Reporting of serious PTEs will follow the procedure described for SAEs.~~

Rationale for Change: Correction of study procedures.

CCI [redacted]

Change 45: The term "adverse events of special interest" was removed from the description of the safety analyses.

The primary change occurs in 13.1.5: Safety Analysis

Deleted text: Standard summaries of TEAEs, ~~AESIs,~~ clinical safety labs, vital CCI [redacted]

Rationale for Change: correction

Change 46: A footnote was added to the Schedule of Study Procedures table to allow optional pre-screening on a case-by-case basis.

The changes occur in Appendix A Schedule of Study Procedures and in Appendix B

Added text: [a] **Optional pre-screening testing on a case-by-case basis as approved by Takeda. PI is responsible for performance and interpretation of nPSG/MSLT**

Rationale for Change: Correction of study procedures.

Change 47: The measurement of O2 saturation was added to the Schedule of Study Procedures table.

The primary change occurs in Appendix A Schedule of Study Procedures

Description of changes: A row was added for O_2 saturation measurement at screening.

Rationale for Change: clarification of study procedures.

CCI [redacted]

Rationale for Change: Correction of study procedures.

Change 49: It was added to the Schedule of Study Procedures that urine drug screen and pregnancy test results should be available before dosing on Day 1 of Treatment Period 1

The primary change occurs in Appendix A Schedule of Study Procedures

Description of changes: Footnote j "Urine drug screen and pregnancy test results should be available before dosing on Day 1 of Treatment Period 1." was added.

Rationale for Change: clarification of study procedures.

CCI [redacted]

Rationale for Change: correction of study procedures.

This change also occurs in Section 9.6: Blood Volume

Change 51: The urine pregnancy test was moved from Study Day-1 to Study Day -2 in the Schedule of Study Procedures table.

The primary change occurs in Appendix A Schedule of Study Procedures

Description of changes: the X for the urine pregnancy test was moved from Study Day -1 to Study Day -2.

Rationale for Change: correction of study procedures.

Change 52: A footnote was added to the Schedule of Study Procedures table to clarify that

glycosylated hemoglobin will be assessed only in diabetic subjects.

The primary change occurs in Appendix A Schedule of Study Procedures

Added text: **h Glycosylated hemoglobin only in diabetic subjects.**

Rationale for Change: clarification of study procedures.

This change also occurs in Section 9.4: Laboratory Assessments/Procedures, Table 9.a Clinical Laboratory Tests.

Change 53: Footnotes were added to the Schedule of Study Procedures table to clarify site staff will make every effort to keep subjects awake following completion of clinical testing procedures on Study Day -2 and during the day from 0700 until between 2200-2300 on Study Days 2 and 4.

The primary change occurs in Appendix A Schedule of Study Procedures

Added text: **n Following completion of clinical testing procedures, site staff will make every effort to keep subjects awake until between 2200-2300.**

o On Study Days 2 and 4, site staff will make every effort to keep subjects from sleeping during the day from 0700 until between 2200-2300.

Rationale for Change: clarification of study procedures.

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	05-Mar-2020 14:24 UTC
	Clinical Pharmacology Approval	06-Mar-2020 09:28 UTC
	Clinical Science Approval	06-Mar-2020 17:29 UTC