TAKEDA PHARMACEUTICALS

PROTOCOL

A Dose-Blind Extension Study With Double-blind, Placebo-Controlled, Randomized Withdrawal Period to Evaluate the Safety and Explore the Pharmacokinetics and Pharmacodynamics of TAK-994 in Adults With Narcolepsy With Cataplexy (Narcolepsy Type 1)

TAK-994 Extension and Randomized Withdrawal Study in Adult Subjects With Narcolepsy Type 1

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington MA 02421 USA		
Study Number:	TAK-994-1504		
IND Number:	142658	**EudraCT Number:**	2021-000251-39
Compound:	TAK-994		
Date:	03 February 2021	**Version/Amendment Number:**	Initial version

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center Americas, Inc. 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	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance: US and Canada: PVSafetyAmericas@tpna.com Rest of World: eupc@tgrd.com Fax: +1 224 554 1052
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Name: [redacted] MD Telephone/office: [redacted] Mobile : [redacted] E-mail: [redacted]
24-hour urgent medical contact	US TMA: [redacted] Toll-Free: [redacted] Mobile: [redacted] EU TMA: [redacted] Mobile: [redacted] JAPAN TMA: [redacted] Toll-Free: [redacted] Mobile: [redacted] IQVIA 24 hr Medical Emergency Contact Center US numbers: **+1 973-659-6677** or **+1 512 652 0191** Eu number: **+33186990019**

EU: European Union; TMA: Takeda Medical Affairs; US: United States.

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 Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

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

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

[redacted] MD, PhD	Date	[redacted] PhD	Date
Global Clinical [redacted], [redacted]		[redacted]	
Neuroscience Therapeutic Area Unit		Biostatistics	

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 B).

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington MA 02421 USA	**Compound:** TAK-994	
Title of Protocol: A Dose-Blind Extension Study with Double-blind, Placebo-Controlled, Randomized Withdrawal Period to Evaluate the Safety and Explore the Pharmacokinetics and Pharmacodynamics of TAK-994 in Adults With Narcolepsy With Cataplexy (Narcolepsy Type 1)	**IND No.:** 142658	**EudraCT No.:** 2021-000251-39
Study Number: TAK-994-1504	**Phase:** 2	

Study Design:

This is a phase 2, multicenter, 8-week dose-blind extension study of TAK-994-1501, followed by a 4-week double-blind randomized withdrawal period. Subjects who have completed Part B of TAK-994-1501 will be eligible to participate. An interactive response technology system will be used for the randomization of subjects to treatment.

Up to 112 adult male and female subjects with narcolepsy type 1 (NT1) who have completed Part B of TAK-994-1501 and who satisfy the inclusion and exclusion criteria will be enrolled.

During the first, 8-week active drug extension period, all subjects will be randomized to TAK-994 (low, middle, or high dose used in TAK-994-1501 Part B). For blinding purposes the randomization ratio will not be disclosed. The first intake in the current study will take place on Day 57 in TAK-994-1501 Part B, immediately after all final TAK-994-1501 assessments have been completed. The last dose in TAK-994-1501 Part B is planned on Day 56. No dosing gap is expected.

Data from the final assessments in TAK-994-1501 Part B, performed on Days 55 to 57 of that study, will serve as baseline for the active drug extension period of TAK-994-1504 (ie, Baseline I).

Upon completion of the 8-week active drug extension period, subjects will continue into a 4-week double-blind randomized withdrawal period and will be randomized in a 1:1 ratio to TAK-994 or placebo with the same dose or placebo. Subjects randomized to active treatment will remain at the same dose as used before the randomized withdrawal period.

Data from the final assessments in the 8-week active drug extension period of the study, performed before the first dose in the randomized withdrawal period, will serve as baseline for the double-blind randomized withdrawal period of the study (ie, Baseline II).

During the 8-week active drug extension period, assessments are planned at Weeks 1, 2, 4, 6, and 8. During the randomized withdrawal period, assessments are planned weekly. Subjects will continue to complete the daily electronic patient reported outcome diary to record self-reported narcolepsy symptoms [redacted] started in TAK-994-1501 Part B; other measurements [redacted] will also continue from TAK-994-1501 Part B. Subjects will stay overnight at the clinic on Days 55 and 56 (end of the active drug extension period) and Day 83 (end of the randomized withdrawal period). Subjects will be discharged on Day 57 and 84, respectively. [redacted] All other visits will be outpatient visits. (Note that subjects are also staying overnight at Day -2 and -1 [part of TAK-994-1501 Part B].)

Primary Objectives:

The primary objective is to evaluate the safety and tolerability of TAK-994 in the active drug extension period of the study over a period of up to 8 weeks.

Secondary Objectives:

The secondary objective is to evaluate the safety and tolerability of TAK-994 versus placebo in the randomized withdrawal period of the study over a period of up to 4 weeks.

Exploratory Objective(s)

[redacted]

Subject Population: Male and female subjects with NT1 who have completed Part B of TAK-994-1501

Number of Subjects: Up to 112 subjects	**Number of Sites:** Estimated total: up to approximately 70 sites globally
Dose Level(s): Active drug extension period: TAK-994 twice daily at a low, middle, and high dose for 8 weeks Randomized withdrawal period: TAK-994 twice daily at a low, middle, or high dose or placebo for 4 weeks.	**Route of Administration:** Oral
Duration of Treatment: Active drug extension period: 8 weeks Double-blind randomized withdrawal period: 4 weeks	**Period of Evaluation:** 12 weeks plus a 2-week follow-up period

Criteria for Inclusion:

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

1. Subject with a diagnosis of NT1 who has completed TAK-994-1501 Part B before enrollment (which will occur immediately following the final TAK-994-1501 assessments), and for whom the investigator has no clinical objection they be enrolled.
2. Subject is capable of understanding and complying with protocol requirements.
3. Male subject who is not sterilized and sexually active with a female partner of childbearing potential, must use barrier contraception from signing of informed consent until 5 half-lives of TAK-994 plus 90 days after the last dose of study drug. In addition, they must be advised not to donate sperm during this period.
4. Female subject of childbearing potential who is sexually active with a male partner who is not sterilized, must agree to use **highly effective methods of contraception** from signing of informed consent until 5 half-lives of TAK-994 plus 30 days after the last dose of study drug. In addition, they must be advised not to donate ova during this period.
5. Subject must agree to participate by providing written informed consent.

Criteria for Exclusion:

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

1. Subject has a clinically significant moderate or severe ongoing adverse event (AE) related to the study drug from the prior study.
2. Subject has used/uses disallowed concomitant medication.
3. Subject, in the opinion of the investigator, is unlikely to comply with the clinical study protocol or is unsuitable for any reason.
4. The subject is an employee of the sponsor or study site or an immediate family member (eg, spouse, parent, child, sibling) of an employee of the sponsor or study site who is directly involved in the conduct of the study.
5. The subject has a known hypersensitivity to any component of the formulation of TAK-994 or related compounds.
6. The subject has a positive pregnancy test or is a lactating/breastfeeding woman.
7. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before Baseline I (excluding samples taken as part of TAK-994-1501).
8. The subject's renal creatinine clearance is ≤50 mL/min.
9. Has liver function tests (alanine aminotransferase, aspartate aminotransferase) higher than 1.5 times the upper limit of normal at any visit in TAK-994-1501.
10. The subject has a risk of suicide according to endorsement of Item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) at any visit during TAK-994-1501 and/or has made a suicide attempt during TAK-994-1501.
11. The subject has past or current epilepsy or seizure, except for a single febrile seizure in childhood.
12. The subject has a clinically significant history of head injury or head trauma per the judgment of the investigator.
13. The subject has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation.
14. The subject has known coronary artery disease, a history of myocardial infarction, angina, cardiac rhythm abnormality, or heart failure.
15. The subject has an electrocardiogram (ECG) with a QT interval with Fridericia correction method >450 ms (men) or >470 ms (women) at Baseline I.
16. The subject has a resting heart rate outside of the range of 40 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes at Baseline I.
17. The subject has medical condition other than narcolepsy, such as medically significant unstable cardiovascular, pulmonary, hepatic, renal, or gastrointestinal disease, that would preclude enrollment in the view of the

investigator.

18. The subject has current or recent (within 6 months) gastrointestinal disease that is expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
19. The subject is an excessive (>600 mg/day) caffeine user 1 week before Baseline I.
20. The subject used any product with stimulating or sedating properties, anticataplexy medications, selective serotonin reuptake inhibitor, tricyclic antidepressants, or sodium oxybate at any time post baseline during TAK-994-1501.
21. The subject has any other medical condition, such as anxiety, depression, heart disease, or significant hepatic, pulmonary, or renal disease, that requires the subject to take excluded medications or at the time of Baseline I the subject is being treated with nasal/oro-nasal positive airway pressure for any reason.
22. The subject is unwilling to abstain from driving and operating dangerous or hazardous machinery during study participation.
23. The subject has a positive urine screen for drugs of abuse (findings confirmed) and/or positive alcohol test during any visit in TAK-994-1501.
24. The subject has a history of drug or alcohol abuse within the 12 months before Baseline I (Diagnostic and Statistical Manual of Mental Disorders, Edition 5 criteria).
25. The subject has a 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 portions of the study.
26. The subject has a usual bedtime later than 2400 (12:00 AM, 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 Baseline I.

Criteria for Evaluation and Analyses:

Primary Endpoints:

- Subjects with at least 1 treatment-emergent adverse event (TEAE) during the active drug extension period of the study.
- Subjects with at least 1 markedly abnormal value (MAV) for postdose laboratory values during the active drug extension period of the study.
- Subjects with at least 1 MAV for postdose vital signs during the active drug extension period of the study.
- Subjects with at least 1 MAV for postdose ECG parameters during the active drug extension period of the study.

Secondary Endpoints:

- Subjects with at least 1 TEAE during the randomized withdrawal period of the study.
- Subjects with at least 1 MAV for postdose laboratory values during the randomized withdrawal period of the study.
- Subjects with at least 1 MAV for postdose vital signs during the randomized withdrawal period of the study.
- Subjects with at least 1 MAV for postdose ECG parameters during the randomized withdrawal period of the study.

Exploratory Endpoints:

[redacted]

Statistical Considerations:

Baseline Definitions:

Baseline I is defined as the last measurement before the first dose in the active drug extension period of this study.

Baseline II is defined as the last measurement before the first dose in the randomized withdrawal period of this study, with the exception of [redacted], which will be averaged over the last week.

Safety Analysis:

Active Drug Extension Period

TEAEs, safety clinical laboratory measurements, vital signs, 12-lead ECG, and C-SSRS parameters will be summarized by treatment and overall. Observed values and change from Baseline I in these parameters will be summarized by treatment and overall.

TEAEs will be summarized using the active drug extension safety set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Data will be summarized by treatment and overall using Preferred Term and primary System Organ Class.

Randomized Withdrawal Period

TEAEs, safety clinical laboratory measurements, vital signs, 12-lead ECG, and C-SSRS parameters will be summarized by treatment and overall. Observed values and change from Baseline II in these parameters will be summarized by treatment and overall.

TEAEs will be summarized using the randomized withdrawal safety set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using MedDRA. Data will be summarized using Preferred Term and primary System Organ Class.

[redacted]

Sample Size Justification: There is no sample size justification for this study. All subjects in Part B of TAK-994-1501 willing and eligible to participate and meeting the selection criteria will be enrolled in the active drug extension period of the study. Subjects who complete the active drug extension period and willing to continue to the randomized withdrawal period will 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 study-related responsibilities template. 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 Coordinating Investigator

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

3.3 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bpm	beats per minute
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
[redacted]	[redacted]
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DNS	disturbed nighttime sleep
DTA	diphtheria toxin A
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDS	excessive daytime sleepiness
ePRO	electronic patient-reported outcome
[redacted]	[redacted]
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
hCG	human chorionic gonadotropin
HR	heart rate
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
KO	knockout
LFT	liver function test
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MSLT	multiple sleep latency test

[redacted]	[redacted]
NOAEL	no-observed-adverse-effect level
[redacted]	[redacted]
NT1	narcolepsy type 1
NT2	narcolepsy type 2
OAB	overactive bladder
OAB-qLF	Overactive Bladder Questionnaire – Long Form
OX	orexin
OX1R	orexin type 1 receptor
OX2R	orexin type 2 receptor
PD	pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PPBC	Patient Perception of Bladder Control
PROMIS	Patient-Reported Outcomes Measurement Information System
PSG	polysomnography
PTE	pretreatment event
[redacted]	[redacted]
QTc	corrected QT
QTcF	QT interval with Fridericia correction method
REM	rapid eye movement
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	treatment-emergent adverse event
TG	transgenic
TK	toxicokinetic
ULN	upper limit of normal
VAS	visual analog scale
[redacted]	[redacted]
WT	wild-type

3.4 Corporate Identification

TDCA	Takeda Development Center Americas, Inc.

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease Background

The orexinergic system is a major wake-promoting system of the brain. It is comprised of 2 types of wake promoting orexin (OX) neurons, localized in a specific region of the lateral and posterior hypothalamus and have excitatory projections to wide areas of the central nervous system (CNS) including the basal forebrain and brainstem nuclei involved in maintaining wakefulness (ie, cholinergic neurons of the reticular activating system, histaminergic tuberomammillary nucleus, noradrenergic locus coeruleus, dopaminergic ventral lateral area, and the serotonergic dorsal raphe nucleus). The OX system acts to coordinate and synchronize the wake-promoting centers of the brain and when absent (ie, in patients with narcolepsy type 1 [NT1], sleep/wake instability results). The orexinergic system is also involved in several other functions, such as feeding, reward, and sympathetic activity.

Two orexinergic neuropeptides, OX-A and OX-B, have been identified to date. These neuropeptides exert effects via 2 types of G protein–coupled OX 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 NT1 [2]. Narcolepsy is a rare, acquired, chronic neurologic disorder that alters sleep-state stability. The cardinal symptom of narcolepsy is excessive daytime sleepiness (EDS), described as a sudden overpowering need to sleep during the day normal periods of alertness. Intrusion of REM sleep phenomena into wakefulness also can also occur. These REM-like phenomena may include cataplexy (sudden loss of muscle tone triggered by strong emotions), hypnagogic/hypnopompic hallucinations (hallucinatory phenomenon that can include mental, auditory, tactile, or uncinate events typically occurring during the transitions into and out of sleep), and sleep paralysis (similar to cataplexy, ie, acute onset of muscle atonia accompanied by a somatic feeling of general paralysis, usually occurring during the transition from wakefulness into sleep). Disturbed nighttime sleep (DNS) is a common narcolepsy related symptom, with difficulty maintaining continuous nocturnal sleep manifested by frequent awakenings with prompt return back into sleep. Together, these 5 clinical features (EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and DNS) comprise the narcolepsy symptom pentad. It has been estimated that only 20% to 30% of patients have all components of the pentad at any one time. Narcolepsy type 2 (NT2) or narcolepsy without cataplexy accounts for 20% to 40% of all cases of narcolepsy but it is

important to know that cataplexy onset can occur many years after the onset of EDS (cases of 10- to 20-year delay have been described).

Narcolepsy has been classified by the International Classification of Sleep Disorders – Third Edition diagnostic criteria as either NT1 or NT2, on the basis of the presence or absence of cataplexy and on levels associated with demonstrably absent or low levels of OX1 in the cerebrospinal fluid (CSF) (if measured). NT1 is characterized by EDS and the presence of cataplexy. CSF levels of OX are absent or less than one-third of normal (typically <110 pg/mL). In contrast, patients with NT2 do not have cataplexy, and CSF levels of OX1 range from >110 pg/mL to normal levels. Both in NT1 and NT2, patients have exhibited sleep-onset REM periods on polysomnography (PSG)/multiple sleep latency test (MSLT) testing and have average sleep onset latencies of the MSLT of <8 minutes averaged over 5 naps. Approximately 70% of those with narcolepsy are classified as having NT1.

The pathophysiology of NT1 has a presumed, though unproven, autoimmune basis in individuals with a specific genetic predisposition, the most common of which is the HLA DQB1*06:02 (major histocompatibility complex, class II, DQ beta 1) [3,4]. The proposed etiology involves T-cell–mediated destruction of OX-producing neurons in the hypothalamus [4-6]. Loss of OX-producing neurons is reflected by low CSF OX levels [7]. The pathophysiology of NT2 is not well understood.

On the basis of the aforementioned data demonstrating that partial or complete OX deficiency plays an important role in the development of EDS, OX replacement therapy is expected to improve EDS through a pathophysiology-directed mechanism of action. A novel drug that acts to help address the deficiency of OX may address the spectrum of narcolepsy symptoms and may have greater efficacy than currently approved drugs for EDS and cataplexy.

TAK-994 is a first-in-class, orally available, highly selective OX2R agonist being developed by Takeda for the treatment of narcolepsy with or without cataplexy (NT1 or NT2).

4.1.2 Summary of Nonclinical Data

TAK-994 was studied in wild-type (WT) mice and cynomolgus monkeys as well as in 2 narcolepsy models (OX/ataxin-3 transgenic [TG] mice and OX-tTA;TetO diphtheria toxin A [DTA] mice), and OX2R knockout (KO) mice. TAK-994 significantly and dose-dependently enhanced wakefulness, both in WT mice during the sleep phase and in OX/ataxin-3 TG mice during both the active and sleep phase. TAK-994 was active at a 3-fold lower dose in OX/ataxin-3 TG mice compared with WT mice; effective doses of TAK-994 in OX/ataxin-3 TG mice and WT mice were 3 and 10 mg/kg, respectively. TAK-994 also dose-dependently and significantly increased wakefulness in OX-tTA;TetO DTA mice during the active phase. TAK-994 also suppressed cataplexy-like episodes both in OX/ataxin-3 TG mice and OX-tTA;TetO DTA mice during the active phase. In contrast, TAK-994 did not show an arousal effect in OX2R KO mice, consistent with selectivity for OX2R. Nonhuman primates such as cynomolgus monkeys are diurnal animals whose sleep/wake structure is monophasic and resembles that of humans. TAK-994 also significantly enhanced wakefulness in cynomolgus monkeys during the sleep phase.

In in vivo cardiovascular studies, blood pressure (BP) increases were observed at ≥20 mg/kg (10 mg/kg, twice daily) in conscious telemeterized monkeys. The increased BP was attributed to the pharmacological action of TAK-994 at OX2R in the CNS, since it has been reported that intracerebroventricular administrations of OX increased arterial BP in rats mainly via OX2R [8]. The prolongation of PR interval and shortening of QT/corrected QT (QTc) intervals observed at ≥100 mg/kg and 1000 mg/kg, respectively, were deemed to be of no toxicological importance because of the low magnitude of these changes. The no-observed-effect level on the cardiovascular system in monkeys could not be determined on the basis of the BP and heart rate (HR) increases seen at the lowest dose tested, 20 mg/kg. However, after 1-week repeated oral administration of TAK-994 in conscious telemeterized monkeys at 100 mg/kg, the increased BP and HR observed on the first day of dosing was attenuated on the second day of dosing and had disappeared by the final day of dosing. Since no arrhythmias were observed, and the values of the shortened QTc intervals at nighttime did not deviate largely from those during the daytime, the prolonged PR intervals at ≥100 mg/kg/d and shortened QT and QTc intervals at 1000 mg/kg/d were considered to be nonadverse.

In toxicity studies up to 39 weeks (9 months) duration in monkeys and up to 26 weeks (6 months) in rats, safety margins were achieved compared with the doses planned for clinical studies.

- A Good Laboratory Practice (GLP)-compliant 26-week oral gavage toxicity and toxicokinetic (TK) study was conducted in Sprague-Dawley rats at dose levels of 0, 50, 150, and 1000 mg/kg/d with an 8-week recovery period. Adverse fluorosis was observed at 1000 mg/kg/d with evidence of increased fluoride levels in the plasma. Based on these results, the no-observed-adverse-effect level (NOAEL) was set at 150 mg/kg/d.
- A GLP-compliant 39-week oral gavage toxicity and TK study was conducted in cynomolgus monkeys at dose levels of 0, 60, 200, and 1000 mg/kg/day (0, 30, 100, and 500 mg/kg twice daily with a 6-hour interval between doses). No adverse findings were noted at any dose level. Based on these results, the NOAEL of TAK-994 was set at 1000 (500 twice daily) mg/kg/d for both sexes.

Additional details on the nonclinical data for TAK-994 are available in the TAK-994-1501 parent protocol and the investigator's brochure.

4.1.3 Clinical Study Experience

At the time of protocol writing, 1 clinical study of TAK-994 has been completed (TAK-994-1001) and 2 clinical studies are ongoing (TAK-994-1501 and TAK-994-1503).

TAK-994-1001 was a first-in-human (FIH), phase 1, double-blind, safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) study of single and 14-day multiple rising oral doses of TAK-994 in healthy non-Japanese and Japanese adult subjects, as well as healthy elderly subjects. The study also assessed the effect of food on the PK of a single dose of the tablet formulation of TAK-994. The study included assessment of TAK-994 CSF concentrations to evaluate the CNS penetration relative to systemic exposure in support of dose selection as well as exploratory PD/efficacy.

Following single- and multiple-dose oral administration of TAK-994 to healthy subjects under fasted conditions, TAK-994 was readily absorbed into the systemic circulation. After single-dose administration, peak exposure increased near dose proportionally, while total exposure increased slightly greater than dose proportionally. At steady-state, peak and total exposure of TAK-994 appeared to increase dose proportionally when comparing the twice daily dose regimens where TAK-994 was administered at the same amount for 14 consecutive days.

After single-dose administration, TAK-994 displayed a multiexponential disposition phase with an estimated mean terminal elimination half-life ranging from 3.053 to 12.472 hours across doses. There were no apparent dose-related trends in TAK-994 clearance across the groups assessed. TAK-994 exposure did not appear to accumulate after once or twice daily dosing in any of the dose groups and study parts (≤9%) with the exception of the 120 mg AM/60 mg PM dose group where a slight drug accumulation was observed when comparing Day 14 to Day 1. Overall, urinary excretion of TAK-994 was minimal and not impacted by dose level.

Further, ingesting a high-fat, high-calorie meal immediately before administering a low dose (30 mg) of TAK-994, increased the peak (~50%) and total exposure (~25%) of TAK-994. Ingesting a standardized, non–high-fat meal immediately before administering a higher dose (180 mg) of TAK-994, increased peak exposure (42%) but had no effect on total exposure.

There were no deaths or SAEs in any treatment group of any part throughout the study. All reported treatment-emergent adverse events (TEAEs) were mild or moderate in severity, except 1 severe TEAE syncope, that was assessed as not related to study drug by the investigator. Two subjects discontinued due to TEAEs. One subject treated with placebo discontinued from Part B due to presyncope, which was assessed as moderate in intensity and related to study drug by the investigator. One subject who received TAK-994 200 mg twice daily discontinued from Part E due to alanine aminotransferase (ALT) increased, which was assessed as mild and related to the study drug by the investigator.

Considering all parts together, 1 or more renal and urinary TEAEs were reported (incontinence, pollakiuria, micturition urgency, dysuria) in 24 subjects, including 1 in the placebo group. No related medical history was reported in these subjects; however, no subjects discontinued due to these TEAEs. These were mild or moderate in intensity and all events resolved within a few days. There events were reported in subjects with no specific relation with dose levels, sex, race, or age. These events were assessed related to the study treatment. No actions were taken in response to the event. Higher frequency of renal and urinary TEAEs were noted in the TAK-994 treated group compared with the placebo.

A total of 8 subjects reported increased alertness (hypervigilance) ranging for a few hours to a few days. All events were assessed related to the study drug, resolved, and had no specific relation with dose levels, sex, race, or age. Two subjects reported mild euphoria that were resolved. These events were assessed related to the study treatment and occurred in subjects receiving TAK-994. No actions were taken in response to the event. Twenty-four subjects (2 subjects in placebo group and 22 in the TAK-994 group) also reported insomnia within the first 2 to 3 days of first dose. These were mild or moderate in intensity and all events resolved. The events were reported in

subjects with no specific relation with dose levels, sex, race, or age. These events were assessed related to the study treatment. No actions were taken in response to the event.

Three subjects exposed to TAK-994 had ALT elevations. All events were mild, related, and resolved without treatment. Three subjects exposed to TAK-994 had glutamate dehydrogenase (GLDH) elevations (reference range <6.4 U/L). In addition, 1 subject treated with placebo had elevated GLDH.

Transient increases in BP and PR were observed across all parts receiving multiple dosing on the basis of markedly abnormal values (MAVs); however, no notable trend was observed. One subject receiving 200 mg TAK-994 in Part B had a TEAE of BP increased. The event was assessed as moderate in intensity and drug-related by the investigator. No other clinically significant changes in BP from baseline were reported for any subject during the study and no subjects discontinued from the study due to an elevation in BP.

No clinically significant electrocardiogram (ECG) abnormalities were reported during the study.

TAK-994 was considered to be safe and well tolerated up to 450 mg single dose and 200 mg twice daily 14-day repeat dose both in healthy adults and elderly subjects. The maximum repeated dose tested in healthy subjects was 200 mg twice daily and it was well tolerated.

Additional details on the clinical data for TAK-994 are available in the investigator's brochure.

4.2 Rationale for the Proposed Study

Nonclinical pharmacology studies showed that wake-promoting effects of TAK-994 were observed following chronic dosing for up to 14 days. Clinical information from FIH study TAK-994-1001 in healthy subjects showed that TAK-994 is safe when administered at a dose of up to 450 mg single dose and up to 200 mg twice daily repeat dose both in healthy adult and elderly subjects.

Narcolepsy is a long-term illness and maintenance therapy is recommended to prevent relapse. This study is being conducted to evaluate the safety of subjects on continued treatment with TAK-994 as well as during a withdrawal period. The primary objective of the current study is, therefore, to evaluate the safety and tolerability of TAK-994 in the active drug extension period of the study over a period of up to 8 weeks (for subjects who received active treatment in TAK-994-1501). The secondary objective is to evaluate the safety and tolerability of TAK-994 vs placebo in the randomized withdrawal period of the study over a period of up to 4 weeks. The primary endpoint will be assessed upon completion of the active drug extension period of the study; the secondary endpoint will be assessed upon completion of the randomized withdrawal part of the study.

Additional rationale relating to the study design, TAK-994 dose administered, and study endpoints is provided in Section 6.2.

4.3 Benefit-Risk Profile

This 8-week extension study followed by a 4-week randomized withdrawal period will include safety/tolerability, [redacted] evaluations in subjects with NT1 after multiple-dose oral administration of TAK-994.

Patients with NT1 are deficient in OX and hence are the first individuals who would most benefit from treatment with an OX2R agonist. If TAK-994 is efficacious for EDS and catalepsy, subjects receiving the drug may benefit during the period of study drug administration. Subjects will also receive medical examinations and information about their overall health. Results of this study are critical in planning future clinical studies with TAK-994, and it is possible that the information obtained in the study will be beneficial to patients with narcolepsy in the future.

Safety data informing the risk profile for TAK-994 are limited to the mode of action, data from nonclinical toxicology studies, and safety and tolerability data from TAK-994-1001:

- Based on nonclinical safety pharmacology data, the primary potential risk is increased BP. A safety pharmacology study of TAK-994 in monkeys found mild to moderate degrees of transient elevated BP at all doses tested on initial dosing, although effects on BP and HR were no longer observed at 7 days of dosing. The cardiovascular effects noted in nonclinical models with OX2R agonists are considered potentially on-mechanism on the basis of published literature [9]. In TAK-994-1001, BP elevation (>5 mm Hg above placebo) was observed on Day 1; however, the elevations were not sustained beyond Day 4. In addition, preliminary results from TAK-994-1501 confirmed that there appears to be no clear dose-response relationship for BP elevation. However, to mitigate a potential BP risk, BP will be measured frequently in this study; stopping rules for individual subjects (as well as the treatment of increased BP) and the overall study have been established and are noted in Section 7.5 and Section 6.3, respectively.
- Other effects in nonclinical studies included vomiting at high doses and minor changes in ECG parameters. ECG findings in the study were considered nonadverse. The ECG data in healthy subjects in TAK-994-1001 and preliminary results from TAK-994-1501 showed no clinically significant findings. To mitigate any possible risk, ECG parameters will be monitored in this study.
- Additionally, it is possible that a long half-life may result in insomnia, which has been seen in healthy subjects in TAK-994-1001. Though insomnia is thought less likely to occur in patients with NT1 due to their marked OX deficiency, stopping rules have been created for severe and/or persistent insomnia (Section 7.5).
- The TEAEs that have occurred in TAK-994-1001 have primarily been graded as mild. TEAEs generally increased in number with increasing dose or exposure. The tolerability of 200 mg twice daily in the multiple rising dose cohort was acceptable, although TEAEs of urinary frequency and urgency have been reported, and this will be monitored in the current study. In addition, subjects will be asked to complete the Overactive Bladder Questionnaire - Long Form (OAB-qLF) and Patient Perception of Bladder Control (PPBC) Questionnaire at several time points throughout the study.

- The TAK-994–related hepatocellular injury observed in the non-Tg rasH2 mice is thought to be of limited relevance to human safety risk assessment. In TAK-994-1001, a pooled aggregate analysis of liver function tests (LFTs) and GLDH that included observed and change from baseline by visit date was conducted and did not show clinically meaningful difference between TAK-994 and placebo arms. In addition, there were no clinically significant changes of fluoride laboratory test results. LFTs will be monitored throughout the study; however, no specific monitoring of GLDH is planned. Weekly measurements are felt to be sufficient to adequately monitor for evidence of injury. See Section 7.5 and Section 6.3 for individual and cohort stopping rules related to LFT changes.

This study has been designed to mitigate potential safety risks on the basis of clinical and nonclinical findings. The principal mitigation strategy for these risks includes appropriate selection of the study population; intermittent use of the inpatient clinical research unit setting, which permits close monitoring and rapid institution of appropriate care as needed; appropriate specified monitoring procedures; periodic laboratory tests, ECGs, and vital signs assessments; and use of experienced staff trained in study procedures.

Overall, there is manageable risk associated with the noninvasive procedures planned for this study. Potential risks relating to study procedures include the following:

- Study procedure-specific risks, including issues relating to blood collection for safety [redacted] assessments (eg, venipuncture may cause bruising).
- Acute hypersensitivity/anaphylactic reactions to new chemical entities, which is always a possible risk in any clinical study. Appropriate procedures will be used to manage such possible risks.

Review of available data supports a favorable benefit-risk ratio for this study of TAK-994. To date, the observed nonclinical and clinical safety data for TAK-994, including mild and manageable adverse events (AEs), are acceptable considering its potential clinical benefit.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to evaluate the safety and tolerability of TAK-994 in the active drug extension period of the study over a period of up to 8 weeks.

5.1.2 Secondary Objective

The secondary objective is to evaluate the safety and tolerability of TAK-994 versus placebo in the randomized withdrawal period of the study over a period of up to 4 weeks.

5.1.3 Exploratory Objective(s)

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

- Subjects with at least 1 TEAE during the active drug extension period of the study.
- Subjects with at least 1 MAV for postdose laboratory values during the active drug extension period of the study.
- Subjects with at least 1 MAV for postdose vital signs during the active drug extension period of the study.

- Subjects with at least 1 MAV for postdose ECG parameters during the active drug extension period of the study.

5.2.2 Secondary Endpoints

- Subjects with at least 1 TEAE during the randomized withdrawal period of the study.
- Subjects with at least 1 MAV for postdose laboratory values during the randomized withdrawal period of the study.
- Subjects with at least 1 MAV for postdose vital signs during the randomized withdrawal period of the study.
- Subjects with at least 1 MAV for postdose ECG parameters during the randomized withdrawal period of the study.

5.2.3 Exploratory Endpoints

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2, multicenter, 8-week dose-blind extension study of TAK-994-1501, followed by a 4-week double-blind randomized withdrawal period. Subjects who have completed Part B of

TAK-994-1501 will be eligible to participate. An interactive response technology (IRT) system will be used for the randomization of subjects to treatment.

Up to 112 adult male and female subjects with NT1 who have completed Part B of TAK-994-1501 and who satisfy the inclusion and exclusion criteria, listed in Sections 7.1 and 7.2, will be enrolled.

During the first, 8-week active drug extension period, all subjects will be randomized to TAK-994 (low, middle, or high dose used in TAK-994-1501 Part B). For blinding purposes the randomization ratio will not be disclosed. The first intake in the current study will take place on Day 57 in TAK-994-1501 Part B, immediately after all final TAK-994-1501 assessments have been completed. The last dose in TAK-994-1501 Part B is planned on Day 56. No dosing gap is expected.

Data from the final assessments in TAK-994-1501 Part B, performed on Days 55 to 57 of that study, will serve as baseline data for the active drug extension period of TAK-994-1504 (ie, Baseline I).

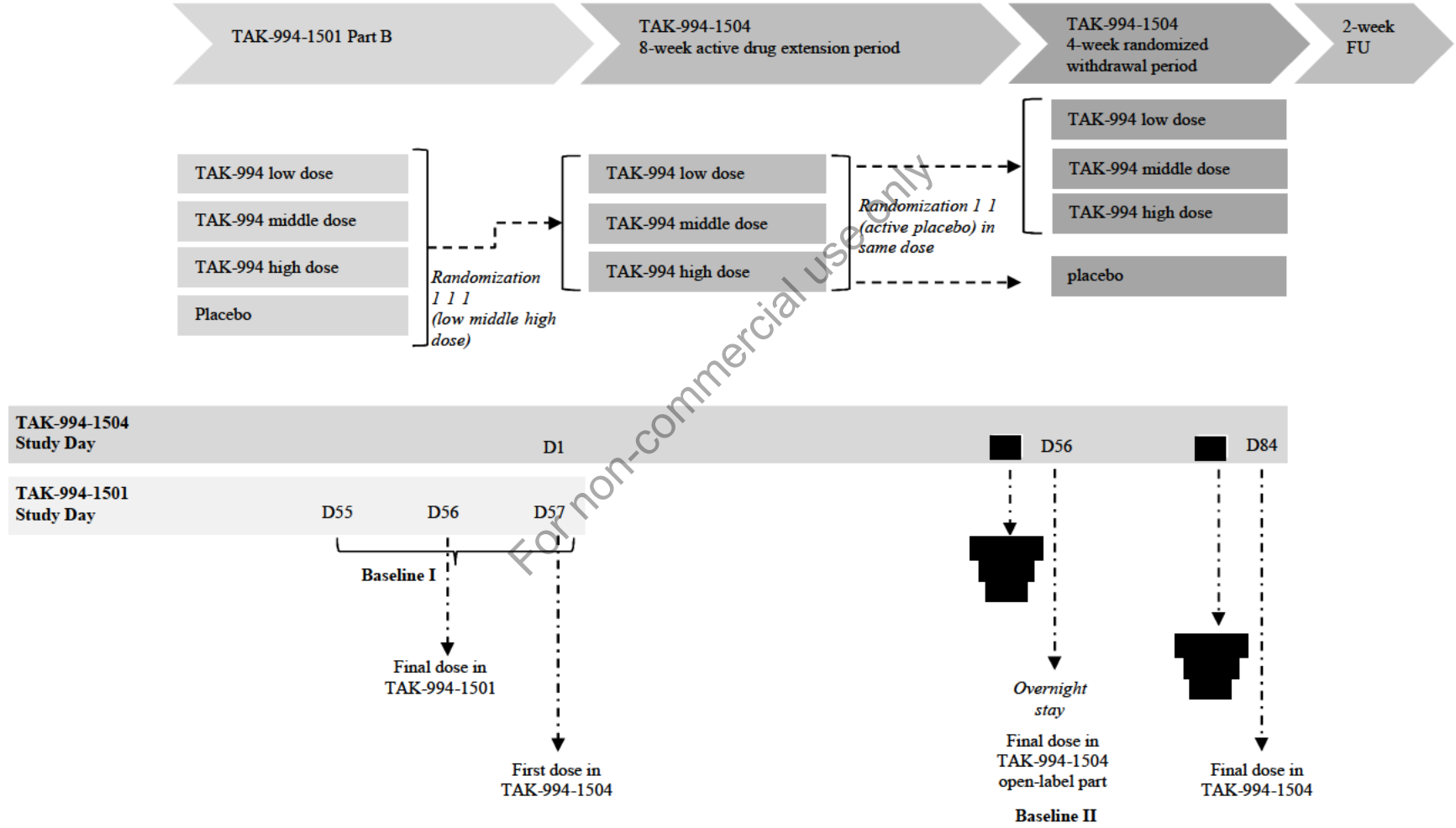
Upon completion of the 8-week active drug extension period, subjects will continue into a 4-week double-blind randomized withdrawal period and will be randomized in a 1:1 ratio to TAK-994 or placebo with the same dose or placebo. Subjects randomized to active treatment remain at the same dose as used before the randomized withdrawal period.

Data from the final assessments in the 8-week active drug extension period of the study, performed before the first dose in the randomized withdrawal period, will serve as baseline for the double-blind randomized withdrawal period of the study (ie, Baseline II).

During the 8-week active drug extension period, assessments are planned at Weeks 1, 2, 4, 6, and 8. During the randomized withdrawal period, assessments are planned weekly. Subjects will continue to complete the daily electronic patient-reported outcome (ePRO) diary to record self-reported narcolepsy symptoms [redacted] started in TAK-994-1501 Part B; other measurements [redacted] will also continue from TAK-994-1501 Part B. Subjects will stay overnight at the clinic on Days 55 and 56 (end of the active drug extension period) and Day 83 (end of the randomized withdrawal period). Subjects will be discharged on Days 57 and 84, respectively [redacted] All other visits will be outpatient visits. (Note that subjects are also staying overnight at Days -2 and -1 [part of TAK-994-1501 Part B].)

A schematic of the study design is included as Figure 6.a. A Schedule of Study Procedures is provided in Appendix A.

Figure 6.a Schematic of Study Design



D: day; [redacted].

During confinement, study drug will be administered TAK-994/placebo orally in the morning (at approximately 0800) and in the afternoon (approximately 1300) per the Schedule of Study Procedures (Appendix A) and Section 8.1.3. Study assessments will be obtained per the Schedule of Study Procedures (Appendix A) in accordance with the priority specified in Section 9.1.1. Subjects will remain as inpatient from check-in at Days 55 and 83 and will be discharged after completion of all planned assessments on Days 57 and 84, respectively.

While at home, subjects will take TAK-994/placebo orally twice daily at approximately the same times each day, with the first dose given in the morning and the second dose approximately 5 hours later and will continue to complete the daily ePRO diary.

Subjects will return to the clinic for safety, [redacted] assessments on in-clinic visit days. Subjects will return home on the discharge day after each in-clinic period.

A follow-up will be planned approximately 2 weeks after the final study drug intake.

Sites should see subjects at the study site to conduct the in-clinic study procedures. In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures (Appendix A), contingency measures may be implemented. Restrictions of human activities or institution activities placed by hospitals, local, state, and national governments may prevent conduct of study procedures according to the Schedule of Study Procedures (Appendix A). Alternative approaches to study procedures and data collection for the current study are described in Section 9.1.2.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design Rationale

Several key considerations were taken into account when designing the study, because the information generated will inform the design and dose selection for the further development of TAK-994 as a potential treatment for NT1. These considerations are described below.

Due to the character of the disorder, long-term studies are necessary to demonstrate that the short-term effect is maintained over time. As recommended in the Food and Drug Administration (FDA) Guidance for Industry [10], a randomized withdrawal study is the most appropriate design to use to evaluate the maintenance of treatment effect.

The current dose-blinded study will evaluate safety and efficacy over a period of up to 12 weeks, bringing the total exposure in combination with TAK-994-1501 Part B up to 20 weeks. With that this study can further characterize the safety of TAK-994. Further, a 4-week randomized withdrawal period was chosen to assess [redacted] of continued treatment with TAK-994 versus switching to placebo to investigate the potential for relapse in subjects treated with TAK-994 for up to 16 weeks. The 4-week period was estimated to be sufficient to capture any withdrawal effect, if present, taking into account the potential that after a longer exposure the [redacted].

6.2.2 Dose Rationale

Subjects enrolled in this study will continue receiving the same dose levels (low, middle, high) previously selected for Study TAK-994-1501 Part B.

6.2.3 Endpoint Rationale

6.2.3.1 Safety Endpoints

This study will include the standard safety endpoints for early clinical development. On the basis of available nonclinical and clinical data, 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 and pulse and respiratory rate.
- 12-lead ECGs.
- Clinical laboratory safety evaluations (standard hematology, blood chemistry, and urinalysis).

In addition, adequate measures have been taken regarding the methodology of this study to assess suicidal risk. The selection criteria exclude the participation of subjects at significant risk for suicide. Throughout the study, signs of suicidal risk will be assessed both by rating scale assessment and by investigator's clinical judgment. Subjects will be withdrawn from the study in case of such risk. Furthermore, subjects will be screened for the history of suicidal behavior. To more accurately and systematically assess the potential relationship between antidepressant agents and suicidality, the Columbia Suicide Severity Rating Scale (C-SSRS) will be implemented in this study [11,12].

Further, in addition to monitoring urinary-related AEs, [redacted]

Finally, considering the short PK half-life of TAK-994, the 14-day follow-up period is considered sufficient to monitor safety.

6.2.3.2 [redacted]

[redacted]

6.2.3.3 [redacted]

[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 benefit-risk profile for the product, 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.
- A finding (eg, [redacted]) from another nonclinical or clinical study using the study treatment results in the study being stopped for a nonsafety-related reason.

- Data from drug(s) of the same class or methodology(ies) used in this study become available and result in the study being stopped for a nonsafety-related reason.
- The study is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.
- Unanticipated concerns of safety to the study subjects arise from this clinical study or additional nonclinical or clinical studies with TAK-994 or drug(s) of the same class.
- Study-specific stopping criteria are met by any of the following criteria:
  - BP increase: If 4 or more subjects in the same arm meet the individual subject stopping criteria for BP increases defined in Section 7.5, then further dosing will be stopped.
  - Insomnia: If 4 or more subjects in the same arm meet the individual subject stopping criteria for severe insomnia defined in Section 7.5, then further dosing will be stopped.
  - LFT: If 3 or more subjects in the same arm meet the individual subject stopping criteria for abnormalities, as defined in Section 7.5, then further dosing will be stopped.
  - SAE: If 3 or more subjects in the same arm meet the individual subject stopping criteria or 3 or more experience an SAE that is drug-related in investigator's and sponsor's opinions, then further dosing will be stopped.
- The study will be paused for further evaluation if any of the following criteria are met:
  - ≥10% or 3 subjects in the same arm, whichever is higher, experience a similar SAE.
  - ≥10% or 3 subjects in the same arm, whichever is higher, experience a similar severe AE, with the exception of insomnia.
  - ≥10% or 3 subjects in the same arm, whichever is higher, discontinue study for safety reasons.
  - ≥1 death in the same arm determined by the investigator to be related to study drug.
- The sponsor terminates or suspends the study, or any study cohort, at any time for any other clinical or administrative reasons.

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, if the site (including the investigator) 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

If 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. If the site closure is due to coronavirus disease 2019 (COVID-19), this should be captured on the electronic case report form (eCRF), end of treatment disposition page.

6.4 Study Beginning and End/Completion

6.4.1 Definition of Beginning of the Study

The study begins when the first subject signs the study informed consent form.

6.4.2 Definition of End of the Study

The study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), withdraws from the study, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.4.3 Definition of Study Completion

For an individual subject, study completion is defined as when the subject is examined after receiving all planned intervention/treatment to collect final data for all primary, secondary, and exploratory endpoints.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before randomization or first dose or other.

7.1 Inclusion Criteria

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

1. Subject with a diagnosis of NT1 who has completed TAK-994-1501 Part B before enrollment (which will occur immediately following the final TAK-994-1501 assessments), and for whom the investigator has no clinical objection they be enrolled.
2. Subject is capable of understanding and complying with protocol requirements.
3. Male subject who is not sterilized and sexually active with a female partner of childbearing potential, must use barrier contraception from signing of informed consent until 5 half-lives of TAK-994 plus 90 days after the last dose of study drug. In addition, they must be advised not to donate sperm during this period. Definitions and procedures for adequate contraception, pregnancy avoidance, and reporting responsibilities are defined in Sections 9.1.3 and 9.1.4.
4. Female subject of childbearing potential who is sexually active with a male partner who is not sterilized, must agree to use **highly effective methods of contraception** from signing of informed consent until 5 half-lives of TAK-994 plus 30 days after the last dose of study drug. In addition, they must be advised not to donate ova during this period. Definitions and procedures for adequate contraception, pregnancy avoidance, and reporting responsibilities are defined in Sections 9.1.3 and 9.1.4.

5. Subject must agree to participate by providing written informed consent.

7.2 Exclusion Criteria

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

1. Subject has a clinically significant moderate or severe ongoing AE related to the study drug from the prior study.
2. Subject has used/uses disallowed concomitant medication.
3. Subject, in the opinion of the investigator, is unlikely to comply with the clinical study protocol or is unsuitable for any reason.
4. The subject is an employee of the sponsor or study site or an immediate family member (eg, spouse, parent, child, sibling) of an employee of the sponsor or study site who is directly involved in the conduct of the study.
5. The subject has a known hypersensitivity to any component of the formulation of TAK-994 or related compounds.
6. The subject has a positive pregnancy test or is a lactating/breastfeeding woman.
7. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before Baseline I (excluding samples taken as part of TAK-994-1501).
8. The subject's renal creatinine clearance is ≤50 mL/min.
9. Has LFTs (ALT, aspartate aminotransferase [AST]) higher than 1.5 times the upper limit of normal (ULN) at any visit in TAK-994-1501.
10. The subject has a risk of suicide according to endorsement of Item 4 or 5 on the C-SSRS at any visit during TAK-994-1501 and/or has made a suicide attempt during TAK-994-1501.
11. The subject has past or current epilepsy or seizure, except for a single febrile seizure in childhood.
12. The subject has a clinically significant history of head injury or head trauma per the judgment of the investigator.
13. The subject has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation.
14. The subject has known coronary artery disease, a history of myocardial infarction, angina, cardiac rhythm abnormality, or heart failure.
15. The subject has an ECG with a QT interval with Fridericia correction method (QTcF) >450 ms (men) or >470 ms (women) at Baseline I.
16. The subject has a resting HR outside of the range of 40 to 100 beats per minute (bpm), confirmed on repeat testing within a maximum of 30 minutes at Baseline I.

17. The subject has a medical condition other than narcolepsy, such as medically significant unstable cardiovascular, pulmonary, hepatic, renal, or gastrointestinal disease, that would preclude enrollment in the view of the investigator.
18. The subject has current or recent (within 6 months) gastrointestinal disease that is expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
19. The subject is an excessive (>600 mg/d) caffeine user 1 week before Baseline I.
20. The subject used any product with stimulating or sedating properties, anticataplexy medications, selective serotonin reuptake inhibitor, tricyclic antidepressants, or sodium oxybate at any time post baseline during TAK-994-1501.
21. The subject has any other medical condition, such as anxiety, depression, heart disease, or significant hepatic, pulmonary, or renal disease, that requires the subject to take excluded medications (see Section 7.3) or at the time of Baseline I the subject is being treated with nasal/oro-nasal positive airway pressure for any reason.
22. The subject is unwilling to abstain from driving and operating dangerous or hazardous machinery during study participation.
23. The subject has a positive urine screen for drugs of abuse (findings confirmed) and/or positive alcohol test during any visit in TAK-994-1501.
24. The subject has a history of drug or alcohol abuse within the 12 months before Baseline I (Diagnostic and Statistical Manual of Mental Disorders, Edition 5 criteria).
25. The subject has a 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 portions of the study.
26. The subject has a usual bedtime later than 2400 (12:00 AM, 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 Baseline I.

7.3 Excluded Medications

Excluded medications and dietary products are shown in Table 7.a.

Excluded medications are the same as those excluded in TAK-994-1501; however, washout periods for these medications do not apply for this study as subjects should have already completed washout before the first dose of study drug in TAK-994-1501.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Prohibited Drug or Drug Category	Drugs Restricted From Baseline I [a] Until 1 Week After Final Study Drug Intake (Unless Otherwise Specified)
Any investigational drug other than TAK-994	<60 days before Baseline I or 5 half-lives, whichever is longer
Psychostimulants	Methylphenidate hydrochloride, modafinil, armodafinil, methamphetamine hydrochloride, solriamfetol, atomoxetine, and pitolisant are not allowed
Sodium or multisalt oxybate	Not allowed
Antipsychotic drugs	Not allowed
Antianxiety/sleeping drugs (tranquilizers/sleeping medications including benzodiazepines, nonbenzodiazepine drugs, and melatoninergic agonists)	Not allowed
Antidepressants	Not allowed
Mood stabilizers (such as lithium or valproic acid or other antipsychotic drugs)	Not allowed
Anticonvulsants	Not allowed
Sleeping pills	Including Chinese medicine (*Yokukansan, Yokukansankachinpihange*) used for insomnia Not allowed
Anti–Parkinson disease drugs (completely excluded)	Not allowed
Adrenocorticosteroids (excluded except for inhaled and topical)	Systemic administration permissible during the study for purposes of treating an AE only
Interferon, interleukin-formulation (excluded)	Not allowed
Muscle-relaxant drug (eg, baclofen)	Not allowed
Antihistamines	Only centrally acting antihistamines are prohibited. Loratadine is also prohibited. The use of antihistamines and steroids are allowed for the management of severe allergic reactions.
Antitussives with CNS action	Not allowed
Antiemetics with CNS action	Not allowed
Narcotic analgesics and nonnarcotic analgesics, varencicline (CHANTIX)	Use of over-the-counter pain medications (acetaminophen; excluding occasional use of ibuprofen, naproxen, and aspirin) is prohibited unless otherwise approved by the principal investigator after consultation with the sponsor or designee (ie, medical monitor)
St. John's wort, health foods containing melatonin	Not allowed
Known moderate and strong CYP3A inhibitors or inducers are available in reference [b]	Not allowed

Table 7.a Excluded Medications, Supplements, and Dietary Products

Prohibited Drug or Drug Category	Drugs Restricted From Baseline I [a] Until 1 Week After Final Study Drug Intake (Unless Otherwise Specified)
Known P-gp inhibitors (azithromycin, captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor)	Not allowed
Known CYP3A substrates with narrow therapeutic range including but not limited to ergot alkaloids, fentanyl, pimozide, astemizole, terfenadine, systemic corticosteroids (dose equivalent to ≥10 mg prednisone per day), nisoldipine, lovastatin, simvastatin, midazolam, triazolam, buspirone, almorexant, lemborexant, suvorexant, lurasidone, naloxegol, tilidine, sildenafil, vardenafil, cilostazol, and eletriptan	Not allowed
Known sensitive OATP1B1 substrates including but not limited to pravastatin, rosuvastatin, pitavastatin, atorvastatin, elagolix, repaglinide, valsartan	Not allowed
Sensitive P-gp substrates with narrow therapeutic range: digoxin, dabigatran etexilate, fexofenadine	Not allowed
Sensitive BCRP substrates: sulfasalazine	Not allowed
Chinese herbal medicine	Topical use is allowed; Systemic use is not allowed

AE: adverse event; BCRP: breast cancer resistance protein; CNS: central nervous system; CYP: cytochrome P450; OATP: organic anion transporter type; P-gp: P-glycoprotein.
If medications are required to treat an AE, certain medications, including supplements, may be allowed after discussion and agreement between the sponsor and principal investigator, unless the investigator or designee considers immediate administration necessary.
[a] Baseline I of the current study (TAK-994-1504) is the completion date (final discharge date) of the preceding study (TAK-994-1501).
[b] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and -inducers, Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inductors, Accessed 27 January 2021.

Subjects may take any medication that is not prohibited in Table 7.a. The investigator or subinvestigator will consult with the sponsor medical monitor or designee before allowing any concomitant medication during the study. Subjects will also be instructed not to take any medications, including over-the-counter drugs, without prior consultation with the investigator or subinvestigator.

The use of any investigational drug other than TAK-994 is not permitted throughout any study participation period.

7.4 Diet, Fluid, Activity Control

- Consumption of all fruit juices and fruit other than grapefruit fruit and grapefruit juice is allowed on all days of the study.

- Alcohol use will be restricted for 7 days before check-in or site visit and not allowed until discharge. During other periods, alcohol consumption is limited to no more than approximately 2 alcoholic beverages or equivalent (1 alcoholic beverage is approximately equivalent to beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz]) per day.
- [redacted] At all other times, caffeinated beverages (including caffeinated tea) or xanthine-containing products will be limited to amounts of no more than 600 mg per day.
- [redacted] Subjects may smoke during the study outside the confines of the center but must be willing to abstain during the period of confinement in the inpatient or in laboratory sleep center.
- During confinement, subjects should remain upright (seated, standing, or ambulatory) for 4 hours following dose administration, except as necessitated by the occurrence of an AE or study procedure (eg, obtaining 12-lead ECG).
- Subjects should refrain from strenuous physical activity (eg, weightlifting, running, bicycling) from 72 hours before check-in until checkout for scheduled study visits. Subjects may engage in usual activities at other times with the exception of driving or operating hazardous machinery.

Instructions on the timing of study drug intake in relation to food and fluids are provided in Section 8.1.3.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the eCRF. The following criteria for discontinuation or withdrawal of a subject will apply to all parts of the study:

1. Pretreatment event (PTE) or AE: The subject has experienced a PTE, SAE, 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, SAE, or AE.
    - 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 9.3.8), if the following circumstances occur at any time during the study drug treatment:
        - ALT or AST >5 × ULN, or
        - ALT or AST >3 × ULN in conjunction with elevated 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%), or

  - ALT >3 × ULN twice consecutively at least 24 to 48 hours apart.

- Suicidality: Study drug should be discontinued immediately for subjects at imminent risk of suicide per the C-SSRS (endorsement on items 4 or 5) or per the investigator's clinical judgment.
- BP increase: Study drug should be discontinued immediately if the median of 3 in-clinic BP measurements (at least 10 minutes apart) meets any of the following criteria:
  - Systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg.
  - Neurologic or cardiac findings associated with increases in BP.

  In the event of BP values meeting the criteria above, the subject will be treated for elevated BP according to the best judgment of the investigator and in accordance with good medical practice, and, if needed, further emergency medical evaluation sought. If the study drug is discontinued in any subject due to a BP increase, the subject will not be rechallenged with TAK-994.

  Any subject found to have significantly elevated BP as an outpatient should be treated per standard to care to obtain BP lowering. The sponsor or designee (ie, medical monitor) should be notified and consulted.
- Pulse rate increase: Increased from baseline earlier in the day and sustained pulse rate >100 bpm measured during the in-clinic visit will result in stopping treatment.
- Insomnia: Study drug should be discontinued for subjects with sustained severe or serious insomnia as determined by the principal investigator after consultation with the sponsor or designee (ie, medical monitor).

2. Significant protocol deviation: The discovery postrandomization 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 3 attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents. A certified letter can be sent as a last attempt.
4. Voluntary withdrawal: The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category). If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19–related AE), this should be specified as the reason for subject withdrawal in the eCRF.
5. Pregnancy, as described in Section 9.1.4.

6. Study termination: The sponsor, IRB, IEC, or regulatory agency terminates the study. Criteria for premature cohort and/or study termination are provided in Section 6.3.
7. Lack of efficacy.
8. Other: The reason for discontinuation should be entered into the eCRF including unavoidable circumstances such as the COVID-19 pandemic.

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. The investigator should consult with the sponsor or designee (ie, medical monitor) before subject discontinuation whenever possible.

Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

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

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study Drug

Details regarding the dosage form description and strengths of the active drug and matching placebo can be found in the pharmacy manual. Study drug will be packaged to support enrollment as required.

Tablet strengths for this study are 10, 30, and 90 mg.

On occasion in unavoidable circumstances such as the COVID-19 pandemic, additional drug supply may be provided to subjects (either at an in-person visit or delivered to subject's residence) to cover extended periods between on-site visits. Any additional re-supply must be reviewed and approved in advance by the sponsor or designee.

8.1.1.2 Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.1.3 Ancillary Materials

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.

8.1.1.4 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following: TAK-994 and matching placebo.

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. Receipt and dispensing of study drug at the study site must be recorded by authorized personnel.

8.1.3 Dose and Regimen

Each subject in this study will be instructed to take study drug twice daily: the first dose will be taken in the morning upon awakening and the second dose will be taken approximately 5 hours later. Both doses should be taken without food. A minimum of 4 hours apart is required between the morning and afternoon doses. The second dose should be taken no later than 1400 based on the elimination half-life of TAK-994.

During the confinement periods (as indicated in Section 6.0), the first dose of TAK-994/matched placebo will be administered in the morning by mouth (at approximately 0800) with 240 mL of water after an overnight fast of at least 8 hours; subjects will then be allowed to have a morning meal approximately one-half to one hour after study drug administration. The second dose of TAK-994/matched placebo will be administered orally approximately 5 hours later at the site. Subjects may consume water ad libitum. Standardized meals (approximately 30% fat content relative to total calories) will be administered at approximately 4 (lunch) and 10 (dinner) hours after the morning dose.

Note: The first dose of TAK-994 in TAK-994-1504 will need to be held until after the Day 57 assessments in TAK-994-1501.

While at home, subjects will be instructed to take TAK-994/matched placebo upon arising in the morning as close to 0800 as possible (±1 hour) and have breakfast approximately one-half to one hour after study drug intake whenever possible. Subjects will be instructed to take the second dose approximately 5 hours after the morning dose and no later than 1400 in the afternoon. The second dose should be taken without food on an empty stomach (approximately 1 hour before eating or 2 hours after eating) whenever possible. Subjects are encouraged to take study drug at approximately the same time each day in the morning (first dose) and afternoon (second dose).

Breakfast and lunch should be standard meals each containing approximately 30% fat (relative total calories). Subjects will be provided written instructions by the site on how to take study drug (dosing and mealtimes) at home. Subjects should avoid meals with high-fat content (typically >50% calorie content).

Tablets should be taken with a large glass of water (approximately 240 mL total). Subjects should swallow the study drug whole and not chew it or manipulate it in any way before swallowing. Subjects should be instructed to take not more than the prescribed dose at any time. If a subject fails to take the TAK-994/matched placebo dose within the time frame specified, they should be instructed to take it at least 30 minutes before the next scheduled meal. Under no circumstance should a subject repeat a dose or double-up doses. If the second dose is missed, that dose should be skipped and should not be taken again until the next morning. Both doses should never be taken at one time.

Subjects will be instructed to record their dose of TAK-994/matched placebo each day, or any skipped or mistimed doses, in their electronic dosing diary. Additional steps may be taken to ensure subjects understand the dosing instructions and that they follow the correct TAK-994 dosing regimen, such as additional site communication with the subject throughout the treatment course, that is, on-site visits, phone or video calls, or other methods to demonstrate compliance and understanding of dose instructions may be employed.

Subjects will adhere to the medication and dietary restrictions described in Sections 7.3 and 7.4.

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 on an overdose page of 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 eCRF(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

All consented subjects will be given a unique subject number (site number plus a unique sequential number) that will be used to identify the subject for all procedures that occur during the study. Each subject will be assigned only 1 subject number. Subject numbers must not be reused for different subjects.

On the first day of the active drug extension period and the first day of the double-blind randomized withdrawal period, subjects will be assigned a randomization number at the clinical

site. The randomization number encodes the subject treatment assignment according to the randomization schedule generated before the study.

Subject and randomization numbers will be recorded on the eCRF. Each subject will be dispensed blinded study drug assigned by the IRT system throughout the study.

8.3 Randomization Code Creation and Storage

Before the start of the active drug extension period and before the start of the randomized withdrawal period, randomization personnel of the sponsor or designee will generate the randomization schedule for the IRT system. The randomization will be stratified by regions: North America, Europe, Japan, and South Korea. Details are in the IRT system specifications. The pharmacy manual includes instructions for emergency unblinding.

8.4 Study Drug Blind Maintenance

The investigator and subjects will be blinded to treatment assignment. Emergency randomization code access will be made available through the IRT system in accordance with the standard operating procedures of the clinical site.

The study drug blind will be maintained through a randomization schedule held by the IRT system.

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 sponsor or designee (ie, medical monitor) should be contacted before the blind is broken. Unblinding will be performed per the standard operating procedures of the study site.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

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.

When subjects come back to the site visit, they need to bring back the study drug. The site will check and confirm the compliance.

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, assessments should be performed as close to the scheduled time as possible. In the event of conflicts between scheduled procedures, the following rules should be applied:

- BP assessments should be completed first, followed by ECG [redacted] assessments. [redacted]
- Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.1.2 Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 or Other Unavoidable Circumstances

In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures (Appendix A), contingency measures may be implemented. In acknowledgement of study site, hospital, local, state, and national restrictions established in response to circumstances like COVID-19, the following measures are being taken for the current study:

- For subjects active in the study, all attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:
  - Sites impacted by the COVID-19 pandemic or similar unavoidable circumstances, must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection due to COVID-19 or other unavoidable circumstances.
  - Sites may seek approval from the sponsor or designee to continue subjects in the study despite departures from the Schedule of Study Procedures (Appendix A). The principal investigator is expected to evaluate the impact to the safety of the study participants and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study drug and remain compliant with the protocol.

- Other than discharge visits, alternative methods for conducting subject visits (eg, video conferencing, telephone visits, or in-home study visits conducted by study site personnel or designated medical personnel, contingent upon local regulations) may be used per approval by the sponsor or designee:
  - Under these circumstances, collection of certain study assessments may be omitted and visit windows may be extended.
  - When approval is given for a subject to miss an in-person study visit, a study site physician will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status.
  - The study site physician or other qualified site personnel should conduct the following assessments within specified-visit window time frames: AE assessments, documentation of concomitant medication, administration of C-SSRS (at applicable visits), and an assessment of clinical symptoms.
  - For this study, home nurses or other qualified clinical personnel may be deployed at the request of the site, when appropriate. Advance approval from the sponsor or designee should be obtained.
  - Other study assessments may be collected using an alternative method as feasible and may involve audio or video recording where allowed by local regulation. This will be documented in the study records.
  - Subjects may choose to get a COVID-19 vaccine at any time during this study.
  - In some instances, sites may need to split visits or sites may only be able to perform a few procedures on site and some procedures may need to be performed remotely. Sites should inform sponsor or designee when this occurs.
  - Sites may seek approval to extend a visit window in order to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window or within the visit window granted by the sponsor or designee will be considered missing data and such departures will be recorded in the study records.
  - There will be no interval longer than 2 weeks between successive visits at which clinical laboratory tests are performed and vital signs are measured. Should the period of 2 weeks be met for a particular subject, the site should reach out to the sponsor or designee to discuss withdrawal of the subject.
- Study site personnel may dispense additional study drug to subjects at a visit to allow for potentially longer intervals between visits than originally planned per protocol, or study drug may be supplied to subjects via delivery by site personnel or by courier.
- Early termination visits should be performed in person. When it is not possible for the subject to come to the study site and the protocol-specified visit window cannot be extended further, the preferred alternative for the early termination visit is for qualified

study site personnel or designated clinical personnel to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at a subject's residence should comply with applicable local regulations. If neither option is available with sponsor or designee approval, sites may conduct early termination procedures remotely as is feasible.

All subject discontinuations and alternative approaches to study procedures (ie, procedures not conducted per the Schedule of Study Procedures) due to the COVID-19 pandemic must be documented in the study records. Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the statistical analysis plan (SAP).

For this study, subjects may receive the COVID-19 vaccination. Sites should document the vaccination dosing on concomitant medication page.

9.1.3 Contraception and Pregnancy Avoidance Procedure

9.1.3.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 5 half-lives PLUS 90 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception detailed in Section 9.1.3.3.

9.1.3.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 5 half-lives PLUS 30 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use 2 highly effective methods of contraception (from the list detailed in Section 9.1.3.3).

In addition, they must not donate ova during this period.

9.1.3.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, that is, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those aged <45 years) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post–bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, the only acceptable methods of contraception are:

   - Nonhormonal Methods:
     - Intrauterine device.
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success).
   - Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound or concomitant medications, which may reduce the efficacy of the contraception method. Therefore, study subjects using hormonal contraception must also use an additional barrier method (male condom, female condom, or diaphragm) throughout the duration of the study, and for 5 half-lives PLUS 30 days after last dose of study drug.
     - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation. Contraception must be initiated at least 3 months before the first dose of study drug. The options below are included in the category of combined hormonal contraception:
       - Oral.
       - Intravaginal (eg, ring).
       - Transdermal.
     - Progestogen-only hormonal contraception associated with inhibition of ovulation. Important: Progestogen-only hormonal contraception must be initiated at least 3 months before the first dose of study drug. If female subjects have been taking progestogen-only hormonal contraception for less than 3 months before the first dose of study drug, female subjects must also (or partners of male subjects are advised to) employ a barrier method (male condom, female condom, or diaphragm) until she has been on contraceptive for 3 months. The options below are included in the category of progestogen-only hormonal contraception:
       - Oral.
       - Injectable.
       - Implantable.

2. Unacceptable methods of contraception are:
    - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
    - Spermicides only.
    - Withdrawal.
    - No method at all.
    - Use of female and male condoms together.
    - Cap/diaphragm/sponge without spermicide and without condom.
    - Declared sexual abstinence is NOT an acceptable method of contraception (unless approved by the investigator).
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and ova/sperm donation as part of the study procedures.
5. In addition to a negative serum hCG pregnancy test at the start of the study, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses). Subjects must also have a negative urine pregnancy test within 24 hours before receiving the first dose of investigational drug as close as possible and before the first dose of investigational drug, preferably on the same day.

9.1.3.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in male subjects with pregnant partners.
- Assessment of subject compliance through questions such as:
    - Have you used the contraception consistently and correctly since the last visit?
    - Have you forgotten to use contraception since the last visit?
    - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”).
    - Is there a chance you could be pregnant?

9.1.4 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 5 half-lives PLUS 90 days after the last dose, should also be recorded following authorization from the subject's partner.

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

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

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

9.2 Administrative Procedures

9.2.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters into the study, and before any protocol-directed procedures are performed. The requirements of the informed consent (and e-consent, if applicable, as per local regulations) are described in Appendix C. Additional information on the informed consent procedure is provided 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; this subject number will be used throughout the study.

9.2.2 Demographics, Medical History, and Medication History Procedure

Demographic information obtained during TAK-994-1501 will be used for this extension study and will include date of birth, sex, race (reported by the subject), Hispanic ethnicity information, height, weight, caffeine consumption, alcohol consumption, and smoking status. (Note that only Baseline I height and weight will be obtained from TAK-994-1501; additional measurements are planned in the current study.). Information on the primary disease was also collected in TAK-994-1501 and will be included in this extension study's database.

Medical history information obtained during TAK-994-1501 will be used for this extension study and will include any significant conditions or diseases, including those reported as AEs during TAK-994-1501, relevant to the disease under study that resolved at or before signing of informed consent. Ongoing conditions, including AEs that started during TAK-994-1501 and were ongoing

at start of this study, are considered concurrent medical conditions in this extension study (see Section 9.2.4).

Medication history information obtained during TAK-994-1501 will be used for this extension study and will include any medication, including that administered during TAK-994-1501, relevant to eligibility criteria and efficacy/safety evaluation stopped at or before signing of informed consent. The nonproprietary name, route of administration, dates of initial and final administrations, and reasons for use must also be recorded.

9.2.3 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

The nonproprietary name, route of administration, dates of initial and final administrations, and reasons for use must also be recorded.

9.2.4 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent of this extension study. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at baseline examination, according the judgment of the investigator and thus also include AEs that started during TAK-994-1501 that were ongoing at that study's final visit. The condition (ie, diagnosis) should be described.

9.3 Clinical Procedures and Assessments

9.3.1 AE Monitoring

A complete description of PTE and AE collection procedures is provided in Section 10.0.

9.3.2 Vital Sign Procedure

Vital signs, including body temperature, respiratory rate, BP (systolic and diastolic, resting more than 5 minutes), and pulse (bpm), will be obtained at the times indicated in the Schedule of Study Procedures (Appendix A).

Body temperature will be measured with an oral (temperature taken at floor of the mouth), tympanic, or infra-axillary thermometer. The same method (eg, oral, tympanic, or infra-axillary) must be used for all subsequent measurements for each individual subject.

When assessed in the clinic, BP will be checked (single measurement) with the subject lying in a bed resting for a minimum of 5 minutes with the head of the bed at 30 degrees. In the event of

conflicts between scheduled BP assessment and [redacted], BP assessments should be taken first.

9.3.3 Weight, Height, and Body Mass Index

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

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

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

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m^2.

9.3.4 ECG Procedure

ECG monitoring will be performed at the times indicated in the Schedule of Study Procedures (Appendix A).

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Subjects may need to be shaved to ensure proper lead placement. Subjects should be resting in a semirecumbent position for at least 5 minutes before each ECG measurement and will remain in that position until the ECG is completed. The principal investigator should arrange to have a study cardiologist available as needed to review ECG tracings with abnormalities.

If a subject demonstrates an increase in QTcF interval ≥40 milliseconds compared with a baseline measurement, the ECG will be repeated within 5 minutes. The average value of the QTcF interval from the 2 ECGs will represent the value at that time point. If the average QTcF interval increase from baseline for any postdose time point is ≥40 milliseconds, the subject will continue to be monitored by repeat 12-lead ECGs every 60 minutes for at least 4 hours or until the QTcF interval is within 40 milliseconds of the baseline value. If prolongation of the QTcF interval ≥40 milliseconds persists, a consultation with a study cardiologist may be appropriate and the sponsor should be notified.

If the QTcF interval is ≥500 milliseconds, the sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be considered for transfer to a location where closer monitoring is available.

If the subject has unstable hemodynamics, or has any clinically significant dysrhythmias noted by telemetry, the subject should be immediately transferred to an acute care setting for definitive therapy.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

9.3.5 Physical Examination Procedure

The Baseline I physical examination 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 other physical examinations should assess clinically significant changes from baseline.

9.3.6 [redacted]

[redacted]

9.3.7 C-SSRS

Suicidal ideation will be assessed using the C-SSRS at the times indicated in the Schedule of Study Procedures (Appendix A).

The C-SSRS Since-Last-Visit C-SSRS will be used during this study. Any suicidal ideation or suicidal behavior during the study periods detected by the C-SSRS will be recorded as an AE. The investigator will ensure that any suicidal ideation or behavior is medically addressed, including assessment and treatment by qualified medical personnel.

9.3.8 Clinical Laboratory Procedures and Assessments

All samples will be collected in accordance with acceptable laboratory procedures. A discussion between the investigator and the sponsor or designee will take place to consider additional laboratory assessments when needed.

All laboratory samples will be taken as indicated in the Schedule of Study Procedures (Appendix A). Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis [a]
RBCs	ALT	Blood
WBCs with absolute differential	Albumin	Glucose
Hemoglobin	Alkaline phosphatase	Urine specific gravity
Hematocrit	AST	Nitrite
Platelets	Total bilirubin [c]	Protein
PT/INR [b]	Total protein	
	Creatinine	
	Blood urea nitrogen	
	Creatine kinase	
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Carbon dioxide	
	Triglycerides	
	Lipid panel (HDL, LDL, total cholesterol)	
	Chloride	
	Glucose	
Other:		
Serum	**Serum/Plasma**	**Urine**
Female subjects of childbearing potential only: β-hCG (for pregnancy)	Aldosterone, renin	Female subjects of childbearing potential only: hCG (for pregnancy) For all subjects: drug screening (amphetamines, barbiturates, benzodiazepines, buprenorphine/metabolite, cannabinoids, cocaine/metabolites, MDMA, methadone/metabolite, opiates, oxycodone/oxymorphone, phencyclidine) Confirmatory urine drug screen tests [d]
Alcohol test: with a breathalyzer initially and, if positive, a serum ethanol level will be obtained		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: γ-glutamyl transferase; HDL: high-density lipoprotein; hCG: human chorionic gonadotropin; INR: international normalized ratio; LDL: low-density lipoprotein; MDMA: 3,4-methylenedioxy-methamphetamine; PT: prothrombin time; RBC: red blood cell; WBC: white blood cell.

[a] Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of RBC count/high-power field, WBC/high-power field, and casts.

[b] If ALT or AST >3 times the ULN

[c] If value above the upper limit of normal, total bilirubin will be fractionated.

[d] Applicable throughout the study in regions where available.

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 24 to 48 hours after the abnormality was noted.

As detailed in Section 7.5, subjects with 2 consecutive ALT elevation >3 × ULN should be withdrawn from the study. For subjects with ALT or AST elevated >3 × ULN at any occasion, the investigator must contact the sponsor or medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE.

Refer to Section 7.5 for subject discontinuation criteria regarding abnormal LFTs and Section 10.2.3 for guidance on reporting abnormal LFTs.

9.4 [redacted]

9.4.1 [redacted]

9.4.1.1 [redacted]

9.4.1.2 [redacted]

9.4.2 [redacted]

9.4.2.1 [redacted]

[redacted]

9.4.2.2 [redacted]

[redacted]

9.4.2.3 [redacted]

[redacted]

[redacted]

9.4.2.4 [redacted]

[redacted]

9.4.2.5 [redacted]

[redacted]

[redacted]

9.4.2.6 [redacted]

[redacted]

9.4.2.7 [redacted]

[redacted]

9.4.2.8 [redacted]

[redacted]

[redacted]

9.4.2.9 [redacted]

[redacted]

9.5 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject signs an informed consent form and then does not qualify for this study before dosing on the study drug for this study, the investigator should complete the eCRF. The IRT 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.
- Other <specify reason>.

Subject identification numbers should not be reused.

9.6 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into this study.

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

9.7 [redacted]

[redacted]

9.7.1 [redacted]

[redacted]

9.7.2 [redacted]

[redacted]

9.8 Monitoring Subject Treatment Compliance

Subjects will be required to bring study drug containers/unused study drugs to each dispensing site visit.

If a subject is persistently noncompliant with the study drug, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.9 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.10 Post Study Care

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

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

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 before 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 re-test 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, x-rays) 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 before 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 on an Overdose page of 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:

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
COVID-19 related disease	Neuroleptic malignant syndrome/malignant hyperthermia
COVID-19 pneumonia	Spontaneous abortion/stillbirth and fetal death

AE: adverse event; SAE: serious adverse event.
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

No AEs of special interest have been defined for this study.

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.

10.1.10 Stop 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.

10.1.11 Frequency

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

10.1.12 Action 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, for example, 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.

10.1.13 Outcome

- 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 that 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 AEs (ie, AEs, SAEs, special interest AEs, and abnormal LFTs) will commence at the time the subject takes his/her first dose of TAK-994. Routine collection of AEs will continue until approximately 30 days or 5.5 half-lives, whichever is longer, after the last dose of study drug. For subjects who discontinue before the administration of study drug, AEs will be followed until the subject discontinues study participation.

Because this study is designed to have subjects complete assessments for TAK-994-1501 and then shortly thereafter begin assessments for the current study, the PTE collection window for this protocol is brief. After signing of the ICF, it commences after the first assessment and ends upon intake of the first dose of TAK-994.

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. Nonserious 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.

In addition, additional information regarding following AEs may be collected on eCRF:

10. Increased urinary urgency and frequency (daily urinary frequency), urinary incontinence.

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

10.2.2 Collection and Reporting of SAEs

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

SAEs should be reported via SAE eCRF in Rave electronic data capture (EDC), which is the preferred method of reporting. A Takeda SAE form 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 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 form 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 email address on the fax cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

Email submission of SAE forms (to the appropriate email address listed below) with a 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 email, 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.

Reporting of SAEs that begin before the first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

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, and the subject should be withdrawn from the study. 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 sponsor or designee for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.3.8 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should update SAE eCRF in Rave EDC or complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

10.3.1 Safety Reporting to Investigators, IRBs 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, including the European Medicines Agency, 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 report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB 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 Drug Dictionary.

12.1 eCRFs

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

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

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

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

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date 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 clinical 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 study monitors. 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.

The investigator and the head of the study site agree 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), 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 and the head of the study site 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/or the head of the study site and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution 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 SAP will be prepared and finalized before 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 before 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 Baseline Definition

Baseline I is defined as the last measurement before the first dose in the active drug extension period of this study.

Baseline II is defined as the last measurement before the first dose in the randomized withdrawal period of this study, [redacted], which will be averaged over the last week.

13.1.2 Analysis Sets

13.1.2.1 Active Drug Extension Period

13.1.2.1.1 Active Drug Extension Safety Set

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

13.1.2.1.2 [redacted]

13.1.2.1.3 [redacted]

13.1.2.2 Randomized Withdrawal Period

13.1.2.2.1 Randomized Withdrawal Safety Set

The safety set for the randomized withdrawal period will consist of all subjects who took at least 1 dose of study drug or placebo in the randomized withdrawal period. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries for the randomized withdrawal period. The subjects will be grouped based on the actual treatment received.

13.1.2.2.2 [redacted]

[redacted]

13.1.2.2.3 [redacted]

[redacted]

13.1.3 Analysis of Demographics and Other Baseline Characteristics

13.1.3.1 Active Drug Extension Period

Demography and other characteristics at Baseline I will be summarized by treatment and overall for all subjects using the active drug extension safety set and will be listed. Descriptive statistics will be used to summarize data by treatment and overall for continuous variables like age and weight (number of subjects, mean, median, SD, minimum, and maximum) and for categorical variables like sex, ethnicity, and race (number and percentage of subjects within each category). Medical history and medication history will be listed.

13.1.3.2 Randomized Withdrawal Period

Demography and other characteristics at Baseline II will be summarized by treatment groups and overall using the randomized withdrawal safety set and will be listed. Descriptive statistics will be used to summarize data by treatment and overall for continuous variables like age and weight (number of subjects, mean, median, SD, minimum, and maximum) and for categorical variables like sex, ethnicity, and race (number and percentage of subjects within each category). Medical history and medication history will be listed by subject.

The placebo subject's treatment group will be split based on the active drug extension treatment group.

13.1.4 [redacted]

13.1.4.1 [redacted]

[redacted]

13.1.4.2 [redacted]

[redacted]

13.1.5 [redacted]

[redacted]

13.1.6 [redacted]

[redacted]

13.1.7 Safety Analysis

13.1.7.1 AEs

13.1.7.1.1 Active Drug Extension Period

TEAEs will be summarized using the active drug extension safety set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using MedDRA. Data will be summarized by treatment and overall using Preferred Term and primary System Organ Class.

13.1.7.1.2 Randomized Withdrawal Period

TEAEs will be summarized using the randomized withdrawal safety set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using MedDRA. Data will be summarized by treatment and overall using Preferred Term and primary System Organ Class.

13.1.7.2 Clinical Laboratory Evaluation

13.1.7.2.1 Active Drug Extension Period

Safety clinical laboratory evaluation data will be summarized by treatment group and overall (number of subjects, mean, SD, median, minimum, and maximum) for baseline, postdose, and change from baseline. Observed values and change from Baseline I in these parameters will be summarized by treatment and overall.

Subjects meeting markedly abnormal criteria for safety clinical laboratory assessments will be listed and summarized by treatment group and overall. The MAV criteria will be defined in the SAP.

13.1.7.2.2 Randomized Withdrawal Period

Safety clinical laboratory evaluation data will be summarized by treatment group and overall (number of subjects, mean, SD, median, minimum, and maximum) for baseline, postdose, and change from baseline. Observed values and change from Baseline II in these parameters will be summarized by treatment and overall.

Subjects meeting markedly abnormal criteria for safety clinical laboratory assessments will be listed and summarized by treatment group and overall. The MAV criteria will be defined in the SAP.

13.1.7.3 Vital Signs and ECGs

The relationships between TAK-994 exposure and selected safety measures (such as change from baseline in systolic BP, diastolic BP, and HR) will be explored graphically, as data permit. Details will be described in the SAP.

13.1.7.3.1 Active Drug Extension Period

All vital signs and ECG assessments will be summarized for Baseline I, postdose, and change from baseline by treatment and time, if deemed appropriate.

Subjects meeting markedly abnormal criteria for vital signs and ECG assessments will be listed and summarized by treatment group and overall. The MAV criteria will be defined in the SAP.

13.1.7.3.2 Randomized Withdrawal Period

Where appropriate, BP and pulse measurements will be summarized by treatment group and overall (number of subjects, mean, SD, median, minimum, and maximum) for baseline, postdose, and change from baseline by treatment and time point. Linear mixed-effect models for the repeated measures will be performed to evaluate the drug effect on BP and pulse using data from inpatient monitoring. In these analyses, change from time-matched baseline will be the response and baseline, treatment, time point, and the treatment by time point interaction will be the fixed effects.

All other vital signs and ECG assessments will be summarized for Baseline II, postdose, and change from baseline by treatment and time, if deemed appropriate.

Subjects meeting markedly abnormal criteria for vital signs and ECG assessments will be listed and summarized by treatment group and overall. The MAV criteria will be defined in the SAP.

13.1.7.4 Other Safety Parameters

Physical examination findings and C-SSRS data will be presented in the data listings.

13.2 Interim Analysis

No interim analysis is planned.

13.3 Determination of Sample Size

There is no sample size justification for this study. All subjects in Part B of TAK-994-1501 willing and eligible to participate and meeting the selection criteria will be enrolled in the active drug extension period of the study. Subjects who complete the active drug extension period and willing to continue to the randomized withdrawal period will 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 (contract research organization) 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 (such as the COVID-19 pandemic) 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.

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

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 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 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 B. 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 Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB 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/signing a contract for the clinical study). 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.

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

participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the 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 before 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.

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 before 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 before 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.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject 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.

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

15.4.2 Clinical Trial Registration

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

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial

inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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15. [redacted]
16. [redacted]
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19. [redacted]
20. [redacted]

Appendix A Schedule of Study Procedures

	End of TAK-994-1501 /Start of Active Drug Extension Period Baseline I [a]		Active Drug Extension Period				End of Active Drug Extension Period/ Start of Randomized Withdrawal Period Baseline II		Randomized Withdrawal Period					FU
Day	-2/-1 [b]	1 [c]	7	14	28	42	55	56	63	70	77	83	84 (Final Visit/ ET [d])	98
Week	NA	1	1	2	4	6	8		9	10	11	12		13
Visit Window (Days) [e]	NA	NA	±3	±3	±3	±3	±3		±3	±3	±3	±3		±5
Visit Number	NA	1	2	3	4	5	6		7	8	9	10		NA
Administrative procedures														
Informed consent		X [f]												
Inclusion/exclusion criteria		X												
Demographics, medical history, height		X [g]												
Concurrent medical conditions		X [g]												
Medication history		X [g]												
Concomitant medication		*Throughout the study from the signing of informed consent onwards*												
Pregnancy avoidance counseling [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Call IRT for subject ID/ medication ID		X	X	X	X	X		X	X	X	X		X	
NT1 medication restart														X [i]
Check-in							X					X		

	End of TAK-994-1501 /Start of Active Drug Extension Period Baseline I [a]		Active Drug Extension Period				End of Active Drug Extension Period/ Start of Randomized Withdrawal Period Baseline II		Randomized Withdrawal Period					FU
Day	-2/-1 [b]	1 [c]	7	14	28	42	55	56	63	70	77	83	84 (Final Visit/ ET [d])	98
Week	NA	1	1	2	4	6	8		9	10	11	12		13
Visit Window (Days) [e]	NA	NA	±3	±3	±3	±3	±3		±3	±3	±3	±3		±5
Visit Number	NA	1	2	3	4	5	6		7	8	9	10		NA
Clinical Procedures and Assessments														
AE assessment		*Throughout the study from the signing of informed consent onwards*												
Vital signs		X [g]	X	X	X	X	X	X [j]	X	X	X	X	X [j]	X
Body weight and BMI	X [g]							X					X	
ECG		X [g]	X	X	X	X		X [k]	X	X	X		X [k]	
Physical examination	X [g]												X	
OAB-qLF/PPBC	X [g]		X	X	X	X		X					X	
TAK-994/placebo administration [a, l]	X [m]	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Laboratory Procedures and Assessments														
Pregnancy test (hCG) [n]	X [g]	X	X	X	X	X	X		X	X	X	X	X	X
Hematology and blood chemistry [o]	X [g]				X			X					X	X
Serum/plasma collection for aldosterone and renin [p]		X	X	X	X	X		X					X	
Plasma sample for exosome research								X					X	
Urinalysis	X [g]		X	X	X	X		X		X			X	X
Urine drug screening [q]	X [g]			X	X	X		X		X			X	
Alcohol screening [r]							X					X		
C-SSRS	X [g]					X		X		X			X	X

	End of TAK-994-1501 /Start of Active Drug Extension Period Baseline I [a]		Active Drug Extension Period				End of Active Drug Extension Period/ Start of Randomized Withdrawal Period Baseline II		Randomized Withdrawal Period					FU
Day	-2/-1 [b]	1 [c]	7	14	28	42	55	56	63	70	77	83	84 (Final Visit/ ET [d])	98
Week	NA	1	1	2	4	6	8		9	10	11	12		13
Visit Window (Days) [e]	NA	NA	±3	±3	±3	±3	±3		±3	±3	±3	±3		±5
Visit Number	NA	1	2	3	4	5	6		7	8	9	10		NA
[redacted]														

AE: adverse event; BMI: body mass index; [redacted]; C-SSRS: Columbia Suicide Severity Rating Scale; ECG: electrocardiogram; eCRF: electronic case report form; [redacted]; early termination; FU: follow-up; hCG: human chorionic gonadotropin; ID: identification; IRT: information response technology; [redacted]; NA: not applicable; [redacted]; NT1: narcolepsy type 1; OAB-qLF: Overactive Bladder Questionnaire – Long Form; [redacted]; PPBC: Patient Perception of Bladder Control.

In-clinic periods are marked in gray highlight. Outpatient periods are clear cells. Subjects will stay overnight at the clinic on Days 55 and 56 (end of the active drug extension period) and Day 83 (end of the randomized withdrawal period). Subjects will be discharged on Day 57 and Day 84, respectively. Subjects are also staying overnight at Day -2 and -1 (part of TAK-994-1501 Part B).

[a] After a [redacted] has been obtained and AE/concomitant medication information has been collected for TAK-994-1501, eligible subjects will immediately continue into the active drug extension period. Following a predose renin/aldosterone sample, subjects will be dosed with TAK-994.

[b] = Days 55 and 56 in TAK-994-1501 Part B.

	End of TAK-994-1501 /Start of Active Drug Extension Period Baseline I [a]		Active Drug Extension Period				End of Active Drug Extension Period/ Start of Randomized Withdrawal Period Baseline II		Randomized Withdrawal Period					FU
Day	**-2/-1 [b]**	**1 [c]**	**7**	**14**	**28**	**42**	**55**	**56**	**63**	**70**	**77**	**83**	**84 (Final Visit/ ET [d])**	**98**
Week	**NA**	**1**	**1**	**2**	**4**	**6**	**8**		**9**	**10**	**11**	**12**		**13**
Visit Window (Days) [e]	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**		**±3**	**±3**	**±3**	**±3**		**±5**
Visit Number	**NA**	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**	**10**		**NA**

[c] = Day 57 in TAK-994-1501 Part B.
[d] All subjects who withdraw early, except those who withdraw their consent and refuse further contact, are to attend a withdrawal visit as soon as possible. Sites are encouraged to schedule ET visits before subjects discontinue study drug (investigator discretion to be applied; exceptions to be made for discontinuation due to [S]AEs). Sites are to complete all assessments described in the Schedule of Study Procedures above as is feasible. In some cases, an abbreviated ET visit (consisting of safety assessments) may be appropriate after discussion with the sponsor or designee.
[e] If the date of a subject visit does not conform to the study plan, the timing of subsequent visits should be planned so that the visit schedule relative to randomization is maintained.
[f] Informed consent needs to be obtained at the latest on Day 1 of the active drug extension period (= Day 57 in TAK-994-1501), before the first dose of TAK-994 in the current study (TAK-994-1504). In case the subject signs an informed consent form for the current study (TAK-994-1504) before Day 57 in TAK-994-1501, AE collection for the current study (TAK-994-1504) will commence immediately following the first dose of TAK-994 in the current study.
[g] The final assessments from TAK-994-1501, performed at Days 55-57, will serve as the Baseline I assessments for TAK-994-1504. All demographic information, medical history, medication history, concomitant medications, as well as all ongoing AEs will be incorporated into the TAK-994-1504 study eCRF or final data listings.
[h] Sites to continue counseling female subjects to avoid becoming pregnant during clinical study participation as is standard practice in clinical studies. Male subjects should also be reminded to follow the contraception requirements described in both protocols. Refer to Appendix D in TAK-994-1501 and Section 9.1.3 in the current protocol for contraception and pregnancy avoidance guidelines.
[i] NT1 medication restart can occur 1 week after the last dose.
[j] On Day 56 and Day 84/ET blood pressure and pulse should be collected predose and then again approximately 1 hour and 3 hours after the morning dose.
[k] On Day 56 and Day 84/ET ECG should be taken predose.
[l] Study drug will be administered orally in the morning (at approximately 0800) and in the afternoon (approximately 1300).
[m] Administration in TAK-994-1501.
[n] Serum hCG for women of childbearing potential will be assessed only at Baseline I, Baseline II, at the Final/ET visit, and at follow-up. At all other visits, urine-stick pregnancy tests will be provided. Pregnancy tests may be repeated at any time at investigator's discretion. Refer to Appendix D in TAK-994-1501 and Section 9.1.3 in the current protocol for contraception and pregnancy avoidance guidelines. Note that in TAK-994-1501, there is a serum pregnancy test at Day 56; in the current study (TAK-994-1504) subjects must also have a negative urine pregnancy test within before receiving the first dose of study drug as close as possible and before the first dose of study drug, preferably on the same day.
[o] Hematology and blood chemistry procedures should occur after at least 8 hours of fasting at each indicated time point.
[p] Blood samples for the determination of aldosterone and renin will be collected at predose (AM) and at approximately 2 hours after the morning dose, right before the afternoon dose, and before discharge at Week 8 (Visit 6) and Week 12 (Visit 10). On Week 4 (Visit 4), the sample should be taken once before the morning dose. At all other indicated visits, only 1 sample will be collected (anytime during the visit). The first sample (Baseline I) will be taken before dosing. Note that for [redacted] and aldosterin/renin the Week 8 (Visit 6) sample to be taken before discharge will be taken on Day 57.
[q] Urine drug screen may be repeated any time at the investigator's discretion. Confirmatory urine drug tests will be performed in study in regions where available at the investigator's discretion.
[r] Alcohol screening will be done with a breathalyzer initially and, if positive, a serum ethanol level will be obtained.
[redacted]

	End of TAK-994-1501 /Start of Active Drug Extension Period Baseline I [a]		Active Drug Extension Period				End of Active Drug Extension Period/ Start of Randomized Withdrawal Period Baseline II		Randomized Withdrawal Period					FU
Day	-2/-1 [b]	1 [c]	7	14	28	42	55	56	63	70	77	83	84 (Final Visit/ ET [d])	98
Week	NA	1	1	2	4	6	8		9	10	11	12		13
Visit Window (Days) [e]	NA	NA	±3	±3	±3	±3	±3		±3	±3	±3	±3		±5
Visit Number	NA	1	2	3	4	5	6		7	8	9	10		NA

[redacted]

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs (and ePROs), hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The

investigator should contact and receive written approval from the sponsor before disposing of any such documents.

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

Appendix C Elements of the Subject Informed Consent

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

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

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

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) That personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) It is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) That personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) That subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) That the subject's identity will remain confidential in the event that study results are published.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active **must use highly effective contraception** (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 5 half-lives PLUS 30 days after last dose. Regular pregnancy tests will be performed throughout

the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

25. Male subjects **must use highly effective contraception** (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 5 half-lives PLUS 90 days after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

A Dose-Blind Extension Study With Double-blind, Placebo-Controlled, Randomized Withdrawal Period to Evaluate the Safety and Explore the Pharmacokinetics and Pharmacodynamics of TAK 994 in Adults With Narcolepsy With Cataplexy (Narcolepsy Type 1)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	15-Feb-2021 19:39 UTC
[redacted]	Biostatistics Approval	15-Feb-2021 20:24 UTC