Title: A Phase 1, Open-Label Positron Emission Tomography Study in Healthy Subjects to Determine the Effect of TAK-041 on Amphetamine-Induced Dopamine Release in the CNS After Single-Dose Oral Administration

NCT Number: NCT02959892

Protocol Approve Date: 21 February 2017

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

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

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

PROTOCOL AMENDMENT

A Phase 1, Open-Label Positron Emission Tomography Study in Healthy Subjects to Determine the Effect of TAK-041 on Amphetamine-Induced Dopamine Release in the CNS After Single-Dose Oral Administration

Phase 1 TAK-041 Single-Dose PET Study

Sponsor: Takeda Development Centre Europe Ltd.
61 Aldwych
London, WC2B 4AE
United Kingdom

Study Number: TAK-041-1002

IND Number: Not Applicable **EudraCT Number:** 2016-002346-23

Compound: TAK-041

Date: 21 February 2017

Amendment History:

Date	Amendment Number	Amendment Type	Region
19 July 2016	Initial version	Not applicable	London, UK
07 October 2016	01	Substantial	London, UK
21 February 2017	02	Substantial	London, UK

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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 should be provided to the site.

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

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical 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 E6 Good Clinical Practice 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 may be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, 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.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

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

PPD _____ Date

PPD _____ Date

1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating amendment No. 02.

The primary reasons for this amendment are to change TAK-041 doses and procedures. Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

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

Changes in Amendment 02

1. Preliminary results from first-in-human (FIH) study TAK-041-1001 were updated.
2. Single doses of TAK-041 ranging from 5 to 40 mg may be evaluated in this study.
3. Possible dose combinations of TAK-041 and amphetamine (AMPH) have changed.
4. Primary and secondary endpoints were revised.
5. An additional PET analysis was added and revisions were made to an existing analysis.
6. PET procedures were modified.
7. Following discharge from Confinement Period 2, subjects will return to the site for pharmacokinetic (PK) and safety assessments after 7 ±2 days, and then return for approximately 3 Follow-up safety and PK assessment Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's maximum observed plasma concentration (C_{max}).
8. At the end of each Follow-up Visit, the next visit will be scheduled ~4 weeks later. If, when the PK results are available, the subject's PK was <5% of their C_{max} value, the site and subject will be informed that their next scheduled visit will be considered their Study Exit/Final Visit.
9. Discrepancies between clinical laboratory tests listed in Table 9.b and Appendix A were resolved:
   a) Leukocytes were removed from urinary analysis.
   b) Diagnostic Screening tests were clarified and inconsistencies corrected.
10. The duration for collection of treatment-emergent adverse events (TEAEs) was changed.
11. Names and credentials of the signatory clinical pharmacologist and statistician for this study were updated.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Centre Europe Ltd.	**Compound:** TAK-041	
Title of Protocol: A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Subjects to Determine the Effect of TAK-041 on Amphetamine-Induced Dopamine Release in the CNS After Single-Dose Oral Administration	**IND:** Not Applicable	**EudraCT:** 2016-002346-23
Study Number: TAK-041-1002	**Phase:** 1	

Study Design:

This is a phase 1, open-label clinical study utilizing positron emission tomography (PET) and the radiolabeled dopamine-2 and -3 (D2/D3) receptor agonist PET ligand [^{11}C]-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho [1,2-*b*][1,4]oxazin-9-ol ([^{11}C]PHNO) to evaluate the effects of single oral doses of TAK-041 on amphetamine (AMPH)-induced dopamine release in the brain in 12 healthy male subjects.

Subjects will continue to be enrolled until 12 evaluable subjects complete all procedures. Each subject will have 1 magnetic resonance imaging (MRI) brain scan and 3 [^{11}C]PHNO PET scans. The MRI brain scan will be performed without gadolinium contrast for all subjects and will be interpreted at the CCI during the Screening Period to determine eligibility. The results of this MRI brain scan will also be used during the study to delineate the anatomical regions of interest for individual PET images.

The study consists of 2 Confinement Periods for each subject during which the PET scans will occur at the CCI . Confinement Periods 1 and 2 will be separated by an interval of 5 to 45 days.

Confinement Period 1:

- The first [^{11}C]PHNO PET scan occurs on Day 1 to serve as the Baseline scan to determine the nondisplaceable binding potential (BP_{ND}) in striatum under untreated conditions for each subject.
- On Day 2, the subject will receive a single oral 0.5 mg/kg dose of AMPH, followed by a [^{11}C]PHNO PET scan at approximately 3 hours post-AMPH dose in order to establish BP_{ND} in striatum after AMPH-induced dopamine release as compared to Baseline.

Confinement Period 2:

- On Day 1, the subject will receive a single oral dose of TAK-041 up to 40 mg, followed by a single oral 0.5 mg/kg dose of AMPH approximately 2 hours after the dose of TAK-041, followed by a [^{11}C]PHNO PET scan at approximately 3 hours post-AMPH administration.

Blood samples for pharmacokinetic (PK) analysis of AMPH will be collected prior to AMPH administration, 1 and 2 hours post-AMPH administration, and immediately prior to and after the [^{11}C]PHNO PET scan to measure plasma levels of AMPH. PK blood samples for TAK-041 will also be collected 1, 2, 12, and 24 hours after TAK-041 administration, immediately prior to and after the [^{11}C]PHNO PET scan, and during each Follow-up Visit. Following discharge from Confinement Period 2, subjects will return to the site for PK and safety assessments after 7 ±2 days, and then return for approximately 3 Follow-up Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's C_{max}.

Using data from the TAK-041-1001 study, AMPH will be administered at the approximate time to reach C_{max} (t_{max}) (plasma) of TAK-041. The [^{11}C]PHNO PET scan will start at the approximate t_{max} (plasma) of AMPH (estimated to be 3 hours post-AMPH dose). The starting dose of TAK-041 in this study will be 20 mg, a dose that has been demonstrated to be well-tolerated in the TAK-041-1001 study and has achieved exposures indicative of the predicted pharmacologically active exposures of TAK-041. A single dose of 40 mg TAK-041 has also been shown to be well-tolerated in the TAK-041-1001 study and may be evaluated in this study to explore the exposure-response relationship of TAK-041. The highest dose of AMPH that will be administered will be an oral dose of 0.5 mg/kg. This dose has been demonstrated to be safe and well-tolerated in healthy subjects and is a dose which has been shown to

induce dopamine release in AMPH-challenge studies.

Safety and tolerability will be assessed through all study visits, including collecting blood and urine samples for laboratory tests. Subjects will complete scheduled study assessments according to the Schedule of Study Procedures.

Each subject will report to CCI ~8 occasions:

1. Screening Visit to determine eligibility (-28 to -2 days prior to Confinement Period 1/Day 1): The screening brain MRI may be performed on a separate day from the other screening procedures, and will be performed and interpreted at the CCI after the other screening activities have been performed and results assessed. MRI should be performed early enough so that MRI scan results are available prior to Baseline Imaging admission for Confinement Period 1.
2. Confinement Period 1: admission to CCI (Day -1), 1 day prior to Baseline [^{11}C]PHNO PET imaging on Day 1; AMPH administration and postdose [^{11}C]PHNO PET imaging on Day 2; discharge on Day 3, the day following the postdose [^{11}C]PHNO PET imaging. All subjects will undergo 1 predose [^{11}C]PHNO PET scan on Day 1 and 1 postdose [^{11}C]PHNO PET scan on Day 2.
3. Confinement Period 2 (5 to 45 days after discharge from Confinement Period 1): admission to CCI (Day -1) 1 day prior to TAK-041 and AMPH administrations and postdose [^{11}C]PHNO PET imaging on Day 1; discharge on Day 2, the day following the postdose [^{11}C]PHNO PET imaging. All subjects will undergo a single postdose [^{11}C]PHNO PET scan on Day 1.
4. Follow-up Safety and PK Assessment Visits: Following discharge from Confinement Period 2, subjects will return to the site for PK and safety assessments after 7 ±2 days, and then return for approximately 3 Follow-up safety and PK assessment Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's C_{max}.
5. Study Exit/Final Visit Day: At the end of each Follow-up Visit, the next visit will be scheduled approximately 4 weeks later. If, when the PK results are available, the subject's PK was <5% of their C_{max} value, the site and subject will be informed that their next scheduled visit will be considered their Study Exit/Final Visit. Subjects who prematurely discontinue the study will have the assessments for Study Exit/Final Visit performed if possible on their last day in the study.

If logistical limitations (such as tracer synthesis failure) prevent the Baseline PET scan from being performed at the scheduled time point, the Confinement Period may be extended or cut short and rescheduled. If a postdose PET scan is delayed, it may be necessary to end the Confinement Period early and reschedule.

This study will utilize an adaptive design to determine the doses of AMPH and TAK-041 to be administered:

- The first 4 subjects in this study will receive a 20 mg dose of TAK-041 and a 0.5 mg/kg dose of AMPH.
- If the results from these subjects do not show at least 10% blunting (lower bound of the one-sided 95% confidence interval [CI] ≤10%) in the AMPH-induced dopamine release in the striatum (as measured by changes in BP_{ND}), the next 4 subjects will receive a 40 mg dose of TAK-041 and a 0.5 mg/kg dose of AMPH.
- If the results from the first 4 subjects show 10% or more blunting (lower bound of the one-sided 95% CI >10%) in the AMPH-induced dopamine release in the striatum (as measured by changes in BP_{ND}), the next 4 subjects will receive a 5 mg dose of TAK-041 (based on observed exposures in the TAK-041-1001 study) and a 0.5 mg/kg dose of AMPH.
- Depending on the results from the first 8 subjects, the last 4 subjects may receive either:
  - A dose of TAK-041 between 5 and 40 mg (based on exposures evaluated in the TAK-041-1001 study) and a 0.5 mg/kg dose of AMPH (if both previously tested TAK-041 dose levels showed a blunting of AMPH-induced dopamine release); or
  - A 40 mg dose of TAK-041 and a 0.25 mg/kg dose of AMPH.

The decision regarding the doses of TAK-041 and AMPH for Subjects 5 to 12 will be based on discussions between Takeda and the CCI. The dose range for TAK-041 is limited by exposures observed in the TAK-041-1001 study. Previous studies with AMPH used doses ranging from 0.3 to 0.5 mg/kg. Testing with the lower AMPH dose is driven by considerations to avoid overstimulation of the dopamine system.

Primary Objective:

To determine brain penetration of single oral doses of TAK-041 and its effects on AMPH-induced dopamine release in the central nervous system (CNS).

- Hypothesis: at 1 or more dose levels, TAK-041 will produce 10% or more blunting in the AMPH-induced dopamine release in the striatum.

Secondary Objective:

To determine a dose/exposure response relationship of TAK-041 on AMPH-induced dopamine release in the CNS.

Exploratory/Additional Objective:

CCI [redacted]

Subject Population: Healthy male subjects, aged 20 to 55 years, inclusive.

Number of Subjects:	**Number of Sites:**
Subjects will continue to be enrolled until 12 evaluable subjects complete all procedures.	2 centers in the United Kingdom (CCI clinical research unit and CCI)
Study Drugs and Dose Levels: Three of the following TAK-041/AMPH (dexamfetamine sulphate) dose combinations will be evaluated (each in a group of 4 subjects): • 20 mg TAK-041 and 0.5 mg/kg AMPH. • 40 mg TAK-041 and 0.25 mg/kg AMPH. • 5 to 40 mg TAK-041 and 0.5 mg/kg AMPH. • 5 mg TAK-041 and 0.5 mg/kg AMPH.	**Route of Administration:** Oral dose of TAK-041 suspension. Oral dose of dexamfetamine sulphate tablet. Intravenous (IV) injection of [^{11}C]PHNO.
Duration of Treatment: A single oral dose of TAK-041. Two single oral doses of AMPH (dexamfetamine sulphate). Three IV injections of [^{11}C]PHNO.	**Period of Evaluation:** Approximately 103 to 173 days from Screening to Study Exit/Final Visit.

Main Criteria for Inclusion:

- The subject understands, signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures and is willing to comply with the study protocol requirements.
- The subject is a healthy male aged between 20 and 55 years, inclusive.
- The subject weighs at least 45 kg and has a body mass index between 18.0 and 30.0 kg/m^2.

Main Criteria for Exclusion:

- Subject has evidence of current cardiovascular, central nervous system, hepatobiliary disease including history of biliary tree disorders and/or cholecystectomy, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory test results (including elevated alkaline phosphatase [ALP], total bilirubin [TBILI], γ-glutamyl transferase [GGT], or 5'-nucleotidase) that represent a reasonable suspicion of a disease that would contraindicate taking TAK-041, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.

- The subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease or subject has the following lab abnormalities: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5 × the upper limits of normal (ULN); ALP >1.5 × ULN in conjunction with elevated TBILI, GGT, 5'-nucleotidase, or AST/ALT; ALP >2 × ULN persisting longer than 3 days; or ALP >3 × ULN.
- Subject has a sustained resting heart rate outside the range 50 to 100 beats per minute (bpm), confirmed on repeat testing within a maximum of 30 minutes at Screening or Check-in.
- Contraindication to MRI based on the standard MRI screening questionnaire. Contraindications include ferromagnetic foreign bodies (eg, shrapnel, ferromagnetic fragments in the orbital area), certain implanted medical devices (eg, aneurysm clips, cardiac pacemakers), or claustrophobia.
- Subjects who have had previous research-related exposure to ionizing radiation, such that, in combination with the exposure from this study, their exposure will be >10 mSv/for the previous year.
- Subjects who have a known hypersensitivity to any component of the formulation of TAK-041 or related compounds, AMPH, or related compounds, or to [^{11}C]PHNO or to any of its components.
- Findings on screening brain MRI scan that will potentially compromise subject safety or the scientific integrity of the study data, if the subject were to participate in this study.

Main Criteria for Evaluation and Analyses

Primary Endpoint: The change in BP_{ND} in the AMPH+TAK-041 condition compared to AMPH alone.

Secondary Endpoint: The change in BP_{ND} in the AMPH+TAK-041 condition compared to AMPH alone as a function of the dose of TAK-041 administered.

Exploratory/Additional Endpoints:

CCI [redacted]

Statistical Considerations:

Safety:

Descriptive statistics will be provided for safety, demographics, and subject disposition data. Descriptive statistics for continuous data will include means, medians, SDs, and ranges, while categorical data may be summarized using frequency counts and percentages.

Imaging Data:

1. Individual BP_{ND} values and descriptive statistics for high uptake regions of interest for all PET scans. Descriptive statistics for BP_{ND} values will include means, medians, SDs, ranges, and 95% CI.
2. The change in BP_{ND} for the AMPH+TAK-041 condition compared to the BP_{ND} for the AMPH alone condition (100*[BP_{ND} AMPH+TAK-041- BP_{ND} AMPH]/ BP_{ND} AMPH).
3. The relative change in BP_{ND} for the AMPH alone condition (100*[Baseline – Post-AMPH]/Baseline) and the relative change in BP_{ND} for the AMPH+TAK-041 condition (100*[Baseline – Post-AMPH+TAK-041]/Baseline).
4. In order to establish a potential dose-dependent effect, we will explore via plots the magnitude of the relative change in BP_{ND} in the AMPH+TAK-041 condition as a function of the dose of TAK-041 administered.
5. Additional analyses may be performed for exploratory purposes.

Pharmacokinetics:

CCI [redacted] and PK parameters will be summarized by dose and treatment using descriptive statistics.

Sample Size Justification: Using previously reported data, assuming a 16% standard deviation for the relative change in BP_{ND} for high uptake regions of interest, 12 subjects will provide approximately 80% power to detect a 20% relative change in BP_{ND} when values from the TAK-041 + AMPH condition are compared to AMPH alone condition using a 2-sample 2-sided t-test with 0.05 significance level. The power for the other regions of interest will be more than 80%.

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 Investigators

Coordinating Investigator

PPD

Imaging Center Investigator

PPD

3.3 List of Abbreviations

%CV	percent coefficient of variation
[^{11}C]PHNO	radiolabeled dopamine D2 ligand
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMPH	amphetamine
AST	aspartate aminotransferase
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
BMI	body mass index
bpm	beats per minute
BP_{ND}	nondisplaceable binding potential
CI	confidence interval
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CV	cardiovascular
D2/D3	dopamine-2 and -3
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ET	early termination
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GPR139	G-protein-coupled receptor 139
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
hERG	human ether-à-go-go–related gene
HIV	human immunodeficiency virus
CCI	[redacted]
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiological Protection
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IV	intravenous

K_2EDTA	potassium ethylenediamine tetraacetic acid
LFT	liver function test
MC	methylcellulose
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple-rising dose
MRI	magnetic resonance imaging
NCS	not clinically significant
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
PET	positron emission tomography
PHNO	(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol
PI	principal investigator
PK	pharmacokinetic(s)
PO	oral
PTE	pretreatment event
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
RCF	relative centrifugal force
SAE	serious adverse event
SAP	statistical analysis plan
SERT	serotonin transporter
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal elimination half-life
TBILI	total bilirubin
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

4.1.1 TAK-041

TAK-041 is an orally available, small molecule G-protein-coupled receptor 139 (GPR139) agonist that dose-dependently improves social interaction in animal models of social deficit and has the potential for the treatment of schizophrenia, particularly negative symptoms, and disorders associated with social and cognitive dysfunction.

GPR139 is a novel class A orphan receptor that is expressed in the medial habenula, the septum, hypothalamus, basal ganglia, and thalamus [1,2]. The CNS localization of this receptor suggests its potential contribution to movement and metabolism with a special focus on attention, learning and cognition, motivation and reward, as well as response to stress and social interaction [1,3]. Because patients with schizophrenia are afflicted with behavioral and cognitive deficits in these domains, TAK-041 may provide therapeutic benefit by ameliorating the symptoms linked to this disorder.

In vitro studies support the specificity and the selectivity of TAK-041 for binding to and activating GPR139, as evidenced by increased cellular signaling events downstream of receptor activation. Specifically, with the exception of serotonin transporter (SERT) inhibition at approximately 2 μM, TAK-041 was a potent and selective agonist for GPR139. In vivo studies demonstrated both a cognitive benefit and an enhancement of social interaction in animal models exhibiting cognitive and social interaction deficits that were either pharmacologically induced or naturally occurring.

In the safety pharmacology assessment, TAK-041 had no effect on the CNS or respiratory parameters in rats at single oral (PO) doses up to 200 mg/kg/day, which was the no-observed-adverse-effect level (NOAEL) in the rat repeat-dose toxicity study. At high concentrations (at ≥1 μM or 392 ng/mL free drug), an effect was observed on the human ether-à-go-go–related gene (hERG) potassium currents. The hERG alteration did not translate into an electrocardiogram (ECG) effect at doses up to 125 mg/kg/day, which is associated with a C_{max} of 10,700 ng/mL. The cause for the increase in systolic blood pressure (approximately 15 mmHg or 10%) noted acutely at 125 mg/kg in the dog cardiovascular study 0.5 to 6 hours postdose is unclear; however, neither heart rate nor diastolic blood pressure were elevated. No changes in blood pressure or ECG parameters were noted at 125 mg/kg/day in the 4-week repeat-dose toxicity study in dogs after the 26th or 27th dose, respectively. A diminished trend for systolic blood pressure that occurred at 15 mg/kg was not considered biologically relevant; no effect on systolic blood pressure occurred at 5 mg/kg.

Schizophrenia involves diminished or altered motivation, deficits in social behavior, and difficulties with complex cognitive tasks. To date, there are no effective therapies for the negative and cognitive symptoms, which remain a significant unmet medical need.

Experimental evidence supports the use of TAK-041, a GPR139 agonist, as a potential therapeutic for the negative symptoms and cognitive impairment associated with schizophrenia. Toxicological studies of TAK-041 in rats and dogs with up to 4 weeks of exposure support proceeding with a

study in humans. TAK-041 has been studied in vitro and in vivo to demonstrate its potency and selectivity for binding to and activating GPR139 as well as its efficacy in animal models exhibiting cognitive and social interaction deficits.

Further information from the nonclinical studies, summarized above, can be found in the current Investigator's Brochure.

To date, the FIH study TAK-041-1001 has enrolled and dosed a total of 16 subjects (12 active and 4 placebo) in an alternating panel design (2 cohorts) at 5, 10, 20, and 40 mg. Cohort 1 received 5 and 20 mg single doses and Cohort 2 received 10 and 40 mg single doses. Preliminary PK data from 12 healthy subjects who received single oral administrations of TAK-041 doses of 5, 10, 20, and 40 mg indicate that TAK-041 has a mean terminal elimination half-life ($t_{1/2z}$) of approximately 11 days. Following single oral dose administrations of TAK-041 (5, 10, 20, and 40 mg) under fasted conditions, TAK-041 was rapidly absorbed (median time to reach C_{max} [t_{max}] of 1 to 2 hours) with well-characterized plasma concentration-time profiles up to the last sampled time point. Inter-subject variability across the 5 to 40 mg dose range was low-to-moderate with percent coefficient of variation (%CV) values of approximately 11% to 20% and 9% to 28% for C_{max} and area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}), respectively. Following an 8-fold increase in dose from 5 to 40 mg, mean C_{max} and AUC_{24} for TAK-041 increased by approximately 5.3- and 7.2-fold, respectively.

4.1.2 PHNO and [^{11}C]PHNO Background

4.1.2.1 PHNO and [^{11}C]PHNO Clinical Experience

As of 10 June 2016, both (+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol [PHNO] and radiolabeled [^{11}C]PHNO have been extensively validated in clinical studies. (+)-PHNO is a potent dopamine D2 receptor agonist that was tested in several phase 2 clinical studies for treatment of Parkinson disease [4-7]. Up to 60 mg/day PHNO was safely administered in a 12-week, placebo-controlled, double-blind study in patients with Parkinson disease [4]. These doses are significantly higher than the single dose of 0.5 µg [^{11}C]PHNO to be used per positron emission tomography (PET) scan in this study. Wilson, et al. [8] demonstrated PHNO as a suitable candidate radiotracer for in vivo measurement of D2 receptors using PET. Subsequently [^{11}C]PHNO has been used extensively as a dopamine-2 and -3 (D2/3) agonist PET ligand at CCI , as well as other PET centers world-wide CCI). To date >250 PET examinations have been conducted at CCI using [C]PHNO, and >400 world-wide (for examples, see Boileau, et al. 2009, Boileau et al. 2014, Searle et al. 2013, and Shotbolt et al. 2012 [9-12]. [^{11}C]PHNO has been evaluated in healthy volunteers as well as patients with Parkinson disease, pathological gambling, alcohol abuse, cocaine abuse, and schizophrenia, with individual subjects receiving up to 3 administrations each.

Initial human studies with [^{11}C]PHNO revealed that some subjects experienced transient nausea following administration. Subsequent investigation revealed that limiting the injected dose to

≤30 ng/kg eliminated these adverse events [13]. All studies at CCI maintain this limit and their experience is consistent with other centers as reported by Mizrahi and colleagues.

4.1.2.2 Nonclinical Pharmacology and Toxicology

Wilson, et al. [8] reported the radio synthesis and evaluation of the potent D2 agonist, (+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol. Labeled with carbon-11, [^{11}C]PHNO readily crossed the blood/brain barrier in ex vivo biodistribution studies in rat brain, with saturable binding to dopamine D2 receptors and an excellent signal-to-noise ratio. Binding was highly stereospecific and blocking and displacement studies were consistent with selective and specific binding to the dopamine D2 receptors. Furthermore, [^{11}C]PHNO showed marked and appropriate sensitivity to both increases and decreases in the levels of endogenous dopamine and full D2 agonistic properties [8], making it an excellent radiotracer to evaluate the dopamine D2/D3 receptor system in humans with PET.

4.1.2.3 Dosimetry

The whole body distribution and dosimetry of [^{11}C]PHNO has been measured in 6 healthy volunteers [14]. The mean effective dose was estimated to be 4.5 ± 0.3 µSv/MBq when all subjects were included and the male model was applied for the dosimetry calculation. The organ receiving the highest dose was the liver (17.9 ± 3.9 µSv/MBq), followed by the kidneys (14.3 ± 3.6 µSv/MBq) and the urinary bladder wall (13.5 ± 3.7 µSv/MBq). The maximum radiation exposure for each subject in the study is presented in Table 4.a.

Table 4.a Maximal Exposure Estimation for Study Subjects

Assessments	Maximum Number of PET Scans	Radiation Activity	[^{11}C]PHNO Injected Activity Estimated for Each PET Scan	Maximal Allowed Exposure for an Individual
PET emission scan	3	4.5 µSv/MBq	180 MBq	2.43 mSv
Low-dose CT scan (for attenuation correction)	3	0.36 mSv	NA	1.08 mSv
Total				3.51 mSv

CT=computed tomography, NA=not applicable.

A maximal study exposure of 3.51 mSv per subject places this study in Category IIb (<10 mSv) of the guidance published by the International Commission for Radiation Protection (ICRP). There is no dose limit for research purposes in the United Kingdom but, like many European Union member states, the United Kingdom follows the ICRP 62 guidance that provides a guideline of ≤10 mSv per study where research subjects are not expected to benefit personally [15].

4.2 Rationale for the Proposed Study

Microdialysis studies in rats showed that pretreatment with TAK-041 caused a significant attenuation of amphetamine-induced synaptic dopamine release in the nucleus accumbens, a brain region critical for cognitive processing of aversion, motivation, pleasure, reward, and reinforcement learning. The amphetamine pharmacology model has been used in early clinical

development for centrally acting compounds and has been shown to induce dopamine release in amphetamine challenge studies [16]. PET and [^{11}C]PHNO have been validated as clinical tools to assess amphetamine-induced dopamine release in humans. Therefore, this translational biomarker approach will be utilized to determine whether TAK-041 is brain-penetrant in healthy human volunteers and demonstrates central pathway modulation by blunting amphetamine-induced dopamine release. The assessment of brain penetration of TAK-041 and its effects on amphetamine (AMPH)-induced dopamine release will inform dose selection for subsequent clinical studies.

CCI

[redacted]

4.3 Benefit/Risk Profile

As this is a healthy volunteer study, there is no expected clinical benefit to the study participants. TAK-041 has the potential to be a first-in-class drug; therefore, there are no known class effects. Potential risks are based on clinical findings, the mechanism of action, nonclinical findings, and the known risks of other GPR139 receptor agonists. Preliminary results from the FIH study TAK-041-1001 indicate that single doses of TAK-041 at 5, 10, 20, and 40 mg are well tolerated. To fully assess the safety and PK profile of TAK-041 in subjects receiving 20 and 40 mg TAK-041 doses, follow-up PK blood draws were performed until TAK-041 plasma concentrations were below the lower level of quantitation of the assay. Six AEs were observed that were mild, deemed not related to study drug, and resolved without treatment. No serious AEs and no clinically meaningful safety laboratory results (including 5'-nucleotidase, sorbitol dehydrogenase, and urine osmolality), and no clinically significant physical examination, vital signs, or ECG results were reported for the 16 subjects who received 5 to 40 mg doses of TAK-041 crystalline suspension or matching placebo in TAK-041-1001 Cohorts 1 and 2. The potential risks can be monitored clinically and/or with laboratory tests and are considered in setting up the stopping rules for this clinical study. Appropriate exclusion criteria that exclude individuals with past history or concurrent conditions that increase the risk will be applied.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To determine brain penetration of single oral doses of TAK-041 and its effects on AMPH-induced dopamine release in the CNS.

- Hypothesis: at 1 or more dose levels, TAK-041 will produce 10% or more blunting in the AMPH-induced dopamine release in the striatum.

5.1.2 Secondary Objective

To determine a dose/exposure response relationship of TAK-041 on AMPH-induced dopamine release in the CNS.

5.1.3 Exploratory/Additional Objectives

CCI [redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The change in nondisplaceable binding potential (BP_{ND}) in the AMPH+TAK-041 condition compared to AMPH alone.

5.2.2 Secondary Endpoint

The change in BP_{ND} in the AMPH+TAK-041 condition compared to AMPH alone as a function of the dose of TAK-041 administered.

5.2.3 Exploratory/Additional Endpoints

CCI [redacted]

CCI

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, open-label clinical study utilizing PET and the D2/D3 receptor agonist and radiolabeled ligand [^{11}C]PHNO to evaluate the effects of single oral doses of TAK-041 on AMPH-induced dopamine release in the brain.

Subjects will continue to be enrolled until 12 evaluable subjects complete all procedures. Each subject will have 1 magnetic resonance imaging (MRI) brain scan and 3 [^{11}C]PHNO PET scans. The MRI brain scan will be performed for all subjects without gadolinium contrast and will be interpreted at the CCI [redacted] during the Screening Period to determine eligibility. The results of this MRI brain scan will also be used during the study to delineate the anatomical regions of interest for individual PET images.

The study consists of 2 Confinement Periods for each subject during which the PET scans occur at the CCI [redacted]. Confinement Periods 1 and 2 will be separated by a 5 to 45 day interval.

- Confinement Period 1:
  - The first [^{11}C]PHNO PET scan occurs on Day 1 to serve as the Baseline scan to determine the BP_{ND} in striatum under untreated conditions for each subject.
  - On Day 2, the subject will receive a single oral 0.5 mg/kg dose of AMPH, followed by a [^{11}C]PHNO PET scan at approximately 3 hours post-AMPH dose in order to establish BP_{ND} in striatum after AMPH-induced dopamine release as compared to Baseline.
- Confinement Period 2:
  - On Day 1, the subject will receive a single oral dose of TAK-041 up to 40 mg, followed by a single oral 0.5 mg dose of AMPH approximately 2 hours after the dose of TAK-041, followed by a [^{11}C]PHNO PET scan at approximately 3 hours post-AMPH administration.

Blood samples for PK analysis of AMPH will be collected prior to AMPH administration, 1 and 2 hours post-AMPH administration, and immediately prior to and after the [^{11}C]PHNO PET scan to measure plasma levels of AMPH. PK blood samples will be collected 1, 2, 12, and 24 hours after TAK-041 administration, and immediately prior to and after the [^{11}C]PHNO PET scan to measure plasma levels of TAK-041.

Only TAK-041 dose levels that were well-tolerated in the TAK-041-1001 study and had achieved exposures indicative of the predicted pharmacologically active exposures of TAK-041 will be administered in this study.

Amphetamine tablets will be provided as the commercial product dexamfetamine sulphate [17] with the manufacturer's original label, and will be sourced locally by the study site. Amphetamine will be administered at the time that approximately coincides with the t_{max} of TAK-041 to allow an informative evaluation of TAK-041 coadministered with amphetamine. The highest dose of AMPH that will be administered will be an oral dose of 0.5 mg/kg. This dose has

been demonstrated to be safe and tolerated in healthy subjects and is a dose which has been shown to induce dopamine release in AMPH-challenge studies [16,18].

Safety and tolerability will be assessed through all study visits, including collecting blood and urine samples for laboratory tests. Subjects will complete scheduled study assessments according to the Schedule of Study Procedures (Appendix A).

CCI [redacted]

Each subject will report to CCI [redacted] on approximately 8 occasions:

1. Screening to determine eligibility (-28 to -2 days prior to Confinement Period 1/Day -1): The Screening brain MRI may be performed on a day separate from the other screening procedures, and will be performed and interpreted at the CCI [redacted] after the other screening activities have been performed and results assessed. MRI should be performed early enough so that MRI scan results are available prior to Baseline Imaging for Confinement Period 1.
2. Confinement Period 1 (Day -1 to Day 3): admission to CCI [redacted] (Day -1), 1 day prior to Baseline [^{11}C]PHNO PET imaging on Day 1; AMPH administration and postdose [^{11}C]PHNO PET imaging (Day 2); discharge on the day following the postdose [^{11}C]PHNO PET imaging (Day 3). All subjects will undergo a single Baseline [^{11}C]PHNO PET scan on Day 1 and a single postdose [^{11}C]PHNO PET scan on Day 2.
3. Confinement Period 2 (5 to 45 days after discharge from Confinement Period 1): admission to CCI [redacted] (Day -1) 1 day prior to TAK-041 and AMPH administration and postdose [^{11}C]PHNO PET imaging (Day 1), discharge on the day following the postdose [^{11}C]PHNO PET imaging (Day 2). All subjects will undergo a single [^{11}C]PHNO PET scan on Day 1 of Confinement Period 2.
4. Follow-up Safety and PK Assessment Visits (Days 8-92): Following discharge from Confinement Period 2, subjects will return to the site for PK and safety assessments after 7±2 days, and then return for approximately 3 Follow-up PK and safety assessment Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's C_{max} (see Section 9.3.2 and Appendix A).
5. Study Exit/Final Visit: At the end of each Follow-up Visit, the next visit will be scheduled approximately 4 weeks later. If, when the PK results are available, the subject's PK was <5% of their C_{max} value, the site and subject will be informed that their next scheduled visit will be considered their Study Exit/Final V 3.3 and Appendix A). Subjects who

prematurely discontinue the study will have the same assessments on their last day in the study, if possible.

A schematic of the study design is shown in Figure 6.a. The Schedule of Study Procedures is in Appendix A.

Figure 6.a Schematic of Study Design

Screening	Confinement Period 1				Interval (a)	Confinement Period 2			Follow-up Visits (b)	Study Exit/Final Visit
Days -28 to -2	Day -1	Day 1	Day 2	Day 3	5-45 days	Day -1	Day 1	Day 2	Days 8-92 (±2)	ET (c)
CCI	CCI Check-in	PET Imaging Baseline		CCI Discharge		CCI Check-in		CCI Discharge	Return to CCI for safety and PK assessments	Return to CCI for safety assessments
			AMPH				TAK-041 + AMPH			
			PET Imaging postdose				PET Imaging postdose			

ET=early termination
Note: Subjects who drop out prior to completion of all PET scans will have assessments done as described in Section 9.3.3 and Appendix A for ET and a follow-up telephone call approximately 2 days after the ET Visit.
(a) There will be a 5 to 45 day interval between confinement periods beginning after discharge from Confinement Period 1.
(b) Following discharge from Confinement Period 2, subjects will return to the site for PK and safety assessments after 7 ±2 days, and then return for approximately 3 Follow-up PK and safety assessment Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's C_{max}.
(c) At the end of each Follow-up Visit, the next visit will be scheduled approximately 4 weeks later. If, when the PK results are available, the subject's PK was <5% of their C_{max} value, the site and subject will be informed that their next scheduled visit will be considered their Study Exit/Final Visit.

If logistical limitations (such as tracer synthesis failure) prevent a Baseline PET scan from being performed at the scheduled time point, the Confinement Period may be extended or cut short and rescheduled. If a postdose PET scan is delayed, it may be necessary to end the Confinement Period early and reschedule after a sufficient interval.

CCI [redacted]

The date the final subject completes the Follow-up Call/Visit will be considered the end of study date for transparency reporting.

6.1.1 Dose Decisions

All decisions concerning dose levels will be made by the sponsor and the CCI [redacted].

This study will utilize an adaptive design to determine the dose(s) of AMPH and TAK-041 to be administered:

- The first 4 subjects in this study will receive a 20 mg dose of TAK-041 and a 0.5 mg/kg dose of AMPH.
- If the results from these subjects do not show at least 10% blunting (lower bound of the one-sided 95% CI ≤10%) in the AMPH-induced dopamine release in the striatum (as measured by changes in BP_{ND}), the next 4 subjects will receive a 40 mg dose of TAK-041 and a 0.5 mg/kg dose of AMPH.
- If the results from the first 4 subjects show 10% or more blunting (lower bound of the one-sided 95% CI >10%) in the AMPH-induced dopamine release in the striatum (as measured by changes in BP_{ND}), the next 4 subjects will receive a 5 mg dose of TAK-041 (based on observed exposures in the TAK-041-1001 study) and a 0.5 mg/kg dose of AMPH.
- Depending on the results from the first 8 subjects, the last 4 subjects may receive either:
  - A dose between 5 and 40 mg of TAK-041 (based on exposures evaluated in the TAK-041-1001 study) and a 0.5 mg/kg dose of AMPH (if both previously tested TAK-041 dose levels showed a blunting in AMPH-induced dopamine release); or
  - A 40 mg dose of TAK-041 and a 0.25 mg/kg dose of AMPH.

Decisions regarding the doses of TAK-041 and AMPH that Subjects 5 to 12 will receive will be based on discussions between Takeda and the CCI Investigator. The dose range for TAK-041 is limited by exposures observed in the TAK-041-1001 study. Previous studies with AMPH used doses ranging from 0.3 to 0.5 mg/kg. Testing with the lower AMPH dose is driven by considerations to avoid overstimulation of the dopamine system.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

The primary objective of this study is to determine brain penetration of single oral doses of TAK-041 and its effects on AMPH-induced dopamine release in the brain in healthy subjects. The study will therefore be conducted in healthy subjects to ensure that the evaluation of pathway modulation of TAK-041 is not confounded by disease or concomitant medications that are frequently taken in the target population (patients with schizophrenia). As reproductive toxicity studies have not been completed, only male subjects will be eligible for enrollment and male subjects who are sexually active with a female partner of childbearing potential will be required to use an acceptable form of contraception (see Section 9.1.10).

Some studies have found that AMPH-induced receptor internalization affects the time course of subsequent ligand binding [12]. An interval of 5 to 45 days between the 2 Confinement Periods is therefore included to control for potential effects of sensitization.

The preliminary PK data from Study TAK-041-1001 indicate that TAK-041 has a mean terminal elimination half-life of approximately 11 days. Therefore, a fixed-order study design wherein

TAK-041 is administered in Confinement Period 2 only is appropriate (see Figure 6.a, Study Schematic). Subjects in the TAK-041-1001 study who received single doses of 20 and 40 mg TAK-041 were followed approximately weekly until the plasma concentrations of TAK-041 were <1 ng/mL (up to 146 days) and there were no clinically significant safety issues. Subjects in this study who receive TAK-041 will be monitored monthly until the concentration of TAK-041 in plasma is <5% of the subject's C_{max}. Following discharge from Confinement Period 2, subjects will return to the site for PK and safety assessments after 7 ±2 days, and then return for approximately 3 Follow-up Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's C_{max}.

6.2.2 Doses

Overall there is an expectation of sufficient systemic exposure to TAK-041 and duration of action in humans. Taking account of the exposure required for efficacy in animal models and current available evidence of the modeling of the human PK, it is expected that the dose ranges of TAK-041 that will be evaluated will achieve a sufficient range of plasma exposures with a margin above and beyond the predicted pharmacologically active exposures (4 to 60 ng/mL).

The starting dose of TAK-041 that will be evaluated in this study is 20 mg, a dose that has been demonstrated to be well-tolerated in the TAK-041-1001 study and has achieved exposures indicative of the predicted pharmacologically active exposures of TAK-041. A single dose of 40 mg TAK-041 has also been shown to be well-tolerated in the TAK-041-1001 study and may be evaluated to explore the exposure-response relationship of TAK-041.

The highest dose of AMPH (dexamfetamine sulphate) to be administered is 0.5 mg/kg. The 0.5 mg/kg dose regimen has been demonstrated to be safe and tolerated in healthy subjects and has been shown to induce dopamine release in amphetamine challenge studies [16,18]. Previous studies with AMPH used doses ranging from 0.3 to 0.5 mg/kg [12,19]. Evaluating with a lower AMPH dose of 0.25 mg/kg will be driven by considerations to avoid overstimulation of the dopamine system.

The intravenous (IV) dose of the ligand [^{11}C]PHNO of approximately 180 MBq is based on the experiences of CCI and other sites using this radiotracer in clinical studies [12].

6.2.3 Endpoints

Preclinical data have shown that TAK-041 blunted AMPH-induced, striatal dopamine release in rodents (see the current Investigator's Brochure). PET and [^{11}C]PHNO have been validated as clinical tools to assess AMPH-induced dopamine release in humans [12]. We are therefore proposing to utilize this translational biomarker approach to establish whether single oral doses of TAK-041 is brain-penetrant in human volunteers, and whether it demonstrates central pathway modulation by blunting AMPH-induced dopamine release.

Within subject test-retest variability of [^{11}C]PHNO, BP_{ND} has been demonstrated to be less than 10% for high uptake regions in the basal ganglia (eg, caudate, putamen, ventral striatum, and globus pallidus) [20]. The purpose of the first dose-level group of 4 subjects is to demonstrate whether TAK-041 has any appreciable blunting effect on AMPH-induced dopamine release as

measured with [^{11}C]PHNO BP_{ND} change from Baseline. Given that due to the above mentioned existing human test-retest variability, it is estimated that one can be reasonably confident to detect an at least 10% change from baseline, this was defined as the "minimum effect level." In line with that expectation, any change less than 10% will be regarded as "no effect," and, consequently, different dose levels of AMPH and/or TAK-041 may be tested.

CCI

[redacted]

6.3 Premature Termination or Suspension of Study or Investigational 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.

1. New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the TAK-041 such that the risk is no longer acceptable for subjects participating in the study.
2. Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
3. Two or more subjects experience any of the Takeda Medically Significant List events (as outlined in Table 10.a).
4. Two or more subjects experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limit of normal (ULN) in the absence of a concomitant bilirubin increase [see #6 below].
5. One or more subjects experience ALT and/or AST elevations >3 × ULN in the presence of a total bilirubin (TBILI) increase >2 × ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or alternative etiology to explain the elevations (ie, "Hy's Law cases").
6. Two or more subjects experience ALT and/or AST elevations >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
7. One or more subjects experience alkaline phosphatase (ALP) elevations >1.5 × ULN in conjunction with elevated TBILI, γ-glutamyl transferase (GGT), ALT, or AST.
8. One or more subjects experience ALP elevations >2 × ULN that persist for longer than 3 days.
9. One or more subjects experience ALP elevations >3 × ULN.

Please note that the study may be terminated prior to full attainment of these criteria (eg, if just 1 subject experiences 1 of these events) if warranted by safety data from the other subjects dosed in the study to that date.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to enrollment on Day 1 of Confinement Period 1.

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is in good health as determined by physical examination, ECG, and laboratory evaluations.
4. The subject is a healthy male aged 20 to 55 years, inclusive, at the time of informed consent.
5. The subject weighs at least 45 kg and has a body mass index (BMI) from 18.0 to 30.0 kg/m^2, inclusive, at Screening.
6. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for a period of 167 days (ie, 90 days after 7 half-lives, estimated using an average half-life value) following TAK-041 administration. The female partner of a male subject should also be advised to use a highly effective method of contraception.

*Definitions and acceptable methods of contraception are listed in Section 9.1.10; reporting responsibilities are defined in Section 9.1.11.

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound or device within 3 months prior to the first Screening Visit.
2. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
3. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the Takeda Medical Monitor may be warranted.

4. The subject has a known hypersensitivity to any component of the formulation of TAK-041 or related compounds, AMPH (dexamfetamine sulphate) or related compounds, or [^{11}C]PHNO or any of its components.
5. The subject has a positive urine/blood drug result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in (Day -1).
6. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of more than 21 units per week) within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study. One unit is equivalent to 8 grams of pure alcohol, which is equivalent to 10 mL of pure ethanol (alcohol) or approximately a half-pint of beer, 1 measure of spirits, or 1 glass of wine.
7. The subject has taken any medication, supplements, or food products during the time periods listed in the Prohibited Medications, Supplements, Dietary Products Table 7.a.
8. Subject has evidence of current cardiovascular, central nervous system, hepatobiliary disease including history of biliary tree disorders and/or cholecystectomy, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, or seizures. There is any finding in the subject's medical history, physical examination, or safety laboratory test results (including elevated ALP, TBILI, GGT, or 5'-nucleotidase) giving reasonable suspicion of a disease that would contraindicate taking TAK-041 or amphetamine or a similar drug in the same class, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
9. The subject has current or recent (within 6 months) gastrointestinal disease that would be 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 know to impact absorption (eg, bariatric surgery or bowel resection).
10. The subject has a history of cancer, except basal cell carcinoma that has been in remission for at least 5 years prior to Day 1 of Confinement Period 1.
11. The subject has a positive test result for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) infection at Screening.
12. Subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 28 days prior to Check-in on Day -1. Cotinine test is positive at Screening or Check-in (Day -1).
13. The subject has poor peripheral venous access.
14. The subject has donated or lost 450 mL or more of his blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days prior to Confinement Period 1.

15. Subject has a Screening or Check-in (Day -1) abnormal (CS) ECG. Entry of any subject with an abnormal (not clinically significant [NCS]) ECG must be approved, and documented by signature by both the principal investigator and the Takeda Medical Monitor.
16. Subject has abnormal Screening laboratory values that suggest a clinically significant underlying disease or subject has the following lab abnormalities: ALT and/or AST >1.5 × ULN; ALP >1.5 × ULN in conjunction with elevated TBILI, GGT, 5'-nucleotidase, AST, or ALT; ALP >2 × ULN persisting longer than 3 days; or ALP >3 × ULN.
17. The subject has a sustained resting heart rate outside the range 50 to 100 beats per minute (bpm), confirmed on repeat testing within a maximum of 30 minutes, at Screening or Check-in.
18. The subject has a QT interval with Fridericia correction method (QTcF) >450 ms or PR outside the range 120 to 220 ms, confirmed on repeat testing within a maximum of 30 minutes, at the Screening Visit or Check-in (Day -1).
19. The subject has a risk of suicide according to the investigator's clinical judgment (eg, per C-SSRS) or has made an attempt in the previous 6 months from Screening.
20. The subject has had previous research-related exposure to ionizing radiation such that, in combination with the exposure from this study, their exposure will be >10 mSv for the previous year.
21. The subject has a contraindication to MRI based on the standard MRI screening questionnaire. Contraindications include ferromagnetic foreign bodies (eg, shrapnel, ferromagnetic fragments in the orbital area), certain implanted medical devices (eg, aneurysm clips, cardiac pacemakers), or claustrophobia.
22. The subject has findings on the screening brain MRI scan that will potentially compromise subject safety or the scientific integrity of the study data if the subject were to participate in this study.
23. Subject has a history of significant allergic skin reactions (hypersensitivity) to adhesives, metals, or plastic. CCI [redacted].

7.3 Excluded Medications, Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until study completion for each subject.

Table 7.a Prohibited Medications, Supplements, Dietary Products

21 Days Prior to Check-in for Confinement Period 1	7 Days Prior to Check-in (Day-1)	72 Hours Prior to Check-in (Day -1)
Prescription medications	OTC medications (a)	Products containing caffeine or xanthine
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	
Immunization/vaccines (b)		Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade, star fruit, apple, orange, or pineapple juices, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats
Nicotine-containing products		Alcohol-containing products
Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6 (c)		

CYP=cytochrome P-450, OTC=over-the-counter.
(a) Occasional use of acetaminophen/paracetamol (≤1 g/day) or other medication is allowed as approved by Takeda on a case-by-case basis.
(b) Inclusive of, but not limited to, H1N1 and flu vaccinations.
(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine.

Subjects must be instructed not to take any medications, including OTC products, without first consulting with the investigator, until their participation in the study is completed.

7.4 Diet, Fluid, and Activity Control

PET scans and imaging-related procedures will take place in the CCI [redacted]. Subjects will be confined overnight at CCI [redacted] until discharge on Day 3 of Confinement Period 1 and Day 2 of Confinement Period 2 (see Appendix A).

During confinement, subjects will be given a standard menu that includes 3 meals and an evening snack, each containing approximately 30% fat (relative to the total calories). The meals served on the day of TAK-041 dosing should be similar in nutritional content for each subject in the study. The meal start and stop time, meal contents, and percentage of the meal will be recorded in the source for all meals served on Confinement Days for all subjects. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.

TAK-041 (oral suspension) will be administered following a fast of at least 8 hours. Subjects will fast for an additional 2 hours after dosing with AMPH. Two hours after the AMPH dose, they can be offered a snack. During confinement on nondosing days, subjects will be given 3 meals and an evening snack, each containing approximately 30% fat (relative to the total calories). Some meals may not be served on dosing days. Water can be consumed ad libitum, except for 1 hour before and after dosing.

Subjects will remain upright (seated, standing, or ambulatory) for 4 hours following the dose administration, except as necessitated by the occurrence of an AE/or study procedures (eg, obtaining 12-lead ECG, lying on the PET scanner table for start of first postdose PET scan). Subjects will refrain from strenuous exercise from 72 hours before Check-in Day-1 in Confinement Period 1 through the Study Exit/Final Visit or ET.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the source and electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.19.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
   - Liver Function Test (LFT) Abnormalities

     Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.9), if any of the following circumstances occur at any time during study medication treatment:

     – ALT or AST >8 ×ULN.
     – ALT or AST >5 ×ULN and persists for more than 2 weeks.
     – ALT or AST >3 ×ULN in conjunction with elevated total bilirubin >2 ×ULN or INR >1.5.
     – ALT or AST >3 ×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
     – ALP > 1.5 × ULN in conjunction with elevated total bilirubin or elevated GGT or elevated AST/ALT.
     – ALP > 2 × ULN, persisting for longer than 3 days.
     – ALP > 3 × ULN.
2. Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject wishes to withdraw from the study.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded. Withdrawal due to an AE should not be recorded in the voluntary withdrawal category.
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Other. The specific reason should be recorded in the "specify" field of the eCRF.
   - Skin reactions (cutaneous hypersensitivity) to one of the wearable digital devices will lead to removal of that device for the remainder of the study and, dependent on the principal investigator's (PI) assessment, the subject would not be required to discontinue the study.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The coordinating investigator or the CCI [redacted] 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 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 coordinating investigator. In addition, efforts should be made to perform all procedures scheduled for the ET Visit. Discontinued or withdrawn subjects may be replaced at the discretion of the sponsor in consultation with the investigators until up to 12 evaluable subjects have completed the study.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication 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 clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

The TAK-041 oral suspension will be used in this study. The TAK-041 crystalline drug substance (milled) will be labeled in an open-label fashion and compounded into oral suspensions that will be labeled for third party dispensing. A pharmacy staff member will manage and prepare doses as needed throughout the study. The oral suspensions will contain 5 to 40 mg of TAK-041 per dose. Compounding instructions will be provided to the clinical site.

8.1.1.1 TAK-041

The oral suspension will be prepared at the site by weighing an appropriate amount of crystalline TAK-041 (milled) into a dosing bottle and mixing with 70 mL of 0.5% Tween 80 in 0.5% methylcellulose (MC) vehicle (Tween/MC vehicle). The composition of the Tween/MC vehicle is in Table 8.a. The composition of crystalline TAK-041 oral suspension is listed in Table 8.b.

Table 8.a Composition of 0.5% Tween 80 in 0.5% (w/v) Methylcellulose Vehicle

Component	Composition per 100 mL of Water
Methylcellulose, Ph Eur or USP	500 mg
Tween 80, Ph Eur or NF	500 mg
Sterile water for irrigation, Ph Eur	100 mL

NF=National Formulary, Ph Eur=European Pharmacopeia, USP=United States Pharmacopeia.

Table 8.b Composition of TAK-041 Oral Suspension

Component	Quantity per Dose
Crystalline TAK-041 (milled)	(a) mg
Tween/MC vehicle	70 mL

(a) Amount shall be in the range of 5 to 40 mg TAK-041, and a concentration range of 0.07 to 0.57 mg/mL TAK-041.

8.1.1.2 Amphetamine

Amphetamine tablets will be sourced locally by CCI as the commercial product dexamfetamine sulphate [17] with the manufacturer's original label, and will be sourced locally by CCI

8.1.1.3 [^{11}C]PHNO

The PET ligand drug substance, [^{11}C]PHNO, is formulated in sterile, non-pyrogenic solution.

8.1.1.4 Sponsor-Supplied Drug

TAK-041 drug substance (milled) will be supplied in powder form, in appropriate packaging, and each container will bear a single panel label that includes all pertinent study information.

8.1.2 Storage

TAK-041 must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. TAK-041 drug substance (milled) is stored at controlled room temperature (20°C to 25°C with excursions allowed from 15°C to 30°C).

Dexamfetamine sulphate must be stored under the conditions specified on the label, and remain in the original container until dispensed.

[^{11}C]PHNO for injection will be prepared prior to use on site.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures. All dosing will be administered to the subjects by the investigator or investigator's designee. The exact time of dose will be recorded in the source documents and on the appropriate eCRF.

Subjects will receive the TAK-041 doses by drinking the entire suspension from the dosing bottle. The dosing bottle will then be rinsed with 35 mL of water and the rinse will be administered in the same manner as the suspension. The rinse and administration will be repeated one more time.

From the commercially available dexamfetamine sulphate tablet strengths (eg, 5 mg), the study site will calculate the amphetamine oral dose of 0.5 mg/kg for each subject based on the subject's body weight. For example, for a 70 kg subject, the dose of dexamfetamine sulphate to be administered will be 35 mg. If the calculation results in a fraction of a mg, the dose should be rounded down to nearest 5 mg. Dexamfetamine sulphate tablets will be administered with 240 mL of still water. The dose administered should be as close as possible to the required dose based on the tablet strengths available. Dosing instructions for TAK-041 and dexamfetamine sulphate will be provided in the Pharmacy Manual.

Intravenous [^{11}C]PHNO injection will be administered as a slow bolus of a 20-mL volume over 20 seconds. The maximum administered mass of PHNO will not exceed 30 ng/kg for each PET scan. The maximum administered dose of [^{11}C]PHNO will not exceed 180 MBq for each PET scan.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational 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, Pretreatment Events and Adverse Events.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

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

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will also be assigned a 4-digit enrollment number. For each dose level X, the number will be assigned by the clinical research unit personnel in sequential order beginning with X001. For example, the enrollment numbers will be 1001 to 1006 if there are 6 subjects for dose level 1, and 2001 to 2006 if there are 6 subjects for dose level 2, etc.

This 4-digit number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results. This 4-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number that is assigned at the time the informed consent is obtained and that is used for all other procedures to identify the subjects throughout the study.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at CCI before being returned to the sponsor or designee or destroyed at CCI

The coordinating investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to CCI or the CCI, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

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

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

- Continuously monitoring expiration dates if expiry or retest date is provided to the investigator or designee.

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

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

The coordinating investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information can be included but is not limited to: protocol number and title, name of investigator, CCI unit identifier and number, description of sponsor-supplied drugs, date and amount dispensed, including initials or signature of the person dispensing the drug, including the initials or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The coordinating investigator or designee cannot destroy study drug without the sponsor's approval. The coordinating investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The coordinating investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

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

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

A unique subject identification number (site 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.

Participation in the wearable device study component is optional for the study subjects.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, sex, race as described by the subject, caffeine consumption, ethanol (alcohol) use, and tobacco use of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions and recorded as medical history.

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A 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.

The physical examination will be performed at Screening, Check-in (Day -1) in both Periods and Study Exit/Final Visit or ET.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the first administration of PET tracer [^{11}C]PHNO must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

A directed physical examination will be performed before discharge from Confinement Periods 1 and 2 and at each Follow-up Visit. A directed physical examination includes an examination of the affected body system(s).

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height is measured at Screening only. BMI is calculated at Screening only using metric units with the formula provided below. BMI should be derived as:

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

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

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. However, if the BMI is used as entry criteria based on a value between 18 and 30 mg/m^2 cut-off point, then this determination must be made after rounding.

Weight (only) will also be collected at Check-in (Day -1) in Confinement Periods 1 and 2, each Follow-up Visit, and at the Study Exit/Final Visit or ET (see Appendix A).

9.1.5 Vital Sign Procedure

Vital signs will include measurement of oral body temperature, blood pressure, respiratory rate, and pulse (bpm). Pulse and blood pressure will be measured after 5 minutes supine. Orthostatic pulse and blood pressure will be measured after standing for 2 minutes.

Vital signs will be recorded according to the schedule in Table 9.a.

Table 9.a Schedule for Recording Vital Signs

Dosing	Time Points
Overview	Screening (Days -28 to -2), Check-in (Day -1 both confinement periods), Follow-up Visits (Days 8-92), and Study Exit/Final Visit or ET.
AMPH only	Within 60 minutes prior to AMPH dosing; at 1, 2, 4, 8, and 12 hours post-AMPH dose; and prior to Confinement Period 1 discharge.
TAK-041 + AMPH	Within 60 minutes prior to TAK-041 dosing; at 3, 4, 6, 10, and 14 hours post-TAK-041 dose; and prior to Confinement Period 2 discharge.

See Appendix A for the schedules of vital sign assessments.

Orthostatic pulse and blood pressure will be measured after standing for 2 minutes at Screening, Check-in (Day -1), prior to discharge in both Confinement Periods, during Follow-up Visits, and at Study Exit/Final Visit or ET.

If a vital signs assessment is scheduled to occur while the subject is in the PET scanner, the assessment should be deferred until the PET scan is completed.

Vital signs may be repeated. All measurements will be recorded on the source documents and in the eCRF. See Appendix A for schedules of vital sign assessments.

If a vital sign is found to be abnormal postdose, it will be collected every 30 minutes until it returns to Baseline or within normal range.

When postdose vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.6 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, OTC medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

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

9.1.8 Wearable Devices Procedures

CCI

[redacted]

CCI

[redacted]

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken according to the Schedule of Study Procedures (Appendix A).

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

Table 9.b Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Erythrocytes/RBC Leukocytes/WBC with differential [define components as absolute values] Hemoglobin Hematocrit Platelets	ALT Albumin Alkaline phosphatase AST TBILI Direct bilirubin Protein (total protein) Creatinine Urea Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium Total serum cholesterol Triglycerides	pH Specific gravity Protein Glucose Blood Nitrite Ketones Bilirubin Urobilinogen Microscopic Analysis^ : Erythrocytes/RBC/high power field Epithelial cells, casts, etc./ low power field ^To be performed if abnormal for blood, protein or nitrite
Diagnostic Screening:		
Serum		**Urine Drug Screen and Ethanol Breath Test**
Hepatitis panel (including HBsAg and anti-HCV), HIV, TSH, and 5'-nucleotidase		Drug screen includes amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine. Breath test for ethanol (alcohol).

RBC=red blood cells, WBC=white blood cells, TSH=thyrotropin.

The local 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. All laboratory safety data will be transferred electronically to Takeda or designee in the format requested by Takeda. The investigator will maintain a copy of laboratory accreditation and the reference ranges for the laboratory used.

If subjects experience ALT or AST >3 ×ULN, ALP > 1.5 × ULN in conjunction with elevated TBILI, GGT, AST or ALT; ALP > 2 × ULN persisting for longer than 3 days, or ALP > 3 × ULN, follow-up laboratory tests (at a minimum, serum ALP, ALT, AST, total bilirubin, GGT, 5'-nucleotidase, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to the elevated liver enzyme values listed above. Initiate close observation for subjects enrolled with Baseline elevations in liver enzymes that are not >3 × ULN, yet worsen by 2-fold increases above Baseline values after study drug exposure.

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

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the coordinating investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator's assessment of NCS before proceeding with enrollment.

All CS laboratory abnormalities must be recorded as an AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.10 Contraception and Pregnancy Avoidance Procedure

Only male subjects may participate in this study.

From signing of informed consent, throughout the duration of the study, and for a period of 167 days (ie, 90 days after 7 half-lives, estimated using an average half-life value) following TAK-041 administration, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly), or sexual abstinence, if it is the preferred and usual lifestyle of the subject. Subjects practicing abstinence as a method of contraception must refrain from heterosexual intercourse throughout the duration of the study and for a period of 167 days (ie, 90 days after 7 half-lives, estimated using an average half-life value) following TAK-041 administration. In addition, they must be advised not to donate sperm during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with a follicle stimulating hormone >40 IU/L or at least 5 years since last regular menses).

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

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

During the course of the study, subjects will receive continued guidance with respect to contraception and sperm donation as part of the study procedures (Appendix A).

9.1.11 Pregnancy

Women are not included in this study.

There are no nonclinical teratogenicity/fetotoxicity data on TAK-041 as no embryo-fetal development toxicity studies have been conducted with the compound. Based on the results of nonclinical toxicity studies, TAK-041 was not mutagenic or clastogenic.

As such, the effect of TAK-041 on fetal development is unknown at this time. TAK-041 has not been administered to women who are pregnant or lactating. No nonclinical reproductive and developmental toxicity studies have been conducted. TAK-041 should not be administered to pregnant or lactating women at this stage in development. Based on this, it is recommended that women of childbearing potential be excluded from this study. Male subjects who are sexually active with a woman of childbearing potential should use a highly effective method of contraception (<1% failure rate/year), which has low user dependency while participating in this study (see Section 9.1.10).

If any female partner of a male subject is found to be pregnant during the treatment period of the study or within 167 days (ie, 90 days after 7 half-lives, estimated using an average half-life value) following TAK-041 administration, and if she agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

If the pregnancy occurs during administration of active study medication, eg, after Day 1 or within 167 days (ie, 90 days after 7 half-lives, estimated using an average half-life value) following TAK-041 administration, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature terminations, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 ECG Procedure

Standard 12-lead ECGs will be recorded at Screening, at multiple time points throughout the study (see Appendix A) and at the final safety evaluation at Study Exit or Early Termination. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety. ECGs will be administered according to the schedules shown in Table 9.c. Single ECGs will be taken at all time points. If an assessment is scheduled to occur while the subject is in the PET scanner, the assessment should be deferred until the PET scan is completed.

Table 9.c Schedule of ECG Recordings

Dosing	Time Points
Overview	Screening (Days -28 to -2), Check-in (Day -1 both confinement periods), Follow-Up Visits (Days 8-92), and Study Exit/Final Visit.
AMPH only	Within 60 minutes prior to AMPH dosing; at 1, 2, 4, 8, and 12 hours post-AMPH dose; and prior to Confinement Period 1 discharge.
TAK-041 + AMPH	Within 60 minutes prior to TAK-041 dosing; at 3, 4, 6, 10, and 14 hours post-TAK-041 dose; and prior to Confinement Period 2 discharge.

When an ECG is scheduled at the same time as the blood draws or vital signs, then the blood draws and vital signs will take priority and the ECG will be obtained within 30 minutes before or after the scheduled blood draw/vital sign assignment. If an ECG coincides with a meal, the ECG will take precedence followed by the meal.

All 12-lead ECG machines will be supplied by CCI Subjects should be in a supine position following an approximate 5 minute rest period for ECG recordings. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

ECGs will be read automatically and the investigator (or a cardiologist at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but NCS, or abnormal and CS. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QT interval with the Bazett correction method (QTcB). QTcB will be calculated automatically by the ECG machine. However, the QT interval with the Fridericia correction method (QTcF) and the RR interval may be calculated manually by the site or automatically by the ECG machine. The QTcF interval is calculated as shown below:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

ECG assessment and parameters will be captured in Takeda eCRF. CCI unit uses a fully validated ECG system. The coordinating investigator assessment is recorded electronically within this system.

All ECGs will be recorded at the time points detailed in the Schedule of Study Procedures (Appendix A).

9.1.13 Screening MRI of Brain

As part of Screening, eligible subjects will undergo an MRI scan without gadolinium contrast at the CCI [redacted] to ensure that there are no brain findings that might potentially compromise subject safety or scientific integrity of the study data. The screening MRI may be performed on a separate day from the other screening procedures. Additionally, the images will be used to identify and delineate the anatomical regions of interest for individual PET images and to aid in image analysis. 3D-T1-weighted images will be acquired on a Siemens 3T scanner. Further details of the complete scanning procedure will be provided by the CCI [redacted] in the MRI Scanning Manual for this study. The screening brain MRI will be performed and interpreted at the CCI [redacted] after the other screening activities have been performed and results assessed. MRI should be performed early enough so that MRI scan results are available prior to Check-in.

In case of a subject being re-screened, an MRI (without any abnormality) obtained at the CCI [redacted] r made within 90 days prior to Baseline Imaging Check-in is acceptable for eligibility.

9.1.14 Assessment of Suicidal Ideation and Behavior

Suicidality will be assessed by the use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) [21].

Two versions of the C-SSRS will be used in this study: the Screening/Baseline C-SSRS Lifetime Version 14Jan2009 and the Since-Last-Visit C-SSRS Version 14Jan2009. These will be administered according to the schedules shown in Appendix A and Table 9.d.

Table 9.d C-SSRS Schedule of Assessments

Study Part	Version	Time Points
	Screening/Baseline	Screening (Days -28 to -2)
Confinement Part 1	Since-Last-Visit	Day 3 (discharge)
Confinement Part 2	Since-Last-Visit	Day 2 (discharge)
	Since-Last-Visit	Study Exit/Final Visit or ET

9.1.15 Pharmacogenomic Sample Collection

Pharmacogenomic samples are not being collected in this study.

9.1.16 Pharmacokinetic Sample Collection

9.1.16.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (one 6-mL sample per scheduled time) for PK analysis of AMPH will be collected into chilled blood collection tubes (Vacutainer) containing anticoagulant ethylenediamine tetraacetic acid (K_2EDTA) according to the schedules in Appendix A.

Blood samples (one 4-mL sample per scheduled time) for PK analysis of TAK-041 and its metabolites (if possible) will be collected into chilled blood collection tubes (Vacutainer) containing anticoagulant K_2EDTA according to the schedules in Appendix A.

Serial blood samples for determination of AMPH and TAK-041 will be collected according to Table 9.e.

Table 9.e Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Period	Scheduled Time (hours)
AMPH	Plasma	1 and 2	Predose (within 60 minutes prior to dosing), 1 and 2 hours post-AMPH administration, and immediately prior to and after [^{11}C]PHNO PET scan.
TAK-041	Plasma	1 or 2	1, 2, 12, and 24 hours post-TAK-041 administration, immediately prior to and after the [^{11}C]PHNO PET scan, and during each Follow-up Visit.

Blood samples for TAK-041 PK will also be collected at ET if TAK-041 was administered. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. When the timing of safety measurements coincides with a PK blood collection, the order should be safety assessments followed by PK blood sample collection at the nominal time. The actual time of sample collection will be recorded on the source document and eCRF.

Sampling time points may be adjusted based on the preliminary emerging concentration data collected from prior subjects, but the total number of samples collected per subject should not exceed the planned number.

When ET is within 1 hour of a scheduled PK sample collection time point and study drug has been administered, the PK sample should be collected.

Instructions for sample processing and shipment are provided in Appendix E.

9.1.16.2 Bioanalytical Methods

CCI [redacted]

9.1.17 Pharmacokinetic Analyses

Plasma concentrations of AMPH and TAK-041 will be listed and only descriptive summaries by dose and (nominal) time points including, arithmetic mean, standard deviation, median, lower and

upper quartiles, and minimum and maximum values will be calculated. Further details of statistical methods will be outlined in the statistical analysis plan (SAP).

9.1.18 [^{11}C]PHNO PET Imaging Procedure, Image Processing and Analysis

PET scans will be acquired on a Siemens Biograph PET/CT scanner at the CCI [redacted]. The procedure is briefly summarized here. The details of the PET imaging procedure, image processing and analysis will be provided by the CCI [redacted] in a TAK-041-1002 PET Imaging Manual.

9.1.18.1 PET Imaging Procedures

Subjects will undergo a total of 3 PET scans with [^{11}C]PHNO during 2 confinement periods in this study. PET scans will be scheduled such that the post-AMPH scans are performed at the approximately the same time of day for a given subject.

Environmental conditions should be controlled for approximately 6 hours prior to [^{11}C]PHNO administration (covering the total time for TAK-041 and AMPH uptake) to minimize dopamine release due to environmental stimuli, including video game playing on cell phones.

On PET scan days, the subject will undergo preinjection assessments including vital signs (blood pressure, pulse, respiratory rate, and temperature) (see Appendix A). A venous catheter will be placed in the forearm or antecubital vein for pre-PET scan PK sample collection and [^{11}C]PHNO administration. Additional PK samples will be collected through direct venipuncture or a second catheter will be placed in the opposite forearm or antecubital vein.

The subject will be positioned in the scanner and sufficient padding will be used to minimize head movements during imaging acquisition. The subject will be monitored continuously by a qualified PET technologist. A low dose CT scan will be performed before each injection of [^{11}C] PHNO for subsequent attenuation and scatter correction of the PET data. After the transmission CT scan, the subject will receive a bolus injection of up to 180 mBq of [^{11}C]PHNO administered as a slow bolus over 20 seconds. Dynamic PET imaging will commence at the onset of the tracer injection and continue for approximately 90 minutes. The total time may be shortened based on ongoing analysis of brain tracer dynamics. The technical details of the PET acquisition are contained in the PET Imaging Manual.

9.1.18.2 Image Processing and Analysis

The person performing the PET data analysis will be informed of which is the baseline condition for each subject; however, they will be blinded as to whether the remaining scans they are evaluating for that subject are the TAK-041 + AMPH or the AMPH only scans.

Following reconstruction, scatter correction and attenuation correction, the PET data will be corrected for motion (if required) and coregistered to each subject's structural MRI image. Anatomic regions of interest will be defined using each subject's MRI. Those regions will include, but not be limited to, the caudate, cerebellum, putamen, substantia nigra, and ventral striatum. The

regions of interest will then be applied to the PET emission data to derive regional time-activity curves.

Decay-corrected time-activity curves will be analyzed using a simplified reference tissue model [22,23], with the cerebellum as the reference region to derive regional estimates of BP_{ND}. BP_{ND} is proportional to the available concentration of receptor sites [24].

9.1.18.3 PET Data Analysis

A separate imaging report prepared by the CCI [redacted] will describe the following:

1. Individual BP_{ND} values and descriptive statistics for high uptake regions of interest for all PET scans. Descriptive statistics for BP_{ND} values will include means, medians, SDs, ranges, and 95% CI.
2. The change in BP_{ND} for the AMPH+TAK-041 condition compared to the BP_{ND} for the AMPH alone condition (100*[BP_{ND} AMPH+TAK-041- BP_{ND} AMPH]/ BP_{ND} AMPH).
3. The relative change in BP_{ND} for the AMPH alone condition (100*[Baseline – Post-AMPH]/Baseline) and the relative change in BP_{ND} for the AMPH+TAK-041 condition (100*[Baseline – Post-AMPH+TAK-041]/Baseline).
4. In order to establish a potential dose-dependent effect, we will explore via plots the magnitude of the relative change in BP_{ND} in the AMPH+TAK-041 condition as a function of the dose of TAK-041 administered.
5. Additional analyses may be performed for exploratory purposes.

9.1.19 Biometric Monitoring Using the Wearable Devices

CCI [redacted]

9.1.20 Documentation of Screen Failure

Investigator must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

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

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

9.1.21 Documentation of Study Enrollment

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

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

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in CCI or the CCI. Following administration of the study medication, appropriate mouth checks will be performed to ensure that the dose is swallowed and then noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by CCI pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

Schedules for all study-related procedures are shown in Appendix A. Assessments should be completed at the designated visit/time point(s) detailed in Appendix A footnotes.

9.3.1 Screening

- Informed consent.
- Brain MRI.
- Inclusion/exclusion criteria.
- Demographics and medical history.
- Medication history.
- Physical examination.
- Vital signs.
- Height, weight, and BMI.
- Concurrent medical conditions.
- Concomitant medications.
- 12-lead ECG.
- Safety laboratory evaluations.
- Urine drug screen and ethanol breath test.
- Hepatitis panel (including HBsAg and anti-HCV), HIV, TSH, and 5'-nucleotidase.
- PTE assessment.
- C-SSRS.

9.3.2 Follow-up Visits

- Directed physical examination.
- Vital signs.
- Weight.
- Concomitant medications.
- 12-lead ECG.
- Safety laboratory evaluations.

- PK blood collection for TAK-041.
- AE assessments.
- Return of Actiwatch at first Follow-up Visit. (Skin Patch device is removed 2 days after discharge [CP1 and CP2].)

9.3.3 Study Exit/Final Visit or Early Termination (ET)

- Physical examination.
- Vital signs.
- Concomitant medications.
- 12-lead ECG.
- Safety laboratory evaluations.
- AE assessments.
- C-SSRS.
- Only at ET:
  - PK blood collection for TAK-041, if possible.

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9.4 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.f. Every effort has been made to minimize the blood volumes for the blood tests in this study.

Table 9.f Approximate Blood Volume

Sample Type	Sample Volume (mL)	Number of Samples					Total Volume (mL)
			Confinement			Study Exit/ Final Visit ET (b)	
		Screening	CP1	CP2	Follow-Up Visits (a)		
Safety laboratory tests	9.5	1	0	0	0	0	**9.5**
Safety laboratory tests	4.5		2	2	4	1	**40.5**
PGx sample collection	NA						**NA**
PK blood collection (TAK-041)	4.0	0	0	6	4	1 (c)	**44.0**
PK blood collection (AMPH)	6.0	0	5	5	0	0	**60.0**
		Total Approximate Blood Sampling Volume					**154.00**

NA=not applicable, PGx=pharmacogenomics.
Note: Volumes do not include unscheduled/repeat or additional blood samples.
(a) Four Follow-up Visits are scheduled: one 7 ±2 days after TAK-041 administration in Confinement Period 2 and 3 Follow-up Visits approximately 4 weeks apart or until TAK-041 concentration in plasma is <5% of the subject's C_{max}.
(b) The Study Exit/Final Visit may occur instead of the last scheduled Follow-up Visit.
(c) Blood samples for TAK-041 PK will be collected at ET if TAK-041 was administered.

The maximum volume of blood in any single day is approximately 50.0 mL. The total volume of blood for each subject is approximately 154.0 mL.

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 prior to first administration of PET tracer [^{11}C]PHNO; 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 CS abnormal laboratory finding), 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 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 medication 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 parameters are only considered to be PTEs or AEs if they are judged to be CS (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 re-test and/or continued monitoring of an abnormal value 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 condition, the worsening or complication should be recorded appropriately as a PTE(worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). 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 condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, 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 condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, 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 starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, 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 severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately 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.

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. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

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 Severity 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.

10.1.6 Causality of AEs

The relationship of each AE to study medication(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 drugs 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 drugs and concurrent treatments.

10.1.7 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.

10.1.8 Start Date

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

10.1.9 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.

10.1.10 Frequency

Once: a onetime occurrence; episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 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 (eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE).
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Dose interrupted – the dose was interrupted due to the particular AE.

10.1.12 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 which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the first injection of the ligand [^{11}C]PHNO for the Baseline PET scan in Confinement Period 1 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered [^{11}C]PHNO. Routine collection of AEs will continue through the Study Exit/Final Visit.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. 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 medication 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. Pattern of AE (Frequency).
4. Severity/Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(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 medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

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10.2.2 Collection and Reporting of SAEs

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

A Takeda SAE form must be completed in English 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 medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

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

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

10.2.3 Reporting of Abnormal Liver Function Tests

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

If a subject is noted to have ALT or AST, or ALP >3 ×ULN and TBILI >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory

tests as described in Section 9.1.9 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the investigator should 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, IRB or IEC, 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 (EMA), investigators and IRBs or IECs, 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 an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No study-specific committees are 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 conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

12.1 CRFs (Electronic)

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

The sponsor or its designee will supply investigative sites with eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. Data are captured in CCI database or on paper (C-SSRS for example) and then transcribed into the eCRFs. These eCRF forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

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

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

The coordinating 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 provided by the sponsor should be made by the investigator with use of change and modification records of the eCRFs. The coordinating 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 investigators 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, as well as the MRI scans and PET scans (attenuation-corrected, nonattenuation corrected, and attenuation correction scans), 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, International Conference on Harmonisation (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 Clinical Study Site Agreements between the investigator(s) and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A SAP will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

Safety Set

The safety set will consist of all subjects who are enrolled and receive an investigational drug ([^{11}C]PHNO, AMPH alone, or TAK-041 and AMPH) as part of this study. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

Pharmacokinetic Set

The PK set will consist of all subjects who receive study drug (TAK-041 and AMPH, or AMPH alone) and have at least one measurable plasma concentration for TAK-041 or AMPH.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic data will be summarized by TAK-041 dose level and overall. Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (eg, age, height, weight, and BMI). The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (eg, sex, race, tobacco use) will also be tabulated. Individual subject demographic and baseline characteristics data will be listed.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened, but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

13.1.3 Pharmacokinetic Analysis

All measured concentrations will be listed and descriptive summaries by treatment arm and (nominal) time points including n, arithmetic mean, SD, median, lower and upper quartiles and minimum and maximum values will be made. In addition, geometric mean, standard deviation (SD) of log transformed values and %CV will also be presented.

A more detailed analysis will be presented in the SAP.

The data points will be used for population PK meta-analysis, which will be described in an analysis plan and reported separately.

13.1.4 Safety Analysis

All AEs will be coded by system organ class and preferred term using MedDRA. TEAEs with onset occurring up until Study Exit/Final Visit will be listed and included in the summary tables. TEAEs will be summarized overall, by relationship to study drug, and by severity for each treatment and overall. Similar summary tables will be generated for TEAEs assessed by the investigator as related to study drug.

Individual results for clinical laboratory tests, vital sign, and ECG parameters that meet TDC's markedly abnormal criteria to be defined in the SAP will be listed and summarized. Baseline, postdose, and change from Baseline to postdose clinical laboratory tests, vital signs, and ECG parameters will be summarized for each regimen.

Shift tables will be generated for the investigator's ECG interpretations for each regimen. All ECG data will be provided in the data listings. Physical examination data and suicidal assessments will be presented in data listings.

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13.2 Determination of Sample Size

Using previously reported data [12], and assuming a 16% standard deviation for the relative change in BP_{ND} for high uptake regions of interest, 12 subjects will provide approximately 80% power to detect a 20% relative change in BP_{ND} when values from the AMPH + TAK-041 condition are compared to AMPH alone condition using a 2-sample 2-sided t-test with 0.05 significance level. The power for the other regions of interest will be more than 80%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site(s) 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 institution guarantee access to source documents by the sponsor or its designee and by the IRB or IEC.

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

14.2 Protocol Deviations

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

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 EC, 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. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The timing of the scheduled assessments may be adjusted as necessary to avoid interfering with the PET and fMRI scans and transfer between CCI unit and the CCI [redacted].

The investigator should document all protocol deviations.

Every attempt will be made to collect each PK blood sample at the designated time points, and the actual time of each blood sample will be recorded on the source document and eCRF.

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 Food and Drug Administration [FDA], the United Kingdom

Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study sites are contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution 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 or IEC Approval

IRBs or 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 IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification, no protocol activities, including screening may occur.

The site must adhere to all requirements stipulated by the 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 IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB or 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 are 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 prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

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

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

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

15.3 Subject Confidentiality

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

Subjects who decline to participate in the wearable device optional component, or who consent and later withdraw from this part of the study, may continue to participate in the remainder of the study.

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 clinical 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 Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

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.

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 interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov 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 US investigators), country, and recruiting status will be registered and available for public viewing. For some registries, Takeda will assist callers in locating trial 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 Takeda providing this information to callers must provide Takeda 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 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 clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

Periods	**Days**	**Confinement Period 1**					**Confinement Period 2**			**Follow-up Period**	**Study Exit/ Final Visit (f)**	**ET**
Study Day	**-28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**I**	**Day -1**	**Day 1**	**Day 2**			
Procedures	**Screening (a)**	**Check-in (b)**	**PET Scan Baseline**	**PET Scan Postdose**	**Discharge (c)**	**(d)**	**Check-in (b)**	**PET Scan Postdose**	**Discharge (c)**	**Days 8-92 (±2) (e)**		**(g)**
Informed consent	X											
Brain MRI	X											
Check into CCI		X					X					
Confinement (h)		X	X	X	X		X	X	X			
Release from CCI					X				X			
Inclusion/exclusion criteria	X	X					X					
Demographics and medical history	X											
Medication history	X											
Physical examination (i)	X	X					X				X	X
Directed physical examination (j)					X				X	X		
Vital signs (k)	X	X		X	X		X	X	X	X	X	X
Height, weight, and BMI (l)	X	X					X			X	X	X
Concomitant medications	X	X			X	X	X		X	X	X	X
Concurrent medical conditions	X	X										
12-lead ECG (m)	X	X		X	X		X	X	X	X	X	X

Footnotes on last table page.

Appendix A Schedule of Study Procedures (continued)

Study Day	Days -28 to -2	Confinement Period 1				I	Confinement Period 2			Follow-up Period	Study Exit/ Final Visit	ET
		Day -1	Day 1	Day 2	Day 3		Day -1	Day 1	Day 2			
Procedures	**Screening (a)**	**Check-in (b)**	**PET Scan Baseline**	**PET Scan Postdose**	**Discharge (c)**	**(d)**	**Check-in (b)**	**PET Scan Postdose**	**Discharge (c)**	**Days 8-92 (±2) (e)**	**(f)**	**(g)**
Safety laboratory evaluations (n)	X	X			X		X		X	X	X	X
Urine drug screen and ethanol breath test	X	X					X					
Hepatitis panel (including HBsAg and anti-HCV), HIV, TSH, 5'nucleotidase	X											
AMPH dosing (o)				X				X				
TAK-041 dosing (p)								X				
Insertion of venous catheter			X					X				
[^{11}C]PHNO PET tracer injection			X	X				X				
PET scan			X	X				X				
PK blood collection AMPH (q)				X				X				
PK blood collection TAK-041 (r)								X	X	X		X
PTE assessment	X	X										
AE assessment (s)			X	X	X	X	X	X	X	X	X	X

Footnotes on last table page.

Appendix A Schedule of Study Procedures (continued)

Study Day	Days -28 to -2	Confinement Period 1				I	Confinement Period 2			Follow-up Period	Study Exit/ Final Visit	ET
		Day -1	Day 1	Day 2	Day 3		Day -1	Day 1	Day 2			
Procedures	**Screening (a)**	**Check-in (b)**	**PET Scan Baseline**	**PET Scan Postdose**	**Discharge (c)**	**(d)**	**Check-in (b)**	**PET Scan Postdose**	**Discharge (c)**	**Days 8-92 (±2) (e)**	**(f)**	**(g)**
C-SSRS (t)	X				X				X		X	X
CCI												
CCI												
CCI												
CCI												

(a) The MRI may be scheduled on a second Screening visit.
(b) Admission to CCI
(c) Discharge from CCI
(d) There will be a 5 to 45 day interval (I) between Confinement Periods.
(e) Following discharge from Confinement Period 2, subjects will return to the site for PK and safety assessments after 7 ±2 days, and then return for approximately 3 Follow-up safety and PK assessment Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's C_{max}.
(f) At the end of each Follow-up Visit, the next visit will be scheduled ~4 weeks later. If, when the PK results are available, the subject's PK was <5% of their C_{max} value, the site and subject will be informed that their next scheduled visit will be considered their Study Exit/Final Visit.
(g) Subjects who drop out prior to completion of all PET scans will have assessments done as described for ET and a follow-up telephone call approximately 2 days after the ET Visit.
(h) Subjects will be remain at CCI from Check-in through discharge on Day 3 in Period 1 or Day 2 in Period 2 except when the imaging scans are performed at the CCI .
(i) Physical examinations will take place at Screening, Check-in (Day -1) in both Periods, and at Study Exit/Final Visit or ET.
(j) A directed physical examination will be performed as necessary at discharge in Confinement Periods 1 and 2, and at each Follow-up Visit.
(k) Vital signs will be recorded at Screening (Days -28 to -2) and at Check-in (Day -1) in both Confinement Periods. When both TAK-041 and AMPH are administered, vital signs will be recorded relative to the TAK-041 dose: within 60 minutes prior to TAK-041 dosing; at 3, 4, 6, 10, and 14 hours post-TAK-041 dose, and prior to Confinement Period 2 discharge or ET. When only AMPH is dosed, vital signs will be recorded relative to the AMPH dose: within 60 minutes prior to

AMPH dosing; at 1, 2, 4, 8, and 12 hours post-AMPH dose and prior to Confinement Period 1 discharge. Vital signs will also be recorded during each Follow-up Visit and at the Study Exit/Final Visit or ET. Orthostatic pulse and blood pressure will be measured after standing for 2 minutes at Screening, Check-in (Day -1) and prior to discharge in both Confinement Periods, during each Follow-up Visit, and at Study Exit/Final Visit or ET.
(l) Weight only will be recorded at Check-in for Confinement Periods 1 and 2, at each Follow-up Visit, and at the Study Exit/Final Visit or ET. Height is collected only at Screening; BMI is calculated only at Screening.
(m) ECGs will be recorded at Screening (Days -28 to -2) and at Check-in (Day -1) in both Confinement Periods. When only AMPH is dosed, ECGs will be recorded relative to the AMPH dose: within 60 minutes prior to AMPH dosing; at 1, 2, 4, 8, and 12 hours post-AMPH dose; and prior to Confinement Period 1 discharge. When both TAK-041 and AMPH are administered, ECGs will be recorded relative to the TAK-041 dose: within 60 minutes prior to TAK-041 dosing and at 3, 4, 6, 10, and 14 hours post-TAK-041 dose, and prior to Confinement Period 2 discharge. ECGs will also be recorded during each Follow-up Visit and at the Study Exit/Final Visit or ET.
(n) Clinical safety laboratory tests (hematology, chemistry, and urinalysis) will be collected at Screening, upon Check-in and prior to Discharge in both confinement periods, during each Follow-Up Visit, and at the Study Exit/Final Visit or ET.
(o) AMPH dosing: On Day 2 of Confinement Period 1, subjects will receive a single dose of AMPH alone. On Day 1 of Confinement Period 2, subjects will receive a single dose of TAK-041 followed by a single dose of AMPH at the approximate t_{max} of TAK-041.
(p) TAK-041 dosing: on Day 1 of Confinement Period 2, subjects will receive a single dose of TAK-041 followed by a single dose of AMPH at the approximate t_{max} of TAK-041.
(q) PK AMPH: Confinement Periods 1 & 2, predose (within 60 minutes prior to dosing), 1 and 2 hours after AMPH administration, and immediately prior to and after the [^{11}C]PHNO PET scan.
(r) PK TAK-041: During Confinement Period 2 at 1, 2, 12, and 24 hours after TAK-041 administration, immediately prior to and after the [^{11}C]PHNO PET scan and during each Follow-Up Visit.
(s) Adverse events: Collection of AEs will commence from the time that the subject is first administered [^{11}C]PHNO. Routine collection of AEs will continue through the Study Exit/Final Visit.
(t) C-SSRS: The Baseline C-SSRS will be administered at Screening. The Since Last Visit C-SSRS will be administered on Day 3 (Confinement Period 1), Day 2 (Confinement Period 2), and Study Exit/Final Visit or ET).
(u) CCI [redacted]
(v) CCI [redacted]

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. 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.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. 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.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, 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.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. 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 or the subject's legally acceptable representative 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 medication(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.
    e) that the subject's identity will remain confidential in the event that study results are published.

24. Male subjects must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study and for 90 days after last dose of study medication.
25. 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 medication.
- 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.

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Plasma Samples for PK Analysis of TAK-041 and Amphetamine

1. Collect 4 mL (TAK-041) or 6 mL (AMPH) of venous blood for plasma into a chilled Becton-Dickinson Vacutainer. All TAK-041 and AMPH blood samples should be collected into Vacutainers containing K_2EDTA.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the Vacutainers for 10 minutes at approximately 1500 (relative centrifugal force [RCF]) at 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 0.8 mL final plasma volume after centrifugation needs to be obtained for each sample. Labeling may include protocol number (TAK-041-1002), sample matrix (ie, TAK-041 or AMPH) enrollment number, period, profile day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately in either -20°C or -70°C freezer (stability established at both temperatures) until shipment to PPD, Middleton, WI, USA. No more than 45 minutes should elapse between blood collection and freezing the plasma sample.

Shipping of TAK-041 Plasma Samples

The following instructions are recommended unless they differ from the site's standard operating procedures for labeling, packaging, or shipping of plasma samples.

1. Biological samples (ie, plasma) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
   a) Separate the duplicate SET 2 samples from the SET 1 samples.
   b) Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
   c) Using a permanent marker, write the 4-digit enrollment sequence number, sample matrix (ie, plasma or urine), number of samples, and "SET 1" on each self-sealing bag.

d) Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 2a through 2c above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."

3. An inventory of individual samples should accompany each shipment and should include the sponsor's name (Takeda), study medication (TAK-041), protocol number (TAK-041-1002), investigator's name, sample type (ie, plasma), enrollment number, period, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
4. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
5. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
6. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
7. Affix an address label to each shipping carton. Complete the address label with the following information:

   Plasma Samples for TAK-041
   Jay Schaefgen
   PPD - Middleton
   3230 Deming Way
   Middleton, WI 53562
   Phone: 608-662-7706
   Fax: 608-662-9025

8. Affix a carbon dioxide label on each carton, specifically:

   Carbon Dioxide Solid UN-1845
   Class 9 PKG GR III
   Quantity _____
   (fill in weight to nearest lb/kg and specify unit of measure used)

9. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark **KEEP FROZEN** on each carton. Specify a return address and contact person on the carton.

10. Obtain the airway bill number and a receipt of shipment from the carrier.

After shipping of the TAK-041 samples, **e-mail Jay Schaefgen** at jay.schaefgen@ppdi.com and **Betty Katz** at betty.katz@takeda.com or call Betty at 224-554-2160 to notify them of next day delivery. When calling, provide the following information:

Name of courier or transport company
Time and date the shipment left the clinical site
Airway bill number

Shipping of Amphetamine Plasma Samples

The following instructions are recommended unless they differ from the site's standard operating procedures for labeling, packaging, or shipping of plasma samples.

1. Biological samples (ie, plasma) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
   a) Separate the duplicate SET 2 samples from the SET 1 samples.
   b) Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
   c) Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (ie, plasma or urine), number of samples, and "SET 1" on each self-sealing bag.
   d) Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 2a through 2c above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."
3. An inventory of individual samples should accompany each shipment and should include the sponsor's name (Takeda), study medication (amphetamine), protocol number (TAK-041-1002), investigator's name, sample type (ie, plasma), randomization number, period, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
4. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess

space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.

5. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
6. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
7. Affix an address label to each shipping carton. Complete the address label with the following information:

   Plasma Samples for Amphetamine

   QPS, LLC
   Delaware Technology Park
   3 Innovation Way, Suite 240
   Attn: Sample team
   Newark, DE 19711

   Phone: 302-369-5601
8. Affix a carbon dioxide label on each carton, specifically:

   Carbon Dioxide Solid UN-1845
   Class 9 PKG GR III
   Quantity _____
   (fill in weight to nearest lb/kg and specify unit of measure used)
9. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark **KEEP FROZEN** on each carton. Specify a return address and contact person on the carton.
10. Obtain the airway bill number and a receipt of shipment from the carrier.
11. After shipping of the Amphetamine samples, e-mail Yongdong.Zhu@qps.com and Betty Katz at betty.katz@takeda.com or 224-554-2160 to notify them of next day delivery. When calling, provide the following information:

    Name of courier or transport company
    Time and date the shipment left the clinical site
    Airway bill number

Appendix F Detailed Description of Amendments to Text

This document describes changes in reference to Protocol TAK-041-1002 Incorporating Amendment No. 02.

Change 1: Preliminary results from first-in-human (FIH) study TAK-041-1001 were updated.

The primary change occurs in Section 4.3 Benefit/Risk Profile:

Initial wording:	As this is a healthy volunteer study, there is no expected clinical benefit to the study participants. TAK-041 has the potential to be a first-in-class drug; therefore, there are no known class effects. Potential risks are based on clinical findings, the mechanism of action, nonclinical findings, and the known risks of other GPR139 receptor agonists. Preliminary results from the FIH study TAK-041-1001 indicate that single doses of TAK-041 at 5, 10, 20, and 40 mg are well tolerated. To date, no adverse events and no clinically meaningful safety laboratory, physical examination, vital signs, or ECG results have been reported for the 16 subjects who received TAK-041 or placebo. The potential risks can be monitored clinically and/or with laboratory tests and are considered in setting up the stopping rules for this clinical study. Appropriate exclusion criteria that exclude individuals with past history or concurrent conditions that increase the risk will be applied.
Amended or new wording:	As this is a healthy volunteer study, there is no expected clinical benefit to the study participants. TAK-041 has the potential to be a first-in-class drug; therefore, there are no known class effects. Potential risks are based on clinical findings, the mechanism of action, nonclinical findings, and the known risks of other GPR139 receptor agonists. Preliminary results from the FIH study TAK-041-1001 indicate that single doses of TAK-041 at 5, 10, 20, and 40 mg are well tolerated. ~~To date, no adverse events and no clinically meaningful safety laboratory, physical examination, vital signs, or ECG results have been reported for the 16 subjects who received TAK-041 or placebo.~~ **To fully assess the safety and PK profile of TAK-041 in subjects receiving 20 and 40 mg TAK-041 doses, follow-up PK blood draws were performed until TAK-041 plasma concentrations were below the lower level of quantitation of the assay. Six AEs were observed that were mild, deemed not related to study drug, and resolved without treatment. No serious AEs and no clinically meaningful safety laboratory results (including 5'-nucleotidase, sorbitol dehydrogenase, and urine osmolality), and no clinically significant physical examination, vital signs, or ECG results were reported for the 16 subjects who received 5 to 40 mg doses of TAK-041 crystalline suspension or matching placebo in TAK-041-1001 Cohorts 1 and 2.** The potential risks can be monitored clinically and/or with laboratory tests and are considered in setting up the stopping rules for this clinical study. Appropriate exclusion criteria that exclude individuals with past history or concurrent conditions that increase the risk will be applied.

Rationale for Change:

Safety results were updated because all follow-up PK and safety assessments from all subjects in the FIH study who had received 20 or 40 mg doses of TAK-041 were complete.

The following sections also contain this change:

Section 6.1.1 Dose Decisions.

Section 6.2.1 Study Design

Section 6.2.2 Doses

Change 2: Single doses of TAK-041 ranging from 5 to 40 mg may be evaluated in this study.

The primary change occurs in Section 6.2.2 Doses:

Initial wording:	The starting dose of TAK-041 that will be evaluated in this study will be 20 mg, a dose that does not exceed the highest dose evaluated in the TAK-041-1001 study that has been demonstrated to be well-tolerated, and has achieved exposures indicative of the predicted pharmacologically active exposures of TAK-041. Further dose levels may be evaluated to explore the exposure-response relationship of TAK-041.
Amended or new wording:	The starting dose of TAK-041 that will be evaluated in this study ~~will be~~ **is** 20 mg, a dose ~~that does not exceed the highest dose evaluated in the TAK-041-1001 study~~ that has been demonstrated to be well-tolerated, and has achieved exposures indicative of the predicted pharmacologically active exposures of TAK-041. **A single dose of 40 mg TAK-041 has also been shown to be well-tolerated in the TAK-041-1001 study and** ~~Further dose levels~~ may be evaluated to explore the exposure-response relationship of TAK-041.

Rationale for Change:

Results from the TAK-041-1001 study have confirmed that a single 40 mg dose of TAK-041 was well-tolerated and presented no safety issues.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.2.1 Study Design.
- Section 8.1.1.1 TAK-041, Table 8.b, footnote (a).

Change 3: Possible dose combinations of TAK-041 and amphetamine (AMPH) have changed.

The primary change occurs in Section 6.1.1 Dose Decisions:

Initial wording:

- The first 4 subjects in this study will receive a 20 mg dose of TAK-041 and a 0.50 mg/kg dose of AMPH.
- If the results from these subjects show less than 10% blunting (lower bound of 95% confidence interval [CI]) in the AMPH-induced dopamine release in the striatum (as measured by changes in BP_{ND}), the next 4 subjects will receive the same 20 mg dose of TAK-041, and a 0.25 mg/kg dose of AMPH.
- If the results from the first 4 subjects show 10% or more (lower bound of 95% CI) blunting in the AMPH-induced dopamine release in the striatum (as measured by changes in BP_{ND}), the next 4 subjects will receive a 5 mg dose of TAK-041 (based on observed exposures in the TAK-041-1001 study), and a 0.50 mg/kg dose of AMPH.
- Depending on the results from the first 8 subjects, the last 4 subjects may receive either:
  - A dose between 5 and 20 mg of TAK-041 (based on exposures evaluated in the TAK-041-1001 study) and a 0.50 mg/kg dose of AMPH (if both previously tested TAK-041 dose levels showed a blunting in AMPH-induced dopamine release); or
  - A 5 mg dose of TAK-041 and a 0.25 mg/kg dose of AMPH (if previously a blunting of AMPH-induced dopamine release was only observed with the high dose of TAK-041 and the low AMPH dose).

Amended or new wording:

This study will utilize an adaptive design to determine the dose(s) of AMPH and TAK-041 to be administered:

- The first 4 subjects in this study will receive a 20 mg dose of TAK-041 and a ~~0.50~~ **0.5** mg/kg dose of AMPH.
- If the results from these subjects **do not** show ~~less than~~ **at least** 10% blunting (lower bound of **the one-sided** 95% CI **≤10%**) in the AMPH-induced dopamine release in the striatum (as measured by changes in BP_{ND}), the next 4 subjects will receive ~~the same 20~~ **a 40** mg dose of TAK-041 and a ~~0.25~~ **0.5** mg/kg dose of AMPH.
- If the results from the first 4 subjects show 10% or more (lower bound of **the one-sided** 95% CI **>10%**) blunting in the AMPH-induced dopamine release in the striatum (as measured by changes in BP_{ND}), the next 4 subjects will receive a 5 mg dose of TAK-041 (based on observed exposures in the TAK-041-1001 study) and a ~~0.50~~ **0.5** mg/kg dose of AMPH.
- Depending on the results from the first 8 subjects, the last 4 subjects may receive either:
  - A dose between 5 and ~~20~~ **40** mg of TAK-041 (based on exposures evaluated in the TAK-041-1001 study) and a ~~0.50~~ **0.5** mg/kg dose of AMPH (if both previously tested TAK-041 dose levels showed a blunting in AMPH-induced dopamine release); or
  - A ~~5~~ **40** mg dose of TAK-041 and a 0.25 mg/kg dose of AMPH ~~(if previously a blunting of AMPH-induced dopamine release was only observed with the high dose of TAK-041 and the low AMPH dose)~~.

Rationale for Change: The addition of a 40 mg dose allows greater flexibility in the TAK-041 and AMPH dose combinations to better analyze blunting of AMPH-induced dopamine release.

The following section also contains this change:

- Section 2.0 STUDY SUMMARY

Initial wording:

Study Drugs and Dose Levels:
Three of the following TAK-041/AMPH (dexamfetamine sulphate) dose combinations will be evaluated (each in a group of 4 subjects):

- 20 mg TAK-041 and 0.50 mg/kg AMPH.
- 20 mg TAK-041 and 0.25 mg/kg AMPH.
- 5 to 20 mg TAK-041 and 0.50 mg/kg AMPH.
- 5 mg TAK-041 and 0.50 mg/kg AMPH.
- 5 mg TAK-041 and 0.25 mg/kg AMPH.

Amended or new wording:	**Study Drugs and Dose Levels:** Three of the following TAK-041/AMPH (dexamfetamine sulphate) dose combinations will be evaluated (each in a group of 4 subjects): • 20 mg TAK-041 and ~~0.50~~ **0.5** mg/kg AMPH. • ~~20~~ **40** mg TAK-041 and 0.25 mg/kg AMPH. • 5 to ~~20~~ **40** mg TAK-041 and ~~0.50~~ **0.5** mg/kg AMPH. • 5 mg TAK-041 and ~~0.50~~ **0.5** mg/kg AMPH. • ~~5 mg TAK-041 and 0.25 mg/kg AMPH.~~

Change 4: Primary and secondary endpoints were revised.

The primary change occurs in Section 5.2 Endpoints:

Initial wording:	Section 5.2.1 Primary Endpoint The relative change in nondisplaceable binding potential (BP_{ND}) in the AMPH+TAK-041 condition compared to AMPH alone. Section 5.2.2 Secondary Endpoint The relative change in BP_{ND} in the AMPH+TAK-041 condition compared to AMPH alone as a function of the dose of TAK-041 administered.
Amended or new wording:	Section 5.2.1 Primary Endpoint The ~~relative~~ change in nondisplaceable binding potential (BP_{ND}) in the AMPH+TAK-041 condition compared to AMPH alone. Section 5.2.2 Secondary Endpoint The ~~relative~~ change in BP_{ND} in the AMPH+TAK-041 condition compared to AMPH alone as a function of the dose of TAK-041 administered.

Rationale for Change: To clarify the endpoints.

The following section also contains this change:

- Section 2.0 STUDY SUMMARY

Change 5: An additional PET analysis was added and revisions were made to an existing analysis.

The primary change occurs in Section 9.1.18.3 PET Data Analysis:

Initial wording:

A separate imaging report prepared by the CCI [redacted] will describe the following:

1. Individual BP_{ND} values and descriptive statistics for high uptake regions of interest for all PET scans. Descriptive statistics for BP_{ND} values will include means, medians, SDs, ranges, and 95% CIs.
2. The relative change in BP_{ND} for the AMPH alone condition (Baseline – Post-AMPH/Baseline) and the relative change in BP_{ND} for the AMPH+TAK-041 condition (Baseline – Post-AMPH+TAK-041/Baseline).
3. In order to establish a potential dose-dependent effect, we will explore the magnitude of the relative change in BP_{ND} in the AMPH+TAK-041 condition as a function of the dose of TAK-041 administered via plots.
4. Additional analyses may be performed for exploratory purposes.

Amended or new wording:

A separate imaging report prepared by the CCI [redacted] will describe the following:

1. Individual BP_{ND} values and descriptive statistics for high uptake regions of interest for all PET scans. Descriptive statistics for BP_{ND} values will include means, medians, SDs, ranges, and 95% CI.
2. **The change in BP_{ND} for the AMPH+TAK-041 condition compared to the BP_{ND} for the AMPH alone condition (100*[BP_{ND} AMPH+TAK-041- BP_{ND} AMPH]/ BP_{ND} AMPH).**
3. The relative change in BP_{ND} for the AMPH alone condition (**100*[**Baseline – Post-AMPH**]**/Baseline) and the relative change in BP_{ND} for the AMPH+TAK-041 condition (**100*[**Baseline – Post-AMPH+TAK-041**]**/Baseline).
4. In order to establish a potential dose-dependent effect, we will explore via plots the magnitude of the relative change in BP_{ND} in the AMPH+TAK-041 condition as a function of the dose of TAK-041 administered.
5. Additional analyses may be performed for exploratory purposes.

Rationale for Change:

The PET analysis methods were revised to provide more robust analyses of results.

Section 2.0 STUDY SUMMARY also contains this change.

Change 6: PET procedures were modified.

The primary change occurs in Section 9.1.18.1 PET Imaging Procedures:

Initial wording:	On PET scan days, the subject will undergo preinjection assessments including vital signs (blood pressure, pulse, respiratory rate, and temperature) (see Appendix A). A venous catheter will be placed in the forearm or antecubital vein for [^{11}C]PHNO administration. A second catheter will be placed in the opposite forearm or antecubital vein for blood PK collections.
Amended or new wording:	On PET scan days, the subject will undergo preinjection assessments including vital signs (blood pressure, pulse, respiratory rate, and temperature) (see Appendix A). A venous catheter will be placed in the forearm or antecubital vein for **pre-PET scan PK sample collection and** [^{11}C]PHNO administration. **Additional PK samples will be collected through direct venipuncture or a** second catheter will be placed in the opposite forearm or antecubital vein ~~for blood PK collections~~.

Rationale for Change: The PET procedure was clarified.

Change 7: Following discharge from Confinement Period 2, subjects will return to the site for pharmacokinetic (PK) and safety assessments after 7 ±2 days, and then return for approximately 3 Follow-up safety and PK assessment Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's maximum observed plasma concentration (C_{max}).

The primary change occurs in Section 6.2.1 Study Design:

Initial wording:	The preliminary PK data from Study TAK-041-1001 indicate that TAK-041 has a mean terminal elimination half-life of approximately 11 days. Therefore, a fixed-order study design wherein TAK-041 is administered in Confinement Period 2 only is appropriate (see Figure 6.a, Study Schematic). For the same reason, after discharge from Confinement Period 2, subjects will return to the study site for weekly Follow-up Visits to assess safety and PK until TAK-041 plasma concentrations are below LLOQ.

Amended or new wording:	The preliminary PK data from Study TAK-041-1001 indicate that TAK-041 has a mean terminal elimination half-life of approximately 11 days. Therefore, a fixed-order study design wherein TAK-041 is administered in Confinement Period 2 only is appropriate (see Figure 6.a, Study Schematic). ~~For the same reason, after discharge from Confinement Period 2, subjects will return to the study site for weekly Follow-up Visits to assess safety and PK until TAK-041 plasma concentrations are below LLOQ.~~ **Subjects in the TAK-041-1001 study who received single doses of 20 and 40 mg TAK-041 were followed approximately weekly until the plasma concentrations of TAK-041 were <1 ng/mL (up to 146 days) and there were no clinically significant safety issues. Subjects in this study who receive TAK-041 will be monitored monthly until the concentration of TAK-041 in plasma is <5% of the subject's C_{max}. Following discharge from Confinement Period 2, subjects will return to the site for PK and safety assessments after 7 ±2 days, and then return for approximately 3 Follow-up Visits (once every 4 weeks) or until the concentration of TAK-041 in plasma is <5% of the subject's C_{max}.**

Rationale for Change: Results from the FIH study TAK-041-1001 with both 20 and 40 mg single doses indicated that the 11-day half-life of TAK-041 did not present safety concerns. Therefore, it is possible to maintain safety while reducing the number of follow-up visits and the duration of follow-up.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1 Study Design
- Section 6.1.1 Dose Decisions, Figure 6.a Schematic of Study Design, footnote (b).
- Section 9.4 Blood Volume, Table 9.f Approximate Blood Volume, footnote (a).
- Appendix A Schedule of Study Procedures, footnote (e).

Change 8: At the end of each Follow-up Visit, the next visit will be scheduled ~4 weeks later. If, when the PK results are available, the subject's PK was <5% of their C_{max} value, the site and subject will be informed that their next scheduled visit will be considered their Study Exit/Final Visit.

The primary change occurs in Section 6.1 Study Design:

Initial wording:	Study Exit/Final Visit Day 62 (±4 days): Subjects will return to CCI 12 to 16 days after the last weekly safety and PK Follow-up Visit for final safety assessments (see Section 9.3.3 and Appendix A). Subjects who prematurely discontinue the study will have the same assessments on their last day in the study, if possible.
Amended or new wording:	Study Exit/Final Visit ~~Day 62 (±4 days)~~: ~~Subjects will return to~~ CCI ~~12 to 16 days after the last weekly safety and PK Follow-up Visit for final safety assessments~~ **At the end of each Follow-up Visit, the next visit will be scheduled approximately 4 weeks later. If, when the PK results are available, the subject's PK was <5% of their C_{max} value, the site and subject will be informed that their next scheduled visit will be considered their Study Exit/Final Visit** (see Section 9.3.3 and Appendix A). Subjects who prematurely discontinue the study will have the same assessments on their last day in the study, if possible.

Rationale for Change: Rather than scheduling an additional visit for the Final Visit, the time between follow-up visits is sufficient to have received the PK results so that subjects and sites can be informed in advance to change the next scheduled follow-up visit to a Final Visit.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1.1 Dose Decisions, Figure 6.a Schematic of Study Design, footnote (c).
- Section 6.2.1 Study Design.
- Section 9.4 Blood Volume, Table 9.f Approximate Blood Volume, footnote (b).
- Appendix A Schedule of Study Procedures, footnote (e).

Change 9: Discrepancies between clinical laboratory tests listed in Table 9.b and Appendix A were resolved:

a) Leukocytes were removed from urinary analysis.

b) Diagnostic Screening tests were clarified and inconsistencies corrected.

The primary changes occur in Section 9.1.9 Procedures for Clinical Laboratory Samples, Table 9.b Clinical Laboratory Tests:

a) Initial wording:	Under Urinalysis column/ Microscopic Analysis^ : Leukocytes/WBC/high power field ^To be performed if abnormal for blood, protein, nitrite or leukocyte esterase
Amended or new wording:	Under Urinalysis column/ Microscopic Analysis^ : ~~Leukocytes/WBC/high power field~~ ^To be performed if abnormal for blood, protein, **or** nitrite ~~or leukocyte esterase~~
b) Initial wording:	**Diagnostic Screening:** **Serum** Hepatitis panel, including HBsAg, anti-HIV, and anti-HCV TSH 5'-nucleotidase
Amended or new wording:	**Diagnostic Screening:** **Serum** Hepatitis panel **(including HBsAg,** ~~anti-HIV,~~ **and anti-HCV), HIV,** TSH, and 5'-nucleotidase

Rationale for Change: Corrected mistakes in the table and Appendix A.

The following sections also contain this change:

- Section 9.3.1 Screening
- Appendix A Schedule of Study Procedures

Change 10: The duration for collection of treatment-emergent adverse events (TEAEs) was changed.

The primary change occurs in Section 10.2.1.1 PTE and AE Collection Period:

Initial wording:	Collection of AEs will commence from the time that the subject is first administered [^{11}C]PHNO. Routine collection of AEs will continue through the Follow-up Visit.
Amended or new wording:	Collection of AEs will commence from the time that the subject is first administered [^{11}C]PHNO. Routine collection of AEs will continue through the ~~Follow-up Visit~~ **Study Exit/Final Visit**.

Rationale for Change: To correct the protocol text.

Section 13.1.4 Safety Analysis also contains this change.

Change 11: Names and credentials of the signatory clinical pharmacologist and statistician for this study were updated.

The change occurs in Section 1.2 Approval:

Initial wording:	PPD
Amended or new wording:	PPD

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical VP Approval	22-Feb-2017 14:52 UTC
	Clinical Pharmacology Approval	22-Feb-2017 18:05 UTC
	Clinical Approval	23-Feb-2017 03:45 UTC
	Biostatistics Approval	23-Feb-2017 13:00 UTC