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

SAP Approve Date: 19 May 2017

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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.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-041-1002

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

PHASE 1

Version: Final

Date: 19 May 2017

Prepared by:

PPD

Based on:

Protocol Version: Amendment 02

Protocol Date: 21 February 2017

1.1 Approval Signatures

Study 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

Approvals:

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3.0 LIST OF ABBREVIATIONS

%CV	percent coefficient of variation
[^{11}C]PHNO	radiolabeled dopamine D2 ligand
ADaM	Analysis Data Model
AE	adverse event
ALT	alanine aminotransferase
AMPH	amphetamine
aPTT	activated prothrombin time
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
BP_{ND}	nondisplaceable binding potential
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	conventional units
D2/D3	dopamine-2 and -3
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
GGT	γ-glutamyl transferase
CCI	[redacted]
ICH	International Conference on Harmonization
INR	international normalized ratio
LLN	lower limit of normal
LLOQ	lower limit of quantitation
NCS	not clinically significant
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
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
PK	pharmacokinetics
PT	preferred term
PT	prothrombin
PTE	pretreatment event

QTcB	QT interval corrected with the Bazett correction method
QTcF	QT interval corrected with the Fridericia correction method
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	international system of units
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum observed plasma concentration
ULN	upper limit of normal
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objective

To determine brain penetration of single oral doses of TAK-041 and its effects on amphetamine (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.

4.2 Secondary Objective

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

4.3 Additional Objectives

CCI [redacted]

4.4 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 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 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 will occur at the CCI [redacted]. 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 will 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 maximum observed plasma concentration (C_{max}).

Amphetamine tablets will be provided as the commercial product dexamfetamine sulphate [1] with the manufacturer's original label, and will be sourced locally by the study site. 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 to allow an informative evaluation of TAK-041 coadministered with amphetamine. 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 level 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 [2, 3].

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 in the protocol [4].

CCI [redacted]

CCI [redacted]

Each subject will report to CCI [redacted] on approximately 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 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 on Day 2; discharge on Day 3, the day following the postdose [^{11}C]PHNO PET imaging. All subjects will undergo a single predose [^{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 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 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 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} (see Section 9.3.2 in the protocol [4]).
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 plasma PK concentration value 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 in the protocol [4]). Subjects who prematurely discontinue the study will have the same assessments for Study Exit/Final Visit performed on their last day in the study, if possible.

A schematic of the study design is shown in Figure 4.a.

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.

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

Figure 4.a Schematic of Study Design

Screening	Confinement Period 1				Interval (a)	Confinement Period 2			Follow-up Visits (b)	Study Exit/Final Visit ET(c)
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)	
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 of the protocol [4] 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.

4.4.1 Dose Decisions

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

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% 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.

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 to. 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.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

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

The primary endpoint will be collected, analyzed, and processed by an outside vendor. No analyses are planned on these measures as part of this statistical analysis plan (SAP).

5.2 Secondary Endpoint

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

The secondary endpoint will be collected, analyzed, and processed by an outside vendor. No analyses are planned on these measures as part of this SAP.

5.3 Exploratory/Additional Endpoints

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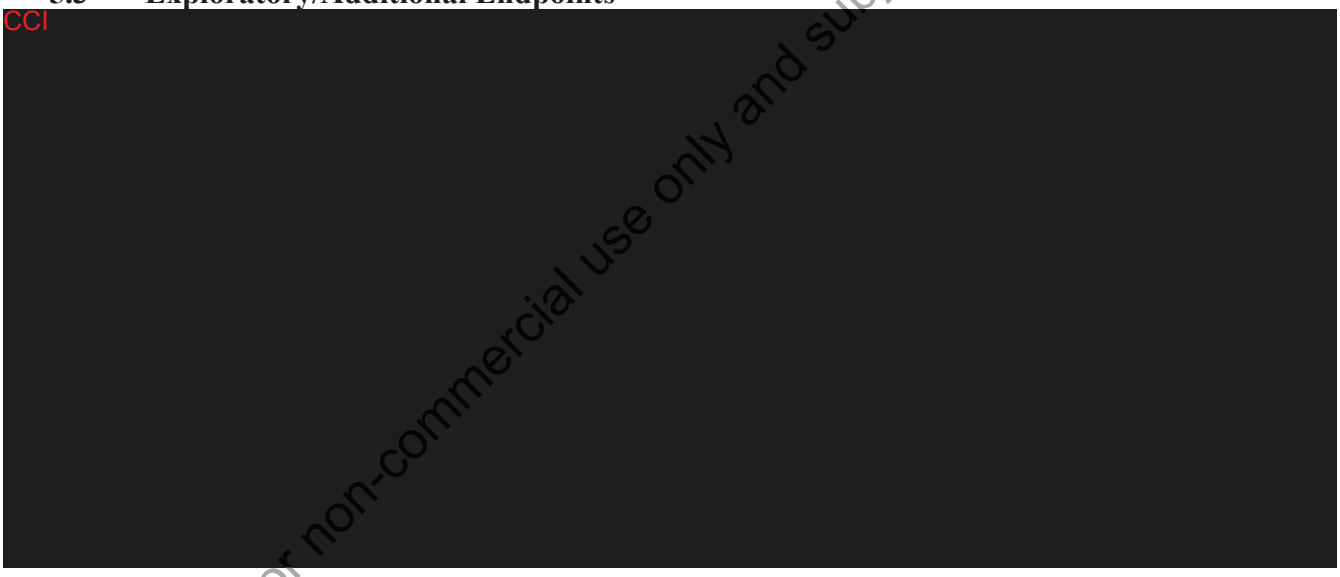

6.0 DETERMINATION OF SAMPLE SIZE

Using previously reported data [5], 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 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%.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This SAP was developed based on International Conference on Harmonization (ICH) E3 and E9 Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRF). This version of the SAP was developed using the information provided in Protocol TAK-041-1002, amendment 02, dated 21 February 2017 [4].

All study-related raw data, including derived data, will be presented in data listings. Continuous data will be summarized using: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data. SDs will be presented to 2 more decimal places than the recorded data.

PET, MRI, and wearable device data collected on the eCRF will be included in listings. PET, MRI, and wearable device data collected by outside vendors will not be listed. All other study related raw and derived data for enrolled subjects will be presented in listings.

All data analyses will be generated using SAS System® Version 9.2 or higher.

7.1.1 Conventions for Missing Data

There will be no imputation of incomplete or missing data. Decisions regarding inclusion or exclusion of data from an analysis for subjects who are noncompliant with the dose schedule, or who have incomplete data, will be made on a case-by-case basis, but the data will be presented in data listings regardless.

Plasma concentrations that are below the lower limit of quantitation (LLOQ) will be treated as zero in the summarizing of concentration values and deriving of PK parameters. These values will be flagged in the data listings, and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

7.1.2 Definition of Study Days and Baseline

Study Day 1 is defined as the date of the first dose of [^{11}C]PHNO PET tracer. Study days prior to the first dose of [^{11}C]PHNO will be calculated as: {date of assessment/event - date of first dose of [^{11}C]PHNO}. Study days on or after the first dose of [^{11}C]PHNO will be calculated as: {date of assessment/event - date of first dose of [^{11}C]PHNO + 1}.

Day within a period is relative to the date of first dose of study drug ([^{11}C]PHNO, AMPH, or TAK-041) in each confinement period.

Study baseline is defined as the last observed value prior to the first administration of study drug ([^{11}C]PHNO, AMPH, or TAK-041).

7.1.3 Derived Datasets and Variables

Derived datasets will be generated according to Clinical Data Interchange Standards Consortium (CDISC) guidance documents: Analysis Data Model (ADaM) Implementation Guide, Version 1.0 or higher.

7.2 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data.

Safety Set

The safety set will consist of all subjects who are enrolled and receive a dose of study drug ([^{11}C]PHNO, AMPH, or TAK-041) 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 either AMPH or TAK-041 and have at least 1 measurable plasma concentration for AMPH or TAK-041.

7.3 Disposition of Subjects

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

Disposition of screen failure subjects including the primary reasons for failure (i.e., pretreatment event (PTE)/AE, significant protocol deviation, lost to follow-up, voluntary withdrawal, study termination, did not meet entrance criteria, or other) will be presented in a data listing.

Disposition of all enrolled subjects will be tabulated by TAK-041+AMPH dose combination and overall. Categories will include:

- All subjects dosed (denominator).
- Subjects who were enrolled but not dosed, if applicable.
- Subjects who completed all study drugs.
- Subjects who prematurely discontinued study drugs.
- Subjects who completed all study visits.
- Subjects who prematurely discontinued study visits.

Primary reasons for discontinuation of study drugs and/or study visits, as entered on the eCRF, will be tabulated. Reasons for discontinuation include PTE/AE, significant protocol deviation, lost to follow-up, voluntary withdrawal, study termination, and other.

Disposition information for enrolled subjects, including study drug dose level, date of first dose of study drug, date and study day of last dose of study drug, date and study day of last visit, and reason for premature discontinuation of study drugs/study visits (if applicable), will be listed. A

listing of inclusion/exclusion criteria not met will be provided for enrolled subjects who did not meet at least one entrance criterion.

Significant protocol deviations captured on the eCRF will be listed.

7.4 Demographic and Other Baseline Characteristics

Demographic data will be summarized by assigned TAK-041+AMPH dose combination and overall. Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (e.g., age at informed consent, height (cm) at screening, weight (kg) at baseline, and body mass index (BMI, kg/m^2) at screening). The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (e.g., gender, race, smoking history, alcohol history, and caffeine consumption) will also be tabulated. Individual subject demographic and baseline characteristics data will be listed by site and subject number.

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

Race will be recorded on the eCRF as American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. Subjects who identify themselves as belonging to more than 1 race on the eCRF will be classified as multiracial for summaries and each race selected will be listed.

There will be no inferential analysis of demographic and baseline characteristics.

7.5 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Concurrent medical conditions are defined as significant conditions or diseases ongoing or present at signing of informed consent.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 19 or higher) coding system.

All medical history and concurrent medical condition data will be listed by site and subject number. The listing will contain subject identifier, study drug dose level, system organ class (SOC), preferred term (PT), and a detail of the medical history or concurrent condition.

There will be no inferential analysis of medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent. Concomitant medications include any medications, other than study drug, taken at any time between informed consent and the end of the study.

Medication history and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHOD h 2016 Enhanced or higher.

All medication history and concomitant medications will be listed by site and subject number. The listings will contain subject identifier, study drug dose level, WHODrug preferred medication name, dose, unit, frequency, route, start date, stop date, whether the medication was ongoing, and reason for use.

There will be no inferential analysis of medication history and concomitant medications.

7.7 Study Drug Exposure and Compliance

The date and time of each study drug ([^{11}C]PHNO, AMPH, or TAK-041) for each subject will be reported in the data listing. Listings and descriptive statistics of PK plasma concentrations for AMPH and TAK-041will be provided for all subjects. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Serial blood samples for determination of AMPH and TAK-041 will be collected according to Figure 7.a.

Figure 7.a 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	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 has been administered. All PK summaries and analyses will be based on the PK set.

Concentrations of AMPH and TAK-041 in plasma will be summarized by dose level over each scheduled sampling time point using descriptive statistics (n, arithmetic mean, SD, %CV, median, minimum, and maximum). Individual plasma concentration data versus time will be presented in a data listing.

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

The need of using the plasma concentrations collected from this study in a PK analysis will be evaluated. If deemed appropriate, a PK analysis plan will be prepared and address the planned analysis.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

PET, MRI, and wearable device data collected on the eCRF will be included in listings.

The imaging analysis (PET and MRI) will be conducted by an outside vendor and are not included in this SAP.

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7.11 Safety Analysis

The safety endpoints including AEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG parameters will be summarized and described in data listings. The Safety Set will be used for all summaries of safety parameters. Physical examination and C-SSRS will be described in data listings.

7.11.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an AE or a serious AE that occurs or gets worse after receiving the first study drug ([^{11}C]PHNO, AMPH, or TAK-041) and until Study Exit/Final Visit. A PTE is defined as any untoward medical occurrence occurs prior to first study drug ([^{11}C]PHNO, AMPH, or TAK-041).

PTE and TEAE verbatim reported terms will be coded by SOC and PT using MedDRA (version 19 or higher) coding system.

TEAEs will be listed and included in the summary tables. TEAEs will be summarized by assigned TAK-041+AMPH dose combination and overall. For each TAK-041+AMPH dose combination, TEAE will be summarized by [^{11}C]PHNO Alone (Period 1 Day 1 after the dosing of [^{11}C]PHNO tracer and before the dosing of AMPH on Day 2 of Period 1), AMPH Alone (Period 1 Day 2 after the dosing of AMPH and before the dosing of the tracer), AMPH+[^{11}C]PHNO (after the tracer administration on Day 2 of Period 1 and before the TAK-041 administration on Day 1 of Period 2), TAK-041 Alone (Period 2 Day 1 after the TAK-041 dosing and before the dosing of AMPH), TAK-041+AMPH (Period 2 Day 1 after the dosing of AMPH and before the dosing of tracer), and TAK-041+AMPH+[^{11}C]PHNO (Period 2 Day 1 after the tracer administration to Study Exit/Final Visit) according to time of onset, and the Entire Study (after the first dose of study drug and until Study Exit/Final Visit).

In general, TEAEs will be tabulated at the following levels: overall summary (subjects with at least 1 AE), by the MedDRA SOC and the MedDRA PT. The tables will include the number and percentage (N [%]) of subjects. The following summary tables will be generated:

- Overview of Treatment-Emergent Adverse Events.
- Treatment-Emergent Adverse Eve Class and Preferred Term.

- Treatment-Emergent Adverse Events by Preferred Term, sorted by the frequency of the overall summary from the most to the least.
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

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

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE with maximum intensity or strongest relationship will be included in the summary.

For TEAE summaries by treatment interval ([11C]PHNO Alone, AMPH Alone, AMPH+[11C]PHNO, TAK-041 Alone, TAK-041+AMPH, and TAK-041+AMPH+[11C]PHNO), subjects reporting more than one occurrence within a treatment interval for the term (level) being summarized will be counted only once for that interval using the most extreme incident (most severe for the severity tables and related for the relationship to study drug tables). For summaries by Entire Study, subjects reporting more than one occurrence during the Entire Study for the term (level) being summarized will be counted only once using the most extreme incident (most severe for the severity tables and related for the relationship to study drug tables).

AEs with missing intensity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. If the relationship of an event is missing, the relationship for the event will be considered to have been related.

Data listings will be provided for TEAEs and PTEs.

7.11.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include hematology, chemistry, urinalysis, and diagnostic screening. Please refer to Table 9.b in the protocol [4] for a list of all clinical laboratory tests.

All laboratory test parameters will be displayed in individual subject data listings in both International System of Units (SI) and conventional units (CV). For test results not in SI units, the conversion to SI units will be done in derived analysis data sets using the known conversion

factors. All summaries and analyses will be based on the values using SI units unless otherwise stated.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of clinical laboratory tests for baseline, post-baseline, and change from baseline to each post-baseline visit will be presented by assigned TAK-041+AMPH dose combination and overall for Confinement Period 1 and Confinement Period 2 through Study Exit. Baseline is defined as the last observed value prior to the first administration of study drug ([^{11}C]PHNO, AMPH, or TAK-041). Unscheduled laboratory assessments will be excluded from the summary statistics unless it is for the baseline derivation. Note that urinalysis tests with character results, such as protein and nitrite, will only be listed. No inferential statistics will be presented.

Individual results for hematology and chemistry laboratory tests that meet the Takeda predefined laboratory markedly abnormal value (MAV) criteria in Appendix A will be indicated in the data listing. If a subject has a MAV for a particular laboratory test, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-baseline markedly abnormal laboratory test result will be summarized by TAK-041+AMPH dose combination and overall. The mapping of the subjects who meet the MAV criteria will be listed as a table by TAK-041+AMPH dose combination and overall. All observations, including ones at unscheduled visits, will be included in the MAV mapping and summaries.

All clinical laboratory data will be listed. The listing will include site number, subject identifier, age (at informed consent), gender, study drug dose level, study visit, and sample collection date. Laboratory data outside of the normal reference range will be indicated in the data listing. In addition, MAVs will be flagged.

7.11.3 Vital Signs

Vital sign parameters include oral body temperature, blood pressure, respiratory rate, pulse, and weight. Pulse and blood pressure will be measured after 5 minutes supine. Orthostatic pulse and blood pressure will be measured after standing for 2 minutes. Please refer to Table 9.a in the protocol [4] for schedules of vital sign assessments.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of vital sign parameters for baseline, post-baseline, and change from baseline to each post-baseline visit will be summarized by TAK-041+AMPH dose combination and overall by scheduled time point. Baseline is defined as the last observed value prior to the first administration of study drug ([^{11}C]PHNO, AMPH, or TAK-041). Unscheduled vital sign assessments will be excluded from the summary statistics unless it is for the baseline derivation. No inferential statistics will be presented.

Individual results for vital sign measurements that meet the Takeda predefined vital signs MAV criteria in Appendix B will be indicated in the data listing. If a subject has a MAV for a particular vital sign parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-baseline markedly abnormal vital sign measurement will be summarized by TAK-041+AMPH dose combination and overall. The mapping of the subjects who meet the listed as a table by TAK-

041+AMPH dose combination and overall. All observations, including ones at unscheduled visits, will be included in the MAV mapping and summaries.

Orthostatic hypotension, identified by the criteria defined in Appendix C, will be calculated at every time point where standing and supine measurements are available using the formula: standing vital measurement - supine vital measurement. The mapping of the subjects who meet the criteria for orthostatic hypotension will be listed as a table by TAK-041+AMPH dose combination and overall. All orthostatic hypotension observations, including ones at unscheduled visits, will be included in the subject mapping.

All vital sign data will be presented in the data listing. The listing will include site number, subject identifier, age (at informed consent), gender, study drug dose level, study visit, and sample collection date. Vital sign MAVs will be flagged.

7.11.4 12-Lead ECGs

ECG parameters include heart rate, PR interval, RR interval, QRS interval, QT interval, QT interval corrected with the Bazett correction method (QTcB), and QT interval corrected with the Fridericia correction method (QTcF). Please refer to Table 9.c in the protocol [4] for schedules of ECG assessments.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) of ECG parameters for baseline, post-baseline, and change from each baseline to each post-baseline visit will be summarized by TAK-041+AMPH dose combination and overall by scheduled time point. Baseline is defined as the last observed value prior to the first administration of study drug ([^{11}C]PHNO, AMPH, or TAK-041). Only the scheduled measurements will be included in the summary unless it is for the baseline derivation. No inferential statistics will be presented.

Individual results for 12-lead ECG measurements that meet the Takeda predefined 12-lead ECG MAV criteria in Appendix D will be indicated in the data listing. If a subject has a MAV for a particular ECG parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-baseline markedly abnormal 12-lead ECG measurement will be summarized by TAK-041+AMPH dose combination and overall. The mapping of the subjects who meet the MAV criteria will be listed as a table by TAK-041+AMPH dose combination and overall. All observations, including ones at unscheduled visits, will be included in the MAV mapping and summaries.

Overall ECG interpretation category (within normal limits, abnormal not clinically significant [NCS], abnormal clinically significant [CS]) is collected in the eCRF at each scheduled visit. Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal NCS, and abnormal CS interpretations with missing, if applicable, and total categories by TAK-041+AMPH dose combination and overall by scheduled time point. Baseline is defined as the last observed value prior to the first administration of study drug ([^{11}C]PHNO, AMPH, or TAK-041). Unscheduled ECG assessments will be excluded unless it is for the baseline derivation.

All ECG data will be presented in the data listing. The listing will include site number, subject identifier, age (at informed consent), gender, study drug dose level, study visit, and sample collection date. ECG MAVs will be flagged.

7.11.5 Other Observations Related to Safety

Physical examination findings and C-SSRS will be presented in data listings. No summary tables will be provided.

7.12 Interim Analysis

No formal interim analysis is planned.

7.13 Changes in the Statistical Analysis Plan

Analyses described in the statistical analysis plan do not differ from those specified in the protocol.

8.0 REFERENCES

1. Dexamfetamine sulphate 5 mg tablets. Summary of Product Characteristics. Middlesex, UK: Auden Mckenzie (Pharma Division) Ltd, Revised 16 November 2015.
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3. Weidner LD, Paris A, Frankle WG, Narendran R. Safety of oral amphetamine administered during positron emission tomography scans in medically screened humans. PLoS One 2015;10(12):e0140647.
4. 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. Takeda Development Center Europe, Ltd., Protocol No. TAK-041-1002, Amendment 02, dated 21 February, 2017.
5. Shotbolt P, Tziortzi AC, Searle GE, Colasanti A, van der Aart J, Abanades S, et al.Within-subject comparison of [^{11}C]-(+)-PHNO and [^{11}C]raclopride sensitivity to acute amphetamine challenge in healthy humans. J Cereb Blood Flow Metab 2012;32(1):127-36.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	<0.8 × LLN	>1.2 × ULN
Hematocrit	Both	<0.8 × LLN	>1.2 × ULN
RBC count	Both	<0.8 × LLN	>1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional	<75 x 10^3/μL	>600 x 10^3/μL
	SI	<75 x 109/L	>600 x 109/L
PT/INR	Both	--	>1.5 × ULN
aPTT	Both	--	>1.5 × ULN

aPTT= activated prothrombin time, INR=international normalized ratio, LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell, PT=prothrombin

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Chloride	Conventional	<75 mEq/L	>126 mEq/L
	SI	<75 mmol/L	>126 mmol/L
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Direct bilirubin	Both	--	>2 ULN
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI	--	>177 μmol/L
Blood urea nitrogen	Conventional	--	>30 mg/dL
	SI	--	>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
CPK	Both	--	>5x ULN
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Creatine kinase	Conventional	--	>5 × ULN
	SI	--	>5 × ULN
Bicarbonate	Conventional	<8.0 mEq/L	--
	SI	<8.0 mmol/L	--
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CPK=creatine phosphokinase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN

Appendix B Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	°C	<35.6	>37.7

Appendix C Criteria for Identification of Markedly Abnormal Orthostatic Changes

Parameter	Criteria
Orthostatic Hypotension	(Orthostatic Systolic Blood Pressure <-20 mm Hg OR Orthostatic Diastolic Blood Pressure <-10 mm Hg) AND Heart Rate Increase >20 beats/min

Note: Orthostatic measurement = standing vital measurement - supine vital measurement.

Appendix D Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	≤80 milliseconds	≥200 milliseconds
QT Interval	≤300 milliseconds	≥460 milliseconds
QTcB Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QTcF Interval	≤300 milliseconds	≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤80 milliseconds	≥180 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	19-May-2017 19:47 UTC
	Statistical Approval	19-May-2017 21:06 UTC
	Clinical Pharmacology Approval	20-May-2017 00:58 UTC
	Pharmacovigilance Approval	23-May-2017 19:50 UTC
	Clinical Approval	25-May-2017 19:03 UTC