Title: Randomized, Double-Blind, Placebo-Controlled, Phase 1, Ascending Oral Single and Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-041 in Healthy Subjects and Subjects with Stable Schizophrenia and a Randomized Open-Label, Single Dose, Parallel Design to Evaluate the Relative Bioavailability and Effect of Food on the Pharmacokinetics of TAK-041 Tablet Formulation in Healthy Subjects

NCT Number: NCT02748694

SAP Approve Date: 27 March 2019

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information 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.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-041-1001

A Randomized, Double-Blind, Placebo-Controlled, Phase 1, Ascending Oral Single and Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-041 in Healthy Subjects and Subjects with Stable Schizophrenia and a Randomized Open-Label, Single Dose, Parallel Design to Evaluate the Relative Bioavailability and Effect of Food on the Pharmacokinetics of TAK-041 Tablet Formulation in Healthy Subjects

Phase 1 TAK-041 First-in-Human Safety, Tolerability, and Pharmacokinetics Study

Version: Final

Date: 27 March 2019

Prepared by: PPD

Based on: Protocol Version: TAK-041-1001, Amendment 5

Protocol Date: 03 June 2018

1.1 Approval Signatures

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

Takeda Approvals:

PPD

Date

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

λ_z	terminal elimination rate constant
%CV	percent coefficient of variation
AE	adverse event
Ae_t	Total amount of drug excreted in urine from time 0 to time t.
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the plasma concentration-time curve from time 0 to infinity
AUClast	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUCτ	area under the plasma concentration-time curve during a dosing interval
CCI	[redacted]
BL-VAS	Bond-Lader Visual Analogue Scale
BMI	body mass index
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
CI	confidence interval
CL_R	Renal clearance, calculated as Ae/AUC_{inf} for single dose
CL/F	Apparent clearance after extravascular administration, calculated as $Dose/AUC_{inf}$
C_{max}	maximum observed plasma concentration
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
CCI	[redacted]
eGFR	estimated glomerular filtration rate
ET	early termination
fe	fraction of drug excreted in urine
FIH	first-in-human
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
MI	multiple imputation
MRD	multiple-rising dose
NOAEL	no observed adverse effect level
PANSS	Positive and Negative Syndrome Scale

PD	pharmacodynamics
PK	pharmacokinetic
PTE	pretreatment event
QD	once daily
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SRD	single-rising dose
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
t_{max}	time to reach C_{max}
V_z/F	apparent volume of distribution during the terminal phase after extravascular administration

4.0 OBJECTIVES

4.1. Primary Objective

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of TAK-041
  - Following oral single and multiple doses in healthy subjects (Parts 1, 2, and 3).
  - As add-on therapy to antipsychotics in subjects with stable schizophrenia (Part 4).
- To assess the oral bioavailability in healthy subjects of TAK–041 administered as a 40 mg immediate release tablet formulation in the fasted state compared to 40 mg oral suspension formulation in the fasted state (Part 3).
- To assess the effect of food on the pharmacokinetics (PK) of 40 mg immediate release tablet formulation of TAK–041 in healthy subjects (Part 3).

4.2. Secondary Objective

To evaluate the PK of TAK-041

- Administered under fasting conditions following oral single and multiple doses in healthy subjects (Parts 1 and 2).
- As add-on therapy to antipsychotics in subjects with stable schizophrenia (Part 4).

4.3. Exploratory Objectives

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4.4. Study Design

4.4.1. Overview

This is a phase 1, first-in-human (FIH), randomized, placebo-controlled, double-blind study to evaluate the safety, tolerability, and PK of TAK-041.

The study is composed of 4 parts: Part 1 is a single-rising dose [SRD] study in healthy subjects, with an alternating panel design (Cohorts 1 and 2) and a sequential panel design (Cohorts 3 to 5), Part 2 is a multiple-rising dose [MRD], sequential panel design in healthy subjects (Cohorts 1 to 4), Part 3 is a randomized, open-label single-dose, parallel design to evaluate the relative bioavailability and food effect on the PK of the TAK-041 immediate release tablet formulation in healthy subjects, Part 4 is a single weekly dosing cohort in subjects with stable schizophrenia.

For Part 1, Cohorts 1 and 2, dose escalation and subsequent dose levels will be determined following a full blinded review of all available safety, tolerability, and PK data from the previous dose level. For Part 1, Cohorts 3 to 5, and all cohorts in Part 2, dose escalation and subsequent dose levels will be based on a sponsor review of at least 21 days of safety, tolerability, and available PK data from the previous dose levels. For Part 3, the subjects will receive a single 40 mg dose of the tablet formulation of TAK-041 (1 x 40 mg tablet) based on safety/tolerability of the same dose in healthy subjects from Part 1 and Part 2. For Part 4, the dose selected will not exceed the highest dose evaluated, deemed safe, and well tolerated in Part 2. The proposed weekly maintenance dose will have a predicted mean average concentration during a dosing interval, at steady state (Cav,ss) below the Cav,ss observed at the no-observed-adverse-effect-level (NOAEL) dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study.

Approximately equal numbers of male and female subjects will be enrolled at each dose level. TAK-041 and matching placebo will be administered as an oral suspension in Parts 1, 2, and 4 and as an immediate-release tablet formulation in Part 3.

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4.4.2. Part 1 Single-Rising Dose: Healthy Subjects

Part 1 will have 5 cohorts to evaluate dose escalation. Cohorts 1 to 5 will have 8 subjects per cohort (6 active: 2 placebo). Cohorts 1 and 2 will participate in a 2-period, alternating-panel, double-blind study design to evaluate single-rising doses of TAK-041 (5, 10, 20, and 40 mg) or matched placebo with a washout period of at least 7 days between treatment periods (Table 4.a). As of Amendment 04, after review of the data from these initial cohorts, Cohorts 3, 4, and 5 will participate in a sequential-panel, double-blind study design to evaluate single-rising doses of TAK-041 or matched placebo. This is a double-blind study; therefore, the subject, the trial site personnel, and the Sponsor staff who are involved in the treatment or clinical evaluation are blinded to treatment or intervention. Certain Sponsor staff not directly involved with the treatment or evaluation maybe unblinded to the treatment or intervention. The planned dose levels of TAK-041 to be evaluated in Cohorts 3, 4, 5 are 80, 120, and 160 mg, respectively (Table 4.a).

As this is an FIH study, a sentinel group will be used for Part 1 Cohort 1 Period 1 (with the initial 2 subjects receiving either active drug or placebo [1:1]) to ensure adequate safety and tolerability prior to dosing TAK-041 to the remaining subjects in this cohort. In Part 1 Cohort 1 Period 1, the remaining 6 subjects will be dosed following a review of 24-hour postdose safety and tolerability data and will only occur following agreement between the investigator and Takeda. The dose administered for subsequent cohorts will be based on a minimum of 21 days of emerging safety, tolerability, and available PK data from the previous cohorts (see schematic of study design below). The highest planned dose is predicted to have Cmax and AUC_{24} values below the corresponding exposure observed at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study. Sentinel dosing may be used for additional cohorts if determined to be necessary based on the emerging safety, tolerability, and available PK data from the preceding cohorts.

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Bond-Lader visual analog scales (BL-VAS) will be performed in Part 1, Day -1, Day 1 at 1, 3, 8, and 24 hours postdose, Day 5, and (if applicable) and at Early Termination.

A schematic of the Part 1 study design is shown in Table 4.a.

Table 4.a Part 1: Study Design

Part 1 (SRD)	Number of Subjects	Period 1 (a)	Washout Period (at least 7 days)	Period 2 (b)
Cohort 1 (n=8), fasted	6	TAK-041 5 mg		TAK-041 20 mg
	2	Placebo		Placebo

Cohort 2 (n=8), fasted	6	TAK-041 10 mg	TAK-041 40 mg
	2	Placebo	Placebo
Cohort 3 (n=8), fasted	6	TAK-041 80 mg	
	2	Placebo	
Cohort 4 (n=8), fasted	6	TAK-041 120 mg	
	2	Placebo	
Cohort 5 (n=8), fasted	6	TAK-041 160 mg	
	2	Placebo	

(a) Doses planned to be administered range from 5 to up to 160 mg. The actual doses administered after 80 mg will be based on emerging safety, tolerability, and PK data from the previous cohorts and may vary from the actual doses shown in the table above.
(b) Subjects will fast for at least 8 hours before dosing on Day 1.

Overall, Part 1 of the study will consist of a Screening Visit (Days -21 to -2), a predose Check-in Day for all subjects (Day -1) during which baseline assessments will be conducted, and a single oral dose administration (Day 1) when all subjects will undergo study-specific assessments. The total confinement period for each subject will be 5 days.

Subjects from Part 1 Cohorts 1 and 2 in each period will be required to remain in the study unit for at least 96 hours after dosing for safety, PK, and all study assessments before discharge. For subjects from Part 1 Cohorts 1 and 2 Period 2, the weekly follow-up safety and PK on-site visits will occur starting from 7 days after last dose administration until TAK-041 is not quantifiable in plasma. All subjects in the cohorts will be brought back in order to maintain the blind. Subjects from Part 1 Cohorts 3 to 5 will be required to remain in the study unit for 96 hours after dosing. For subjects from Part 1 Cohorts 3 to 5, the weekly follow-up safety and PK on-site visits will occur starting from Day 8 until 6 weeks after the dose. For subjects from Part 1 Cohorts 1 to 5, a final visit that completes the study will occur 12 to 16 days after the last weekly safety and PK Follow-up visit. The schedule for Part 1 is shown below.

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Table 4.b Part 1 Cohorts 1 to 2: Study Schedule for Each Period (Healthy Subjects)

Screening	Check-in	Dosing (a) Safety and PK Assessments	Safety and PK Assessments	Discharge	Weekly Follow-up Visits (b)	Final Visit (c)
Days -21 to -2	Day -1	Day 1	Days 2-5	Day 5	TBD (b)	Study Completion

(a) Subjects will fast for at least 8 hours before dosing on Day 1.
(b) Subjects will return to the site for weekly safety and PK Follow-up Visits, starting from 7 days after each Cohort's last treatment period until the plasma concentration of TAK-041 is below the limit of quantitation.
(c) The Final/Study Completion Visit will occur 12 to 16 days after the last weekly safety and PK Follow-up Visit.

Table 4.c Part 1 Cohorts 3 to 5: Study Schedule (Healthy Subjects)

Screening	Check-in	Dosing (a) Safety and PK Assessments	Safety and PK Assessments	Discharge	Weekly Follow-up Visits (b)	Final Visit (c)
Days -21 to -2	Day -1	Day 1	Days 2-5	Day 5	Days 8, 15, 22, 29, 36 and 43	Study Completion

(a) Subjects will fast for at least 8 hours before dosing on Day 1. Subjects will be allowed to eat 4 hours postdose.
(b) The Follow-up PK and safety assessments will occur weekly from 7 days until 6 weeks after the dose. All subjects will be brought back in order to maintain the blind. If abnormal, clinically significant findings are observed after discharge, subjects may be brought back to the study unit for re-evaluation per investigator's discretion.
(c) The Final/Study Completion Visit will occur 12 to 16 days after the last weekly safety and PK Follow-up Visit.

The schedule of procedures in Part 1 (healthy subjects) is shown in Appendix A of Protocol Amendment 5.

4.4.3. Part 2 Multiple-Rising Dose: Healthy Subjects

Part 2 will consist of a 4-cohort, sequential-panel, double-blind, weekly dosing, MRD design. To assess TAK-041 plasma exposure and potential accumulation in Part 2, subjects will receive an initial loading dose of TAK-041 on Day 1 followed by a maintenance dose that is half the initial dose on Days 8, 15, and 22 or will receive placebo on all study dosing days. Four dose cohorts are considered adequate to explore the pharmacologically active exposure range in healthy subjects. However, additional cohorts may be studied if deemed necessary to fully characterize the pharmacological exposure range. Each cohort will be composed of 8 subjects where 6 subjects will be randomized to receive TAK-041 and 2 subjects will be randomly assigned to receive matched placebo. The study population for Part 2 will be composed of a total of up to approximately 32 healthy subjects. Part 2 may commence only after 21 days of safety, tolerability, and available PK data have been collected from Part 1 Cohort 3.

The dose levels for Part 2 Cohorts 2 onwards will be based on emerging safety/tolerability and available PK data from Part 1 and from preceding cohorts in Part 2. Dose escalation and subsequent dose levels will be based on a sponsor review of at least 21 days of safety, tolerability, and available PK data from the previous dose regimen. The highest planned loading dose in Part 2 will not exceed the highest dose evaluated, deemed safe, and well tolerated in Part 1. The highest proposed weekly maintenance dose will have a predicted mean average concentration

during a dosing interval, at steady state (Cav,ss) below the Cav,ss observed at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study. The study schematic for Part 2 is shown in Table 4.d.

Table 4.d Part 2: Study Design (Healthy Subjects, Cohorts 1 to 4)

40 mg on Day 1 and 20 mg on Days 8, 15, and 22	80 mg on Day 1 and 40 mg on Days 8, 15, and 22	120 mg on Day 1 and 60 mg on Days 8, 15, and 22	160 mg on Day 1 and 80 mg on Days 8, 15, and 22
Cohort 1 (n=8; 6 active: 2 placebo)	**Cohort 2** (n=8; 6 active: 2 placebo)	**Cohort 3** (n=8; 6 active: 2 placebo)	**Cohort 4** (n=8; 6 active: 2 placebo)

Overall, for healthy subjects (Cohorts 1 to 4), Part 2 of the study will consist of a Screening Visit (Days -21 to -3), a predose Check-in Day for all subjects (Days -2) during which baseline assessments will be conducted, and multiple oral dose administrations (Days 1, 8, 15, and 22) when all subjects will undergo study-specific assessments.

Subjects from Part 2 Cohorts 1 to 4 will be required to remain in the study unit from Day -2 to Day 3 (48 hours after the first dose) for safety, PK, and all study assessments before discharge. Subjects will be required to return on Day 5 for a safety and PK assessment. Subjects will return on Day 7 to obtain safety laboratory tests before receiving the second dose on Day 8. Subjects will remain in the study unit from Day 7 to Day 10 (48 hours after the second dose). Subjects will return on Day 14 to obtain safety laboratory tests before receiving the third dose on Day 15. Subjects will remain in the study unit from Day 14 to Day 17 (48 hours after the third dose). Subjects will return on Day 21 to obtain safety laboratory tests before receiving the third dose on Day 22. Subjects will remain in the study unit from Day 21 to Day 24 (48 hours after the fourth dose). After discharge on Day 24, subjects will return to the clinic on Days 26, 29, 36, 43, 50, 57, and 64 for safety and PK follow up visits. For subjects from Part 2 Cohorts 1 to 4, a final visit that completes the study will occur 12 to 16 days after the last safety and PK follow-up visit. The schedule for Part 2 is shown below.

BL-VAS will be performed on Day -1; Days 1, 8, 15, and 22 at 1, 3, 8, and 24 hours postdose, Day 24, and (if applicable) at Early Termination.

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Table 4.e Part 2: Study Schedule (Healthy Subjects, Cohorts 1 to 4)

Screening	Check-in	Dose Administration (a, b, c)	Final Discharge	Follow-up Visits (d)	Final Visit (e)
Day -21 to -3	Day -2	Days 1, 8, 15, and 22	Day 24	Days 26, 29, 36, 43, 50, 57, 64	Study Completion

(a) Subjects will fast for at least 8 hours before dosing on Days 1, 8, 15, and 22. On all dosing days, subjects will be allowed to eat 4 hours postdose.
(b) Dosing on Days 8, 15, and 22 will be predicated on the review of safety laboratory results from samples obtained the day before (i.e., on Days 7, 14, and 21).
(c) Subjects will be required to remain in the study unit from Day -2 to Day 3, Day 7 to Day 10, Day 14 to Day 17, and Day 21 to Day 24.
(d) The Follow-up PK and safety assessments will occur until 6 weeks after the last dose. If abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the study unit for re-evaluation per investigator's discretion.
(e) The Final/Study Completion Visit will occur 12 to 16 days after the last safety and PK Follow-up Visit.

The Schedule of Procedures for Part 2 is shown in Appendix B of Protocol Amendment 5 (healthy subjects, Cohorts 1-4).

4.4.4. Part 3: Single Dose: Healthy Subjects Relative Bioavailability and Food Effect Study

Part 3 is a phase 1, randomized, open-label, single-dose, single-center, parallel design study. To evaluate the oral bioavailability of the recently developed TAK-041 tablet formulation relative to the oral suspension and effect of food on the PK of the tablet formulation, healthy subjects will be randomized to receive on Day 1 a single 40 mg dose of TAK-041 (as a single 40 mg tablet) after either at least 10-hours of overnight fast or 30 minutes after starting ingestion of a high-fat, high-calorie breakfast. Blood samples will be collected over 96 hours post-dose to measure TAK-041 plasma concentrations.

The cohort will be randomized where 9 subjects will receive TAK-041 in the fasted state and 9 subjects to receive in the fed state. The study population for Part 3 will be composed of approximately 18 healthy subjects randomized in a 1:1 ratio to receive TAK-041 in the fasted state or in the fed state. The study schematic for Part 3 is shown in Table 4.f.

Table 4.f Part 3: Study Design (Healthy Subjects)

Regimen	Number of Subjects	Dose
Fasted overnight minimum 10 hr	9	TAK-041 1x 40 mg Tablet Formulation
Fed high-fat high-calorie breakfast (a)	9	TAK-041 1x 40 mg Tablet Formulation

(a) Subjects randomized to the fed arm will be dosed 30 minutes after starting ingestion of a high-fat, high-calorie breakfast.

Subjects who satisfy the Screening evaluation and selection criteria may be enrolled in the study. On Day 1, eligible subjects will be randomized to receive TAK-041 as one 40 mg immediate release tablet administered orally after either an at least 10-hours of overnight fast (including no medications) or 30 minutes after starting ingestion of a high-fat, high-calorie breakfast (approximately 800-1000 calories with approximately 50% from fat), and will be required to remain in the study unit for at least an additional 48 hours after dosing for safety and PK, with additional visits for PK and safety assessments on Day 4 and 5 and a final Follow-up visit on Day 17-21. The schedule for Part 3 is shown in Table 4.g.

Table 4.g Part 3 Tablet Formulation / Food Effect Study Schedule (Healthy Subjects)

Pretreatment		Treatment Period			
Screening	**Check-in**	**Dosing and Study Assessments**	**Safety and PK Assessments**		**Follow up (a)**
Day -28 to -2	Day -1	Day 1	Days 1-3	Days 4-5	Study Day 19 (±2)
	◄----------	Confinement (b)	----------	►	

(a) The Follow-up Visit will occur 19 (±2) days post dose.
(b) Subjects will be released from confinement after Day 3 study assessments are complete.

Overall, for healthy subjects, Part 3 of the study will consist of a Screening Visit (Days -28 to -2), a predose Check-in Day for all subjects (Day -1) during which baseline assessments will be conducted, and a single oral dose administration (Days 1) following which all subjects will undergo study-specific assessments. Subjects from Part 3 will be required to remain in the study unit until a minimum 48 hours after the first dose for safety, PK, and study assessments before discharge. Subjects will be required to return to the study unit for safety and PK assessments, and for a final Follow-up visit that completes the study approximately 18 days after dosing. The schedule for Part 3 is shown in Appendix C of Protocol Amendment 5.

4.4.5. Part 4: Multiple Dose: Subjects with Schizophrenia

Part 4 will consist of a double-blind, weekly dosing, parallel group design. Twenty-four subjects with stable schizophrenia will be enrolled. The 24 subjects are considered adequate to explore the pharmacologically active exposure range in subjects with stable schizophrenia. The subjects will be randomly assigned to receive TAK-041 or placebo in a ratio of 2:1 (16 active and 8 placebo). Subjects will receive an initial loading dose of TAK-041 on Day 1 followed by a maintenance dose that will be half the initial dose on Days 8, 15, and 22 or will receive placebo on all study dosing days. Part 4 may commence only after at least 21 days of safety, tolerability, and available PK data have been collected at the equivalent dose cohort in healthy subjects in Part 2.

The dose level for Part 4 will be based on emerging safety/tolerability and available PK data of the same dose in healthy subjects from Part 2. Dose selection will be based on a sponsor review of at least 21 days of safety, tolerability, and available PK data from the preceding cohort. The highest planned loading dose in Part 4 will not exceed the highest dose evaluated, deemed safe,

and well tolerated in Part 2. Subjects in Part 4 will be administered a single TAK-041 loading dose or placebo on Day 1 and weekly maintenance doses on Days 8, 15 and 22.

Overall, Part 4 of the study will consist of a Screening Visit (Days -35 to -3), a predose Check-in Day for all subjects (Day -2) during which some baseline assessments will be conducted, Day -1 during which other baseline assessments will be conducted, and 22 days of treatment when all subjects will be dosed on Days 1, 8, 15, and 22 as well as undergoing all study-specific assessments. After 4 weeks of dosing, subjects will return for follow-up study-specific assessments on Days 26, 29, 36, 43, 50, 57, and 64.

Subjects will be required to remain in the study unit from Day -2 to Day 3 (48 hours after the first dose) for safety, PK, and all study assessments before discharge. Subjects will return on Day 5 for a safety and PK assessment. Subjects will return on Day 7 to obtain safety laboratory tests before receiving the second dose on Day 8. Subjects will remain in the study unit from Day 7 to Day 10 (48 hours after the second dose). Subjects will return on Day 14 to obtain safety laboratory tests before receiving the third dose on Day 15. Subjects will remain in the study unit from Day 14 to Day 17 (48 hours after the third dose). Subjects will return on Day 21 to obtain safety laboratory tests before receiving the third dose on Day 22. Subjects will remain in the study unit from Day 21 to Day 24 (48 hours after the fourth dose). After discharge on Day 24, subjects will return to the clinic on Days 26, 29, 36, 43, 50, 57, and 64 for safety and PK follow up visits. The final visit that completes the study will occur 12 to 16 days after the last safety and PK follow-up visit. The schedule for Part 4 is shown below.

BL-VAS will be performed on Days -1, 1, 8, 15, and Day 22 at 1, 3, 8, and 24 hours postdose, Day 24, and (if applicable) at Early Termination.

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Table 4.h Part 4: Study Schedule (Subjects with Schizophrenia)

Screening	Check-in	Dose Administration (a, b)	Final Discharge (c)	Follow-up Visits (d)	Final Visit (e)
Day -35 to -3	Day -2	Days 1, 8, 15, and 22	Day 24	Days 26, 29, 36, 43, 50, 57, 64	Study Completion

(a) Subjects will fast for at least 8 hours before dosing on Days 1, 8, 15, and 22. On all dosing days, subjects will be allowed to eat 4 hours postdose.
(b) Dosing on Days 8, 15, and 22 will be predicated on the review of safety laboratory results from samples obtained the day before (i.e., on Days 7, 14, and 21).

(c) Subjects will be required to remain in the study unit from Day -2 to Day 3, Day 7 to Day 10, Day 14 to Day 17, and Day 21 to Day 24.
(d) The Follow-up PK and safety assessments will occur until 6 weeks after the last dose. If abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the study unit for re-evaluation per investigator's discretion.
(e) The Final/Study Completion Visit will occur 12 to 16 days after the last safety and PK Follow-up Visit.

The schedule of procedures for Part 4 is shown in Appendices D and E of Protocol Amendment 5.

5.0 ANALYSIS ENDPOINTS

5.1 Primary endpoints

The primary endpoint for all parts of this study is the composite of safety variables to determine the safety and tolerability of oral single and multiple doses of TAK-041 as well as dose-limiting effects of TAK-041. The following safety parameters will be analyzed for each of the study parts as the number and percentage of subjects who:

- Experience at least 1 treatment-emergent adverse event (TEAE).
- Discontinue due to an adverse event (AE).
- Meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- Meet the markedly abnormal criteria for 12-lead ECG parameters at least once postdose.
- Experience clinically significant abnormal changes in continuous 12-lead ECG measurements at least once postdose (except Part 3).

The primary endpoints also include the TAK-041 plasma PK parameters for Part 3, maximum observed concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 96 hours (AUC_{96}).

5.2 Secondary endpoints

The secondary endpoints consist of standard PK variables to determine drug exposure at each dose in each of the study parts. The following PK parameters for TAK-041 will be analyzed as secondary endpoints:

- C_{max}: maximum observed plasma concentration (Parts 1, 2, and 4 only).
- t_{max}: time to C_{max}.
- AUC_{24}: area under the plasma concentration-time curve from time 0 to 24 hours.
- AUC_{96}: area under the plasma concentration-time curve from time 0 to 96 hours (Parts 1, 2 and 4 only).
- AUC_{last}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration.
- AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinity (Part 1 only).
- AUC_{τ}: area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (Parts 2 and 4 only).
- $t_{1/2z}$: terminal disposition phase half-life.

5.3 Exploratory Endpoints

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6.0 DETERMINATION OF SAMPLE SIZE

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) in Part 1 Cohorts 1-5 and Part 2 Cohorts 1-4 is based upon precedents of other first-in-human trials rather than a formal assessment of statistical power. This sample size is considered sufficient for investigating the objectives of the study and characterizing any potential effects on safety parameters.

For Part 3, with a sample size of 16 subjects (8 per regimen), assuming a coefficient of variation (%) for the C_{max} of TAK-041 of 13.8%, a two-sided 90% confidence interval for the difference in log-transformed C_{max} between fed and fasted will extend no more than 0.13 from the observed mean difference. As an example, if the observed ratio between the two regimens is 1.5, representing a 50% increase in exposure due to food, then the confidence interval for the true ratio will extend from 1.32 to 1.71. Similarly, if the observed ratio is 1.0, representing no effect of food, then the confidence interval for the true ratio will extend from 0.88 to 1.14. The expected variability in the AUC_{96} of TAK-041 is larger than in C_{max}. In a worst-case scenario, assuming a coefficient of variation (%) for AUC_{96} of 26.8%, the confidence interval will extend no more than 0.25 from the observed mean difference. If the observed ratio between the two regimens is 1.5, representing a 50% increase in exposure due to food, then the confidence interval for the AUC_{96} ratio will extend from 1.17 to 1.93. If the observed ratio is 1.0, representing no effect of food, then the confidence interval will extend from 0.78 to 1.28. Taken together, these results are considered to represent adequate precision for the estimated food effect. The assumed variability in C_{max} and AUC_{96} are estimates from the completed cohorts in Part 1 of this study. To account for potential discontinuations, 18 subjects (9 per regimen) will be enrolled.

The sample of 24 schizophrenia patients (16 active: 8 placebo) in Part 4 was chosen to provide sufficient data to address the pre-defined study decision criteria, to be specified in this statistical analysis plan (SAP), CCI

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Subjects who drop out for non-safety reasons may be replaced on a case-by-case basis at the discretion of the sponsor in consultation with the investigator. Subjects who replace dropouts will be allocated to the same Cohort as the subject they replace. Subjects who drop out for safety reasons will not be replaced.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This SAP was developed based on International Conference on Harmonization E3 [1] and E9 [2] Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms. This version of the SAP was developed using the information provided in Protocol TAK-041-1001, Amendment 5, dated 3 July 2018 [3] and in the electronic case report form (eCRF) version 7.0, dated 24 September 2018.

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. Where indicated, coefficient of variation (%CV) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

All statistical tests will be 2-tailed at α=0.05 level for significance unless otherwise stated. The p-values less than or equal to α (when rounded to three digits) are reported as "significant". The phrase "no significant difference" indicates that all p-values for the tests are greater than α. All computations will be performed prior to rounding.

Data collected for subjects during the study period in which they received placebo will be pooled together in all safety summaries for each cohort and will be analyzed as one placebo group.

7.1.1. Missing Data

CCI [redacted]

Individual items that are missing responses will be imputed and then used to determine the total scores. The repeated measures analysis will be conducted both with and without using MI. See Section 7.13.7 for further details.

There will be no other 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 limit of quantification 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. Derived Datasets and Variables

Derived datasets will be generated according to CDISC guidance documents: Analysis Data Model (ADaM) Implementation Guide, Version 1.1 (12 Feb 2016); ADaM Data Structure for Adverse Event Analysis, Version 1.0 (10 May 2012).

Body mass index (BMI) will be calculated as weight (kg)/(height (m))^2 and will be presented to 1 decimal place. BMI will be calculated for Screening.

7.1.3. Definition of Study Days and Baseline

For Holter-ECG measurements in Part 2, Baseline is defined as the average of the triplicate measurements taken at Day 1 pre-dose. For all other safety endpoints, Baseline is defined as the last non-missing measurement prior to first dose of study drug in the respective treatment period for Cohorts 1 and 2 in Part 1; Baseline is defined as the last non-missing measurement prior to first dose of study drug for Cohorts 3 to 5 in Part 1 and for Parts 2, 3, and 4.

For all safety endpoints, study day will be calculated relative to the date of first dose. Study day prior to the first dose of treatment will be calculated as: date of assessment/event – date of first dose; study day on or after the date of first dose of treatment will be calculated as: date of assessment/event – date of first dose + 1. For Cohorts 1 and 2 in Part 1, period day will be calculated relative to the date of first dose in the respective treatment period. The calculation for period day is similar to that for study day.

7.2 Analysis Sets

Safety Set	The safety analysis set will consist of all subjects who are enrolled and received at least 1 dose of study drug. 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 and have at least 1 measurable plasma concentration or amount of drug in the urine. If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings.
Pharmacodynamic Set	CCI [redacted]

7.3 Disposition of Subjects

The primary reason for screen failure will be summarized.

The number and percentage of subjects who complete study drug and study visits, prematurely discontinue study drug and study visits will be summarized by pooled placebo, each TAK-041 dose level, TAK-041 overall, and overall total within each part for all randomized subjects in Cohorts 3 to 5 in Part 1 and for Parts 2, 3, and 4. For Cohorts 1 and 2 in Part 1, the data will be summarized by pooled placebo, TAK-041 (Cohort 1), TAK-041 (Cohort 2), TAK-041 overall, and overall total. In addition, the number and percentage of subjects will be summarized for each reason of discontinuation of study drug and study visits by pooled placebo, each TAK-041 dose level, TAK-041 overall, and overall total within each part. Subjects' study completion data, including reasons for premature termination, will be listed by cohort for all subjects within each part.

The number and percentage of subjects who comprised each analysis set will be summarized by pooled placebo, each TAK-041 dose level, TAK-041 overall, and overall total within each part.

7.4 Protocol Deviations

The protocol deviations collected on the eCRF will be provided in a data listing and summarized by pooled placebo, each TAK-041 dose level, TAK-041 overall, and overall total within each part in Cohorts 3 to 5 in Part 1 and for Parts 2, 3, and 4. For Cohorts 1 and 2 in Part 1, the data will be summarized by pooled placebo, TAK-041 (Cohort 1), TAK-041 (Cohort 2), TAK-041 overall, and overall total.

7.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by pooled placebo, each TAK-041 dose level, TAK-041 overall, and overall total within each part for all subjects in Cohorts 3 to 5 in Part 1 and for Parts 2, 3, and 4. For Cohorts 1 and 2 in Part 1, the data will be summarized by pooled placebo, TAK-041 (Cohort 1), TAK-041 (Cohort 2), TAK-041 overall, and overall total. Placebo data will be pooled across the cohorts within each part. Summary statistics (n, mean, SD, median, minimum, and maximum) will be generated for continuous variables (i.e., age, height, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (i.e., sex, race, ethnicity, caffeine consumption, alcohol classification, smoking classification, and female reproductive status).

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

7.6 Medical History and Concurrent Medical Conditions

Medical history obtained includes any significant conditions or diseases that stopped at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent.

Medical history and concurrent medical condition verbatim reported terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No summaries for medical history

and concurrent medical conditions will be provided. All medical history and concurrent medical conditions will be listed.

7.7 Medication History and Concomitant Medications

Medication history information obtained includes any medication stopped at or within 28 days prior to signing of informed consent. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

Medication history and concomitant medications will be coded using World Health Organization Drug Dictionary. No summaries for medication history and concomitant medications will be provided. All medication history and concomitant medications data will be listed.

7.8 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in a data listing for all subjects. Summaries of PK data will be provided by TAK-041 dose level.

Study drug exposure will be summarized using PK concentrations and PK parameters (see Section 7.10)

For Parts 2 and 4, duration of treatment will be calculated in whole weeks as (date of last dose – date of first dose + 7)/7 since dosing is weekly. Percentage compliance in Parts 2 and 4 will be calculated as (number of doses administered*100)/(duration of treatment). Duration, number of doses administered, and compliance will be computed and summarized for the Safety Population only. For Part 2, results will be summarized by placebo, loading/maintenance dose of TAK-041 for active subjects, and overall total; for Part 4, results will be summarized by active, placebo and overall total. Duration and compliance data will be listed.

Meal data will be listed.

7.9 Efficacy Analysis

Not applicable.

7.10 Pharmacokinetic Analysis

7.10.1. Plasma Pharmacokinetic Concentrations

Collection of Blood Samples for Pharmacokinetic Analysis in Part 1, Cohorts 1 and 2

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-041	Plasma	Day 1 of Period 1	Predose (within 60 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, 72, and 96 hours postdose.
TAK-041	Plasma	Day 1 of Period 2	Predose (within 60 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, 72, and 96 hours postdose, and at each weekly Follow-up Visit

Collection of Blood Samples for Pharmacokinetic Analysis in Part 1, Cohorts 3 to 5

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-041	Plasma	1	Predose (within 60 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, 72, and 96 hours postdose, and at each weekly Follow-up Visit (Days 8, 15, 22, 29, 36 and 43).

Collection of Blood Samples for Pharmacokinetic Analysis in Part 2 and Part 4

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-041	Plasma	1	Predose (within 60 minutes prior to dosing), 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, and 96 hours postdose.
TAK-041	Plasma	8 & 15	Predose (within 60 minutes prior to dosing), 1, 2, and 4 hours post dose.
TAK-041	Plasma	22	Predose (within 60 minutes prior to dosing), and 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours postdose, and at each Follow-up Visit (Days 26, 29, 36, 43, 50, 57, 64, and 70).

Collection of Blood Samples for Pharmacokinetic Analysis in Part 3

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-041	Plasma	1	Predose (within 60 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours postdose, and at Follow-up Visit (Day 19).

For each part, the concentration of TAK-041 in plasma will be summarized by TAK-041 dose level and day (as applicable) over each scheduled sampling time using descriptive statistics (n, arithmetic mean, SD, median, minimum, and maximum). Individual plasma concentration data will be presented in data listings by part.

Blood samples for placebo will not be analyzed by the bioanalytical laboratory except for 2 samples per subject receiving placebo, 1 predose and the other around the expected time at which C_{max} occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure from a safety perspective that no additional subjects were on active treatment. These data will be listed but not summarized.

For each part, individual concentrations of TAK-041 in plasma will be plotted by actual time on linear and semilogarithmic scales. Plots of mean TAK-041 plasma concentrations versus nominal time will also be provided on linear and semilogarithmic scales for each part. Additionally, plots of mean TAK-041 plasma concentrations versus nominal for the schizophrenia subjects (Part 4) compared to healthy subjects (Part 2) will be provided on linear and semilogarithmic scales for Day 1 and 22.

7.10.2. Plasma Pharmacokinetic Parameters

The PK parameters of plasma TAK-041 will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated using non-compartmental analysis using Phoenix WinNonLin version 6.4 or higher or SAS version 9.3 or higher.

Symbol/Term	Definition
Plasma	
AUC_{24}	Area under the plasma concentration-time curve from time 0 to time 24 hours, calculated using the linear trapezoidal rule. Note: If a time period other than 24 hours is needed, this will have to be specified (eg, AUC_{72} for time 0 to 72 hours).
AUC_{96}	Area under the plasma concentration-time curve from time 0 to time 96 hours, calculated using the linear trapezoidal rule.
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval, calculated using the linear trapezoidal rule (steady state only).
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration, calculated using the linear trapezoidal rule.
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated using the linear trapezoidal rule as $AUC_{\infty}=AUC_t+C_{last}/\lambda z$ (single dose only).
$R_{ac(AUC)}$	Accumulation ratio (based on AUC), calculated as dose normalized AUC_{τ} at steady state/ dose normalized AUC_{24} after a single dose.
$R_{ac(Cmax)}$	Accumulation factor (based on C_{max}), calculated as dose normalized $C_{max,ss}$ at steady state /dose normalized C_{max} after a single dose.
$C_{av,ss}$	Average plasma concentration at steady state, calculated as AUC_{τ}/τ (steady state only).
C_{last}	Last observed quantifiable plasma concentration.
C_{max}	Maximum observed plasma concentration.
$C_{max,ss}$	Maximum observed steady state plasma concentration during a dosing interval (steady state only).
C_{trough}	Trough plasma concentration (measured concentration at the end of a dosing interval at steady state taken directly before next administration [ie. Predose concentrations in Part 2 on Days 8, 15, and 22]).
CL/F	Apparent clearance after extravascular administration, calculated as Dose/AUC_{∞} after a single dose and Dose/AUC_{τ} at steady state.
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda z$.
t_{max}	Time to reach C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda z$.

Dose-normalized C_{max} and AUCs will also be calculated. Additional information regarding the plasma PK analysis and plasma PK parameter calculation and presentation will be provided in

the Clinical Pharmacology Analysis Plan (CPAP). Additional plasma PK parameters may be calculated if necessary, in accordance with the CPAP.

Descriptive statistics (n, arithmetic mean, SD, median, minimum, maximum, and %CV) will be used to summarize the plasma PK parameters for TAK-041 by TAK041 dose level and day (as applicable) for each part. In addition, geometric mean and %CV will be computed for C_{max} and AUCs. Individual plasma PK parameters will be presented in a data listing for each part.

For Parts 1 and 2, scatter plots of individual plasma TAK-041 ln-transformed C_{max} and AUCs versus ln-transformed dose will be provided. Additionally, box plots of TAK-041 dose-normalized C_{max} and AUCs versus dose will be provided for each Parts 1 and 2.

Box plots comparing TAK-041 C_{max} and AUC_{96} values under high-fat vs. fasted conditions for Part 3 subjects will be provided. Additionally, box plots comparing TAK-041 C_{max} and AUC_{96} values for TAK-041 tablet (Part 3) vs. TAK-041 oral suspension (Part 1 and Part 2 (Day 1)) will be provided.

7.10.3. Urine Pharmacokinetic Concentrations

Collection of Urine Samples for Pharmacokinetic Analysis in Part 1

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-041	Urine	1	Predose (-12 to 0), 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, and 72 to 96 hours postdose.

Collection of Urine Samples for Pharmacokinetic Analysis in Part 2

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-041	Urine	1	Predose (-12 to 0), and 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours postdose.
TAK-041	Urine	22	Predose (-12 to 0), and 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours postdose.

In Part 2 and Part 4 only, 10 mL aliquots should be taken from the urine collections on Days 1 and 22 (predose and 12 to 24 hours postdose) for measurement of 6β-hydroxycortisol/cortisol ratio to assess CYP3A4 induction

Individual urine concentration data versus time interval along with urine volume will be presented in a data listing for each analyte for each part.

7.10.4. Urine Pharmacokinetic Parameters

The PK parameters of urine TAK-041 will be determined from urine concentrations for all evaluable subjects. The following PK parameters will be calculated using SAS version 9.3 or higher.

Urine	
Ae_t	Total amount of drug excreted in urine from time 0 to time t for each interval and cumulative over multiple intervals.
f_e	Fraction of drug excreted in urine time 0 to time t for each interval and cumulative over multiple intervals, calculated as $(Ae_t/Dose)\times 100$.
CL_R	Renal clearance, calculated as Ae_t/AUC_{96} for Day 1, Part 1 and Ae_t/AUC_{48} for Days 1 and 22, Part 2.

Additional information regarding the urine PK analysis and urine PK parameter calculation and presentation will be provided in the CPAP. Additional urine PK parameters may be calculated if necessary, in accordance with the CPAP.

Descriptive statistics (n, arithmetic mean, SD, median, minimum, maximum, and %CV) will be used to summarize the urine PK parameters for TAK-041 by TAK041 dose level and day (as applicable) for each part. Individual urine PK parameters will be presented in a data listing for each part.

7.10.5. Statistical Analysis of Pharmacokinetic Parameters

A power model will be used to assess dose proportionality of single dose TAK-041 (Part 1). The model will include the natural log-transformed AUC_{last}, AUC_{∞}, and C_{max} as response variables and the natural log-transformed dose [ln(dose)] as a continuous covariate, assumed as described by the following equation:

$$\ln(PK\ Parameter) = \beta_0 + \beta_1 \ln(Dose) + \varepsilon$$

where β_0 is the intercept, β_1 is the slope and ε is the random error term. Subject will be included in the model as a random effect. Dose proportionality will be declared when the 90% confidence interval for β_1 lies entirely within the critical region (1+ln(0.80)/ln(r), 1+ln(1.25)/ln(r)), where r is the ratio of the highest dose to the lowest dose in this study. This criterion implies that the 90% confidence interval for the ratio of the central values of PK parameter of interest from the highest dose to the lowest dose is contained completely within the bioequivalent range of (0.80, 1.25).

The following is an example of SAS code to be used:

```
proc mixed data=PK;
    class subject;
```

by parameter;

model ln_aval=lndose / solution alpha=0.1;

random subject;

ods output solutionf=<output>;

run;

Dose proportionality of single dose TAK-041 data for Part 1 combined with Part 2 (Day 1) will also be performed in a similar manner.

Dose proportionality of multiple dose TAK-041 (Part 2) will be assessed using an ANOVA model on natural log-transformed dose-normalized AUC_{τ} and C_{max}, separately, on Day 22. Treatment, as a categorical variable, will be a fixed effect. All treatment differences and corresponding two-sided 90% confidence intervals (CIs) will be extracted from the model, back-transformed, and expressed as central values ratios. If the 90% CI for the central value ratio of two doses is within (0.80 and 1.25), 'no deviation from dose proportionality will be claimed for the two doses.

The following is an example of SAS code to be used:

proc mixed data=PK;

class Treatment;

by parameter;

model ln_Daval=Treatment / solution alpha=0.1;

lsmeans Treatment;

estimate 'Dose Level 2 versus Dose Level 1' Treatment -1 1 0 0 /alpha=0.1 CL;

estimate 'Dose Level 3 versus Dose Level 2' Treatment 0 -1 1 0 /alpha=0.1 CL;

estimate 'Dose Level 3 versus Dose Level 1' Treatment -1 0 1 0 /alpha=0.1 CL;

estimate 'Dose Level 4 versus Dose Level 3' Treatment 0 0 -1 1 /alpha=0.1 CL;

estimate 'Dose Level 4 versus Dose Level 2' Treatment 0 -1 0 1 /alpha=0.1 CL;

estimate 'Dose Level 4 versus Dose Level 1' Treatment -1 0 0 1 /alpha=0.1 CL;

* Difference and CI for difference which needs to be modified based on the actual used treatment identifier and corresponding ordering within SAS proc mixed;

ods output Lsmeans=<output> Estimates=<output>;

run;

The effect of food on TAK-041 exposure will be evaluated in Part 3 using an ANOVA on the natural log-transformed TAK-041 AUC_{96}, and C_{max} with regimen (high-fat vs. fasted) as a fixed effect. The relative bioavailability of TAK-041 administered as a 40 mg immediate release tablet

formulation compared to the 40 mg oral suspension formulation in the fasted state will also be assessed within the framework of the ANOVA model. Subjects administered the 40 mg oral suspension in Part 1 and Part 2 (Day 1 data only) will be pooled together and treated as the reference regimen for this analysis; subjects treated with the TAK-041 40 mg tablet formulation under the fasted condition in Part 3 will be the test regimen. The LS mean difference between regimens and the corresponding two-sided 90% CI will be extracted from the model, back-transformed, and expressed as central value ratios of TAK-041 exposure (fasted/fed or tablet/oral suspension). If the 90% CIs of the central value ratios for both C_{max} and AUC_{96} are within (0.80, 1.25), 'no food effect' on the exposure will be claimed for the food effect portion. Similarly, if the 90% CIs of the central value ratios for both C_{max} and AUC_{96} are within (0.80, 1.25), bioequivalence between the two formulations (tablet versus oral suspension) will be claimed.

The following is an example of SAS code to be used:

```
proc mixed data=PK method=type3;
    class Treatment;
    by parameter;
    model ln_aval=Treatment / solution alpha=0.1;
    lsmeans Treatment;
    estimate 'high-fat tablet vs. fasted tablet' Treatment 1 0 -1  /alpha=0.1 CL;
    estimate 'fasted tablet vs. fasted oral suspension'Treatment 1 -1  0/alpha=0.1 CL
    * Difference and CI for difference which needs to be modified based on the actual used treatment identifier and corresponding ordering within SAS proc Mixed;
    ods output Lsmeans=<output> Estimates=<output>;
run;
```

The comparison of TAK-041 PK parameter data for Day 1 and Day 22 for schizophrenia subjects (Part 4) to that of healthy subjects (Part 2) will be assessed using an ANOVA model. The ANOVA will be performed on the natural log-transformed TAK-041 AUC_{last}, AUC_{∞}, and C_{max} for Day 1 and C_{max} and AUC_{τ} for Day 22, with Part (Part 4 vs. Part 2) as a fixed effect. The LS mean difference between populations and the corresponding two-sided 90% CI will be extracted from the model, back-transformed, and expressed as central value ratios. If the 90% CIs of the central value ratios for both C_{max} and AUCs are within (0.80, 1.25), similar PK will be claimed between healthy and schizophrenia subjects.

7.11 Other Outcomes

CCI [redacted]

7.12 Safety Analysis

Summaries of safety data will be presented by part and treatment group. Specifically, for Part 1, the treatment groups are Pooled Placebo, TAK-041 5 mg, TAK-041 10 mg, TAK-041 20 mg, TAK-041 40 mg, TAK-041 80 mg, TAK-041 120 mg, TAK-041 160 mg, TAK-041 Overall; for Part 2, column headers are Placebo, TAK-041 40/20 mg, TAK-041 80/40 mg, TAK-041 120/60 mg, and TAK-041 160/80 mg; for part 3, column headers are Regimen A and Regimen B, where Regimen A is the fasted TAK-041 40 mg group and Regimen B is the fed TAK-041 40 mg group, and for Part 4, column headers are Placebo and TAK-041.

In Part 1, due to the alternating-panel design for Cohorts 1 and 2, subjects who received the 5 mg dose also received the 20 mg dose and subjects who received the 10 mg dose also received the 40 mg dose. Placebo subjects in Cohorts 1 and 2 participated in two periods. For these subjects, the data included in the pooled placebo group for quantitative lab, ECG and vital signs data at each time point is the average of the results obtained at that time point in each period.

7.12.1. Adverse Events

A TEAE will be defined as an adverse event that occurs or gets worse after receiving the first dose of study drug and within 6 weeks (onset date – last date of dose + 1 ≤ 42) after the last dose of study drug. A TEAE may also be a pretreatment adverse event or a concurrent medical condition diagnosed prior to the date of first dose of study drug that increases in severity after the start of dosing. Adverse events data with onset occurring more than 42 days after last dose of study drug (AE start date – last dose date > 42) will be listed, but not included in the summary tables.

Adverse event verbatim reported terms will be coded by system organ class, high-level term and preferred term using MedDRA.

TEAE summary tables will include numbers and percentages of subjects experiencing at least one AE by SOC and PT and will be tabulated for each study part. TEAEs will be summarized according to treatment group. In Part 1, the treatment group is assigned according the treatment most recently received and includes pooled placebo, TAK-041 xx mg, TAK-041 overall (which includes all TEAEs summarized for any dose level of TAK-041), and overall total. In Part 2, the treatment groups are placebo, loading/maintenance dose of TAK-041 for active subjects in each cohort, and overall total. In Part 3, the treatment groups are Regimen A (fasted group), Regimen B (fed group), and overall total. In Part 4, the treatment groups are Placebo, TAK-041 (for subjects receiving active treatment), and overall total. The following is a list of AE summary tables to be generated:

- Overview of TEAEs.
- TEAEs by SOC and PT at subject level.
- Subject Mappings for TEAEs.
- TEAEs by PT.

- Most Frequent TEAEs by PT.
- Most Frequent Non-Serious TEAEs by PT.
- Relationship of TEAEs to Study Drug by SOC and PT.
- Drug-Related TEAEs by SOC and PT.
- Intensity of TEAEs by SOC and PT.
- Intensity of Drug-Related TEAEs by SOC and PT.
- Pretreatment Events (PTE) by SOC and PT.

A subject with 2 or more different adverse events within the same level of the MedDRA term and treatment group will be counted only once in that level using the most extreme incident for the intensity tables, and related events to study drug for the causality tables.

Most frequent TEAEs are defined as the AEs occurring in at least 2 subjects in any treatment (ie, pooled placebo or individual dose level).

Data listings will be provided for all AEs (including PTEs for randomized subjects), AEs leading to study drug discontinuation, SAEs, and AEs resulting in death.

7.12.2. Clinical Laboratory Evaluations

All clinical laboratory samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken following an overnight fast of at least 8 hours on the days stipulated in the Schedules of Study Procedures (See Protocol Amendment 5 Appendix A, B, C, and D and E for Part 1, 2, 3 and 4 respectively, of the study).

Descriptive statistics (n, mean, median, SD, minimum and maximum) of clinical safety laboratory variables will be summarized for baseline, each post-dose time point, and change from baseline to post-dose time points in SI units. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

Individual results for hematology and chemistry laboratory tests will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix A) using the result and criteria in SI units. All subjects with results that meet the MAV criteria will be presented in a data listing. The number and percentage of subjects with at least one post dose markedly abnormal laboratory test result will be summarized. The mapping of the subjects who meet the MAV criteria for post dose lab results will be listed as a table. Only post-dose clinical lab results meeting the MAV criteria that occur within 42 days of the last dose will be included in the MAV summaries, but all post-baseline MAV results will be included in the data listings.

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

7.12.3. Vital Signs

Vital signs will include oral body temperature measurement, supine and standing blood pressure, respiration rate, and pulse (beats per minute). Pulse and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing for all scheduled time points.

Vital signs may be repeated. All measurements will be recorded on the source documents and in the eCRF. See the Schedules of Study Procedures (See Protocol Amendment 5 Appendix A, B, C, and D and E for Part 1, 2, 3 and 4 respectively, of the study) for the schedules of vital sign assessments.

For each part, descriptive statistics (n, mean, median, SD, minimum, and maximum) of these vital signs will be summarized by body position for baseline, each post-dose time point, and change from baseline to post-dose time points. Only the vital signs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed vital signs.

All individual vital signs that meet Takeda's predefined criteria for markedly abnormal values (Appendix B) will be listed. The number and percentage of subjects with at least one post dose markedly abnormal vital sign measurement will be summarized. The mapping of the subjects who meet the MAV criteria for post dose vital sign parameters will be listed as a table. Only post-dose vital signs meeting the MAV criteria that occur within 42 days of the last dose will be included in the MAV summaries, but all post-baseline MAV vital signs will be included in the data listings.

7.12.4. 12-Lead ECGs

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not CS, or abnormal and CS. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, PR interval, QT interval, QRS interval, and QTc, and QTcF.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position following an approximate 10-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.

ECG results (including electronic tracing) will be captured electronically and reviewed in the site's electronic source data system, ClinBase, and not printed. ECGs can be printed if needed.

ECGs will be administered according to the schedules in all study parts as shown in the Schedules of Study Procedures (See Protocol Amendment 5 Appendix A, B, C, and D and E for Part 1, 2, 3 and 4 respectively, of the study).

Descriptive statistics (n, mean, SD, median, minimum, and maximum) of the quantitative ECG results will be presented. The changes of ECG results from period baseline results will also be summarized.

All individual ECGs that meet Takeda's predefined criteria for MAV (Appendix C) will be listed. The number and percentage of subjects with at least one postdose markedly abnormal ECG measurement will be summarized. Subjects who meet the MAV criteria for post dose ECG will be mapped to their respective qualifying ECG result. Only post-dose ECG results meeting the MAV criteria that occur within 42 days of the last dose will be included in the MAV summaries, but all post-baseline MAV results will be included in the data listings.

For ECG interpretation data, shift tables will be provided by visit for the number of subjects with each interpretation by the interpretation at period baseline.

All other ECG data will be presented in data listings.

7.12.5. Holter ECG Monitoring

Continuous 12-lead Holter ECG monitoring will also be conducted in Part 2 only from Day -1 until 24 hours postdose on Day 1. Triplicate 12-lead ECGs will be extracted from the H-12 flash card approximately 1 minute apart from one another (for each time point, triplicate ECGs with 10 sec. extraction) at the following time points: Day -1 (23, 22, 20, 16, 12 hour before dosing), and Day 1 immediately before dosing [0 hr, within 45 min of dosing], and at 1, 2, 4, 8, 12, and 24 hours postdose. The average of the 3 values at each time point will be calculated and used for all statistical analyses and summaries.

All average Holter ECG values that meet Takeda's predefined criteria for MAV (Appendix C) will be listed. The number and percentage of subjects with at least one postdose markedly abnormal ECG measurement will be summarized. Subjects who meet the MAV criteria for post dose ECG will be mapped to their respective qualifying ECG result. All post dose MAV ECGs, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

Uncorrected and corrected QT intervals, PR, and QRS intervals and heart rate, as well as their changes from baseline will be summarized at each scheduled time point. Baseline is calculated as the average of the triplicate assessment taken at Day 1 pre-dose. Change from baseline will not be calculated for time points prior to baseline.

Dates and times for the start and stop of continuous 12-lead Holter ECG monitoring will be presented in a data listing. The triplicate 12-lead ECG values extracted from the continuous Holter monitoring at each scheduled time point along with the average values will also be presented in a data listing. Holter recordings will be also stored by Takeda, used for additional analyses, and may be sent to a central ECG analysis laboratory for retrospective expert review and estimation of ECG intervals at an appropriate time for the TAK-041 program during or after completion of the present study.

The assessment of the potential QT prolongation using the Holter ECG measurements from Part 2 and the model to assess the relationship between the change from time-matched baseline in QTc and TAK-041 exposure in Part 2 are not covered by this SAP. All analysis of exposure-QTc data will be described and performed independently of this document by Takeda or its designee.

7.12.6. Other Observations Related to Safety

7.1 7.12.6.1 Physical Examination

Physical examinations, including neurological assessments, will be administered according to the schedules in all study parts as shown in the Schedules of Study Procedures (See Protocol Amendment 5 Appendix A, B, C, and D and E for Part 1, 2, 3 and 4 respectively, of the study).

The physical examination findings will be presented in data listings. No summary tables will be provided.

7.2 7.12.6.2 Bond-Lader Visual Analogue Scale

The BL-VAS will be administered in Part 1 on Day -1, Day 1 at 1, 3, 8, and 24 hours postdose (Day 2), Day 5, and (if applicable) at Early Termination; in Part 2 on Day -1; Days 1, 8, 15, and 22 at 1, 3, 8, and 24 hours postdose; Day 24, and (if applicable) at Early Termination; and in Part 4 at 1, 8, 15 and 24 hours from dosing on Day 15.

BL-VAS of Mood and Alertness consists of a questionnaire of 16 analogue scales that derive 3 factors that assess change in Self-Rated Alertness, Self-Rated Calmness, and Self-Rated Contentment. It has proven sensitivity to a wide range of compounds. In the original versions, ratings were performed by the subject by marking a point on a 10 cm line that is meant to represent the full range of the particular dimension (for example, alert-drowsy). 9 items assess alertness, 5 items assess contentedness, and 2 items assess calmness. A mark on the far left side or far right side of the scale represents extremes with regard to the adjectives on each side of the line (eg, a higher or more rightward score on a scale marked awake—drowsy indicates that the subject feels drowsier).

When BL-VAS assessments are scheduled at the same time as blood draws, vital signs, or ECGs, they will be completed within 2 hours before or after the blood draws, vital signs, and ECGs. In this study, the BL-VAS is considered a safety measure.

The BL-VAS results will be presented in data listings. No summary tables will be provided.

7.3 7.12.6.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be assessed by the use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (e.g., 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).

Two versions of the C-SSRS will be used in this study: the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS. These will be administered according to the schedules shown in the Schedules of Study Procedures (See Protocol Amendment 5 Appendix A, B, C, and D and E for Part 1, 2, 3 and 4 respectively, of the study).

C-SSRS data will be presented in data listings. No summary tables will be provided.

7.13 Exploratory Pharmacodynamic Analysis

CCI

[redacted]

7.13.1 CCI

CCI

[redacted]

7.13.2 CCI

CCI [redacted]

7.13.3 CCI

CCI [redacted]

7.13.4 CCI

CCI [redacted]

CCI

[redacted]

7.13.5 CCI

CCI

[redacted]

7.13.6 Mini International Neuropsychiatric interview

The Mini-International Neuropsychiatric Interview (MINI) is a short structured diagnostic interview developed jointly by psychiatrists and clinicians in the United States and Europe for DSM-IV and International Classification of Diseases 10th Revision psychiatric disorders with an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies. These will be administered according to the schedules shown in Appendices D and E in Protocol Amendment 5.

MINI International Neuropsychiatric Interview data will be presented in a data listing.

7.13.7 Modeling of Observed Values and Change from Baseline f[redacted]

[redacted]

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[redacted]

7.13.8 Bayesian Modeling of Change from Baseline CCI

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[redacted]

Table 7.b Blocks of parameters and mutually independent priors.

Population Parameter(s)	Block	Prior
Intercept	A	Normal (0, variance=10^6)
Regression coefficient of treatment	A	Normal (0, variance=10^6)
Regression coefficient of Baseline	A	Normal (0, variance=10^6)
Regression coefficients of visit	B	Normal (0, variance=10^6)
Regression coefficients of treatment-by-visit interaction	C	Normal (0, variance=10^6)
Covariance of Residuals (R-side of mixed model)	E	Inverse Wishart (df=6, scale=Identity)

The posterior mean, standard deviation, and the 95% highest posterior density interval will be extracted for each treatment at each time, along with the posterior mean differences from placebo and associated standard deviations and 95% credible intervals.

In the modeling, for each chain of Markov chain Monte Carlo imputation iterations,

- the starting value for each population parameter will be the prior mean [for example, the 0 in a Normal (0, variance=10^6) prior]
- The seed will be 5235
- 10^6 samples will be taken from the posterior
- An initial burn-in of 1,000 samples will be discarded

For the mean treatment effect and the treatment-by-visit interaction parameters, convergence of the sampling from the posteriors will be concluded if the Brooks-Gelman Ratio (BGR) [5] for each parameter is in the interval (0.8, 1.2). The BGR will be calculated by constructing a second chain with all starting values increased by 100 except for covariance parameters while all other settings stay the same.

If convergence is not obtained,

- the burn-in and sampling numbers will be increased by 50%
- different block structures will be tried
- the R-side covariance structure will be assumed autoregressive, first order

Also, if necessary due to storage limitations, samples will be thinned by 20.

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[redacted]

If either posterior probability is greater than 70%, then a "positive" result will be declared.

7.14 Interim Analysis

Not applicable

7.15 Changes in the Statistical Analysis Plan

CCI [redacted]

The baseline-by-time interaction term has been removed from the repeated measures models and from the Bayesian models for the PD parameters. Due to the small sample size for Part 4, it is expected that the models would not converge if this term is included.

CCI [redacted]

This SAP contains no other changes to the planned analyses described in the Protocol.

8.0 REFERENCES

1. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonisation, Section ICH E3, 1996.
2. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonisation, Section ICH E9, 1998.
3. Protocol Amendment 5: A Randomized, Double-Blind, Placebo-Controlled, Phase 1, Ascending Oral Single and Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK 041 in Healthy Subjects and Subjects with Stable Schizophrenia and a Randomized Open-Label, Single Dose, Parallel Design to Evaluate the Relative Bioavailability and Effect of Food on the Pharmacokinetics of TAK-041 Tablet Formulation in Healthy Subjects. 3 July 2018.
4. Marder, etc. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined result of the North American trials, J Clin Psychiatry, Dec 1997. Vol 58, 12: 538-46.
5. Brooks, SP and Gelman, A. General Methods for Monitoring Convergence of Iterative Simulations, Journal of Computational and Graphical Statistics, 1998. Vol 7: 434–455.

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 × LLN	>1.5 × ULN
Platelet count	Conventional	$<75 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$
	SI	$<75 \times 10^9/L$	$>600 \times 10^9/L$
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	--	>3 × ULN
AST	Both	--	>3 × ULN
GGT	Both	--	>3 × ULN
Alkaline phosphatase	Both	--	>3 × 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	<0.8 × LLN	>1.2 × 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

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, eGFR=estimated glomerular filtration rate, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Values for 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 Markedly Abnormal Values for Electrocardiograms

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	< 50	> 120
PR Intreval	msec	≤ 80	≥ 200
QTcB Interval	msec	≤300	≥ 500 OR ≥ 30 change from baseline and ≥ 450
QTcF Interval	msec	≤300	≥ 500 OR ≥ 30 change from baseline and ≥ 450
QRS Interval	msec	≤ 80	≥ 180

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[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	18-Apr-2019 13:38 UTC