PROTOCOL AMENDMENT

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

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015

Study Number: TAK-041-1001

IND Number: 130074 **EudraCT Number:** Not Applicable

Compound: TAK-041

Date: 03 July 2018 **Amendment Number:** 05

Amendment History:

Date	Amendment Number	Amendment Type	Region
24 March 2016	Initial version	Not applicable	USA
02 June 2016	01	Substantial	USA
24 June 2016	02	Substantial	USA
20 September 2016	03	Substantial	USA
06 December 2017	04	Substantial	USA
03 July 2018	05	Substantial	USA

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Trial contact numbers can be found in the Study Manual, the communication plan, or other similar documents provided to the site.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix F– Responsibilities of the Investigator.

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 05 Summary of Changes

Rationale for Amendment 05

This document describes the changes in reference to the protocol incorporating Amendment No. 05. The primary reasons for this amendment are to modify the study design to include:

- Part 3 to assess the bioavailability and food effect on the pharmacokinetics (PK) of the TAK-041 immediate release tablet formulation in healthy subjects
- CCI [redacted]

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only. For specific descriptions of text changes and where the changes are located, see Appendix I.

Changes in Amendment:

1. Added Part 3 study design, with population, formulation, dosing, food effect regimen, and confinement
2. Added Part 4 study design with stable schizophrenic population, dose levels, dosing days and confinement days.
3. Added objectives and endpoints for Parts 3 and 4.
4. Added the justification for the proposed study design dose and endpoints for Part 3.
5. Added the justification for the proposed study design dose and endpoints for Part 4.
6. Added inclusion and exclusion criteria for Part 3 and 4.
7. Added excluded medications, dietary products and study control of diet, fluid and activity control for Parts 3 and 4.
8. Added TAK-041 tablet formulation to study medication for Part 3 and manufacturing, packaging, labeling, dispensing and randomization to include Part 3 and 4.
9. Added height weight and BMI to Part 3 and 4, with Part 4 subjects have an increased upper limit for BMI of 40.5 kg/m^2.
10. CCI [redacted]
11. Added statistical analysis for Part 3 and Part 4.
12. Added pharmacogenomic sample collections for Part 3 and 4.
13. Added PK parameters and PK blood collections for Part 3 and 4 and PK urine collections for Part 4.
14. Revised the study-specific dose escalation and stopping rule for Part 1 and Part 2.
15. Added exclusion criteria for recent major surgery or donation or loss of blood.

16. Revised exclusion for clinically significant history or head injury or trauma to include loss of consciousness for greater than 15 minutes.
17. Updated exclusion language on risk of suicide considered by the investigator, including specific C-SSRS results.
18. Added unsuitable for inclusion in the opinion of the investigator or sponsor as an exclusion criterion.
19. Detailed specific neurological examinations, and combined as part of physical examination, with required assessment as not clinically significant (NCS) or clinically significant (CS).
20. Updated wearable device timing of placement and removal for Part 2 and added to Part 4.
21. Added laboratory sample collections and blood sampling volumes for Part 3 and 4
22. Added contraception, avoidance procedures and pregnancy statements to Part 3 and 4.
23. Added ECG assessments to Part 3 and 4 and removed triplicate parameter assessments from Holter ECG in part 2.
24. CCI [redacted].
25. Updated the nonclinical information on TAK-041
26. Updated PK analysis for all sample parts.
27. Added PD analysis set for Part 4 only
28. Updated safety analysis.
29. Updated sample size determination for the study.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-041	
Title of Protocol: 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	**IND No.:** 130074	**EudraCT No.:** Not applicable
Study Number: TAK-041-1001	**Phase:** 1	

Study Design

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. This study design in this amendment reflects a modification of the original design, due to the longer than expected half- life of TAK-041 observed after the single-dose administration of the compound to healthy subjects in the first 2 cohorts. 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 in healthy subjects, to evaluate the relative bioavailability and effect of food on the PK of the TAK-041 tablet formulation. Part 4 is a single dose cohort design 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 subjects will receive a single 40 mg dose of the tablet formulation of TAK-041 (1x 40mg tablet) based on safety/tolerability of the same dose in healthy subjects in Part 1 and Part 2. For Part 4, the dose selected will be based on emerging safety/tolerability and available PK data of the same dose in healthy subjects from Part 2. 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 for Part 1, 2 and 4, and as the immediate release tablet formulation for Part 3.

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Part 1 will consist of 5 cohorts with 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 (see schematic of study design below). 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 (see schematic of study design below). Although planned, all subsequent doses after the dose of 80 mg for Cohort 3 will be determined based

on the emerging safety, tolerability, and PK data from the preceding cohorts.

As this is an FIH study, a sentinel group will be used for Part 1 Cohort 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 highest planned dose is predicted to have maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 24 hours (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 will be performed in Part 1, Day -1, Day 1 at 1, 3, 8, and 24 hours postdose, Day 5, and (if applicable) at Early Termination.

Part 1: Schematic of 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 in Cohorts 1-5 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.

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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 lower 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.

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 in the cohorts 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.

Part 2 will consist of a 4-cohort sequential-panel, double-blind, weekly dosing, multiple-rising dose (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 (see schematic of study design below). 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 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 ($C_{av,ss}$) that is below the $C_{av,ss}$ observed at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study.

Part 2: Schematic of 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.

Bond-Lader visual analog scales 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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Part 2: Study Schedule: Healthy Subjects, Cohorts 1 to 4

Screening	Check-in	Dose Administration (a, 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, and 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 weekly 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.

Part 3 will consist of an open label, single-dose parallel design. Approximately 18 healthy subjects will be enrolled to evaluate the oral bioavailability of the TAK-041 tablet formulation relative to the oral suspension and the effect of food on the PK of the tablet formulation. The subjects will be randomly assigned (1:1 ratio) to be administered orally TAK-041on Day 1 as one 40 mg immediate release tablet after either at least 10 hours of overnight fast or 30 minutes after starting ingestion of a high-fat, high-calorie breakfast.

Overall, Part 3 of the study will consist of a Screening Visit (Days -28 to -2), a predose Check-in Day for each subject (Day -1) during which baseline assessments will be conducted. Subjects who satisfy the Screening evaluation and selection criteria will be enrolled. On Day 1, eligible subjects will be randomized to receive a single dose of TAK-041 as one 40 mg tablet administered orally 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, and subjects will return for a final follow-up visit approximately 2 weeks after Day 5.

Part 3: 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.

Part 4 will consist of a 1-cohort, double-blind, weekly dosing design. Subjects with stable schizophrenia will be enrolled. One dose cohort is considered adequate to explore the pharmacologically active exposure range in subjects with stable schizophrenia. The cohort will be composed of 24 subjects where subjects will be randomly assigned to receive TAK-041 or placebo in a ratio of 2:1. 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. The dose selected in Part 4 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 ($C_{av,ss}$) below the $C_{av,ss}$ observed at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study.

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. The single cohort of 24 subjects will be randomized with 16 active : 8 placebo.

Overall, Part 4 of the study will consist of a Screening Visit (Days -35 to -3), a predose Check-in Day for all subjects (Days -2) during which baseline assessments will be conducted, Day -1 during which other baseline assessments will be conducted, and 22 days of treatment period when all subjects will be dosed on Days 1, 8, 15, and 22 as well as undergoing study-specific assessments. After 4 weeks of dosing, subjects will return for weekly follow-up study-specific assessments until Day 64 and study completion on Day 70.

In Part 4, 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 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 for safety and PK weekly 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.

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pre-selected times and (if applicable) at Early Termination.

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Part 4: Study Schedule: Subjects with Schizophrenia,

Screening	Check-in	Dose Administration (a, b, c)	Final Discharge	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) and overall clinical status of the subjects.
(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

Study Objectives

Primary Objective:

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 of TAK–041 in healthy subjects 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 of 40 mg immediate release tablet formulation of TAK–041 in healthy subjects (Part 3).

Secondary Objective:

To evaluate the PK of TAK-041

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

Exploratory Objectives:

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Subject Population: Male and female healthy subjects (Parts 1-3) and subjects with stable schizophrenia (Part 4) aged 18 to 55 years, inclusive.

Number of Subjects:	**Number of Sites:**
Estimated total: 114 subjects **Part 1:** 40 healthy subjects in Cohorts 1 to 5 (8 subjects per cohort: 6 active, 2 placebo) **Part 2:** 32 healthy subjects (8 subjects per cohort: 6 active: 2 placebo) **Part 3:** 18 healthy subjects (9 fasted : 9 fed with a high-fat and high-calorie meal) **Part 4:** 24 subjects with stable schizophrenia (16 active: 8 placebo)	Estimated total: 1 site in the United States
Dose Level(s):	**Route of Administration:**
Part 1: Cohorts 1 to 5, single dose of 5 to up to 160 mg TAK-041 or matching placebo **Part 2:** Single loading doses of TAK-041 from 40 to 160 mg, and weekly maintenance doses of TAK-041 from 20 to 80 mg or matching placebo throughout. **Part 3**: Single dose of 40 mg TAK-041 **Part 4**: Single loading doses of TAK-041, and weekly maintenance doses of TAK-041 or matched placebo throughout. The dose regimens of TAK-041 will be determined based on emerging safety/tolerability data and available PK data from Part 2.	Oral
Duration of Treatment:	**Period of Evaluation:**
Part 1: 1 day **Part 2:** once per week for 4 weeks. **Part 3:** 1 day **Part 4**: once per week for 4 weeks	Part 1 Cohort 1: ~5 months Part 1 Cohort 2: ~4 months Part 1 Cohorts 3 to 5: 3 months Part 2 All Cohorts: 4 months Part 3: ~3 months Part 4: 4 months

Main Criteria for Inclusion:

For healthy subjects and subjects with schizophrenia: Adult men and women of non-childbearing potential who weigh at least 45 kg (99 lb) with a body mass index from 18 to 32 kg/m^2 for healthy subjects or 18 to 40.5 kg/m^2 for subjects with schizophrenia, who are willing to comply with study restrictions described in the protocol.

For subjects with schizophrenia only: Male and female subjects with stable schizophrenia who are on a stable dose of an antipsychotic for at least 2 months as documented by medical history and assessed by site staff.

Main Criteria for Exclusion:

- Subject has known hypersensitivity to any component of the formulation of TAK-041.
- For healthy subjects only: subject has evidence of current active cardiovascular, central nervous system, hepatobiliary disease including history of biliary tree disorders, gallstones, history of endoscopic retrograde cholangio pancreatography (ERCP), and/or cholecystectomy, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory test results

(including elevated alkaline phosphatase (ALP), elevated bilirubin, elevated γ-glutamyl transferase (GGT), elevated 5'-nucleotidase, or abnormal urine osmolality) that in the judgment of the principal investigator represents a reasonable suspicion of a disease that would contraindicate taking TAK-041, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, cholestasis seizure disorders, and cardiac arrhythmias.

- Subject has abnormal Screening or Check-in laboratory values (> ULN for the respective serum chemistries) of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBILI), ALP, GGT, 5'nucleotidase and/or abnormal urine osmolality, confirmed upon repeat testing.
- Subject has a sustained resting heart rate outside the range 40 to 100 beats per minute (bpm), confirmed on repeat testing within a maximum of 30 minutes at Screening or Check-in.
- If female, the subject is of childbearing potential (eg, premenopausal, not sterilized).
- If male, the subject intends to donate sperm during the course of this study or within 145 days (ie, 90 days after 5 half-lives) of the last dose of study drug.
- The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or subjects who within the past year prior to Screening have attempted suicide. Subjects who have positive answers on item 4 or 5 on the C-SSRS (based on the past year) prior to randomization are excluded.
- The subject has a clinically significant history of head injury or trauma associated with loss of consciousness for > 15 minutes.

Main Criteria for Evaluation and Analyses:

A primary endpoint for all parts of this study is the composite of safety variables to determine the safety and tolerability of single and multiple oral 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 electrocardiogram (ECG) parameters at least once postdose.
- Experience clinically significant abnormal changes in continuous 12-lead ECG measurements at least once postdose (Part 1, 2 and 4 only).

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 (AUC) from time 0 to 96 hours.

The secondary endpoints for this study consist of standard PK variables to determine drug exposure at each dose in each of the Parts 1, 2, 3 and 4:

- 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. (Part 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 extrapolated 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 (Part 2 and Part 4 only).
- $t_{1/2z}$: terminal disposition phase half-life.

Exploratory endpoints:
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Statistical Considerations:

Pharmacokinetics: Concentrations of TAK-041 in plasma will be summarized by dose over each scheduled sampling time using descriptive statistics for each study part. Amount of TAK-041 excreted in urine will be summarized by dose over each scheduled sampling interval using descriptive statistics for each study part. Individual PK data will be presented in a data listing. PK parameters of TAK-041 will be summarized by dose using descriptive statistics for each study part. Dose proportionality will be assessed graphically (dose-normalized C_{max} and AUC versus dose) in Part 1 and Part 2. To assess dose proportionality of single dosing (Part 1), a power model will be used. The model will include the natural log-transformed AUC and C_{max} as response variables and the natural log-transformed dose [ln(dose)] as a continuous covariate. Dose proportionality will be assessed using the point estimates and the 90% confidence interval of the slopes. For Part 2, dose proportionality will be assessed using an analysis of variance (ANOVA) model separately for dose-normalized AUC and C_{max} on Day 22. Treatment, as a categorical variable, will be a fixed effect. The dose-normalized parameters will be natural log-transformed prior to the analysis. All treatment differences and corresponding two-sided 90% CIs will be extracted from the model and back-transformed as the ratios on the original scale.

The effect of food on TAK-041 exposure will be evaluated in Part 3 using an ANOVA on the natural log-transformed TAK-041 Cmax and AUC96 with regimen (high-fat vs. fasted) as a fixed effect. 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 after the high-fat meal versus the fasted state. 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 using an 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 ANOVA will be performed on the natural log-transformed Day 1 TAK-041 Cmax and AUC96 with regimen as a fixed effect. 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.

Safety: Safety data will be presented by TAK-041 dose and placebo for Part 1, Part 2, and Part 4 and by regimen (fasted or fed) for Part 3. In each part, all placebo subjects will be pooled into one group in the summaries. TEAEs will be summarized by placebo, each TAK-041 dose level, and TAK-041 overall for each study part. Clinical laboratory variables, vital signs, and ECG parameters will be summarized with descriptive statistics for baseline, postdose, and change from baseline to postdose values by dose. The number and percentage of subjects with postdose values meeting Takeda's criteria for markedly abnormal values for clinical laboratory variables, vital signs, and ECG parameters will be presented by treatment.

12-lead ECG parameters will be extracted in triplicates. The average of the 3 values at each time point will be calculated and used for all statistical analyses and 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. Statistical analyses will be performed to evaluate the relationship between change from baseline in certain ECG parameters and the exposure to TAK-041.

Neurological assessments will be judged normal, abnormal, clinically significant or not clinically significant. Physical examination findings will be presented in data listings.

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Sample Size Justification: The sample size of 8 subjects per cohort (6 active: 2 placebo) in Part 1 Cohorts 1-5 and Part 2 Cohorts 1-4 is chosen based upon precedents of other first-in-human trials rather than a formal assessment of statistical power.

The sample size of 18 subjects (9 per regimen) in Part 3 was chosen to provide adequate precision of the estimated food effect on TAK-041 exposure, assuming at least 16 subjects complete the study. Assuming a coefficient of variation (%) for the C_{max} of TAK-041 of 13.8%, a 2-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.

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3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

PPD

3.3 List of Abbreviations

Term	Definition
5-HT_{2C}	5-hydroxytryptamine subtype 2c
AE	adverse event
AE_t	total amount of drug excreted in urine from time 0 to time t
ALT	alanine aminotransferase
AST	aspartate aminotransferase
A-to-B	apical-to-basolateral
AUC	area under the plasma concentration-time curve
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
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity.
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval
CCI [redacted]	
BMI	body mass index
CCI [redacted]	
B-to-A	basolateral-to-apical
CCI [redacted]	
CCI [redacted]	
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CS	clinically significant
CSR	clinical study report
CV	cardiovascular
CYP	cytochrome P-450
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
EC_{50}	half-maximal response
ECG	electrocardiogram
eCRF	electronic case report form
CCI [redacted]	
eGFR	estimated glomerular filtration rate
ERCP	endoscopic retrograde cholanigo pancreatography
FDA	Food and Drug Administration
Fe	fraction of drug excreted in urine

Term	Definition
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GLP	Good Laboratory Practice
GPCR	G-protein-coupled receptor
GPR139	G-protein-coupled receptor 139
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
hERG	human ether-à-go-go–related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
K_i	inhibition constant
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MRD	multiple-rising dose
mRNA	messenger RNA
NCS	not clinically significant
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PANSS	Positive and Negative Syndrome Scale
P_{app}	apparent permeability coefficient
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
CCI	[redacted]
PK	pharmacokinetic(s)
PO	per os, oral
POC	proof of concept
Poly (I:C)	polyinosinic:olycytidylic acid
PTE	pretreatment event
QD	once daily
CCI	[redacted]

Term	Definition
QTc	corrected QT interval
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SERT	serotonin transporter
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

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

GPR139 is a novel class A orphan receptor that is expressed nearly exclusively in the central nervous system (CNS). Human GPR139 is expressed in the putamen, caudate nuclei, entopeduncular nuclei, olfactory bulbs, hypothalamic nuclei, substantia nigra, cerebellar nuclei, vestibular nuclei and habenular nuclei, where it is predominantly expressed in Synaptotagmin 6 positive neurons of the medial habenula [1,2]. The habenula is a key brain structure involved in specific aspects of social and cognitive behavior that is dysfunctional in schizophrenia and other psychiatric disorders.

In a series of assays, characterization of TAK-041 as an agonist for GPR139 demonstrated the ability of TAK-041 to stimulate extracellular calcium entry into Chinese hamster ovary cells expressing the recombinant mouse, rat, dog, and human receptor at a concentration producing a half-maximal response (EC_{50}) of 98 to 102 nM, 88 to 132 nM, 25 nM, and 23 to 36 nM, respectively. Moreover, the predicted downstream modulation of inositol phosphate (IP1) turnover was observed in the human receptor at an EC_{50} of 422 to 461 nM. Binding affinity to the recombinant dog and human receptor exhibited an inhibition dissociation constant (K_i) of 229 nM and 117 to 301 nM, respectively.

TAK-041 selectivity was evaluated against a panel of 78 enzymes, receptors, and transporters that are functionally relevant to the CNS circuitry of GPR139 using enzyme and binding assays. TAK-041 did not show any activity against most of the proteins tested with the exception of 5-hydroxytryptamine subtype 2c (5-HT_{2C}) and serotonin transporter (SERT). Initial evaluation showed inhibition at 95% and 68% of 5-HT_{2C} and SERT, respectively, at 10 µM of TAK-041. However, only SERT inhibition was confirmed in follow-up experiments. TAK-041 inhibited SERT with a 50% inhibitory concentration (IC_{50}) of 2.29 µM. The results of these studies indicate that TAK-041 is a potent and selective agonist of GPR139.

While in vitro studies used cell-based assays and membranes prepared from cells expressing GPR139, in vivo studies examining both molecular and behavioral consequences of receptor activation were used to assess the ability of TAK-041 treatment to improve social interaction deficits and cognitive dysfunction, which are associated with psychiatric disorders such as schizophrenia. In vivo studies evaluating the molecular effects of TAK-041 demonstrated that c-fos, an immediate early gene that is downstream of GPR139 activation, levels were elevated in a time- and dose-dependent manner after TAK-041 administration. As early as 1 hour after a single 0.3-mg/kg dose, there was an observable, significant ($p<0.05$) increase in c-fos immunoreactivity in this region of the brain. Moreover, the c-fos elevation in the medial habenula of treated mice persisted with subchronic administration of TAK-041. These studies suggest that TAK-041 excites the medial habenula.

Behavioral responses were examined in 2 different mouse models exhibiting social interaction deficits: the Balb/c model and the polyinosinic:polycytidylic acid (poly [I:C]) model. In both models, 0.1 mg/kg TAK-041, dosed either acutely or subchronically (15 days of treatment), mitigated the social deficits that were either naturally occurring (Balb/c) or pharmacologically evoked by the inflammatory stimulus (poly [I/C]). Moreover, haloperidol, a dopamine D2 receptor antagonist, did not provide therapeutic benefit as a stand-alone treatment in the poly (I:C) model and did not abrogate the efficacy associated with TAK-041. Furthermore, the cognitive deficits associated with subchronic phencyclidine (PCP) treatment in a rat set shifting task were significantly attenuated by increasing doses of TAK-041 from 0.3 to 3 mg/kg with 4 hours of pretreatment. This result compared favorably to risperidone, a second generation antipsychotic treatment. Accordingly, the available experimental evidence supports the use of TAK-041, a GPR139 agonist, as a potential treatment for the negative symptoms (including amotivation, anhedonia, and asociality) and cognitive impairment associated with schizophrenia, a debilitating disorder with high unmet medical need.

The PK properties of TAK-041 have been characterized in vitro and in Sprague-Dawley rats and beagle dogs after oral (PO) or intravenous (IV) administration. Pharmacokinetic evaluations were conducted in rats and dogs because these were the major species used in the toxicology program.

TAK-041 was absorbed after PO administration to rats and dogs, with peak plasma concentrations generally occurring within 4 to 8 hours postdose in rats and 0.5 to 2 hours postdose in dogs. The plasma clearance of TAK-041 was low in rats and moderate to high in dogs (~4 and ~11 mL/min/kg, respectively). The terminal elimination half-life ($t_{1/2}$) of TAK-041 after PO administration was 1.5 to 2.8 hours in dogs, and undefined in rats because of a poorly defined terminal phase observed in this species. The oral bioavailability of TAK-041 was high (90.8% to 94.2% in rats; in dogs, the dose-normalized PO exposures were greater than observed after IV dosing, resulting in reported bioavailability up to 100% or greater. Absorption was not likely modulated by P-glycoprotein (P-gp), because TAK-041 had a low P-gp efflux ratio (0.4), as demonstrated in LLC-PK1-MDR1 cells, indicating that TAK-041 is not likely a substrate for P-gp. TAK-041 (1 and 10 µM) plasma protein binding was 95.9%, 95.4 to 96.5%, 96.8 to 97.3%, 95.3 to 95.4%, and 96.8 to 97.1% in plasma from mice (tested at 10 µM only), rats, dogs, monkeys, and humans, respectively. Red blood cell: plasma ratios of TAK-041 at 0.1, 1, and 10 µM were approximately 0.8, 0.8, and 1.1 in rats; 0.4, 0.4, and 1.0 in dogs; and 0.7, 0.6, and 0.8 in humans, respectively. TAK-041 showed no inhibitory effect on the Bile Salt Export Pump transporter in rat and human vesicles up to 200 µM and a moderate inhibitory effect in dog vesicles (IC50 ~ 72 µM).

In vitro metabolism studies with hepatic microsomes and hepatocytes from human donors showed trace amounts of a few metabolites including oxidative N-dealkylation to form an amide metabolite and oxidations at the oxobenzotriazine moiety to form positional isomeric structures. Subsequent glucuronidation of these oxidative isomeric structures yielded their corresponding glucuronide conjugate metabolites. In addition to these metabolites, a glutathione conjugate of TAK-041 and one of its downstream metabolites, a cysteine conjugate, were also detected in rat and dog hepatocytes. No human-specific metabolites were observed. An evaluation of the cytochrome P-450 enzymes (CYPs) responsible for the metabolism of TAK-041 has not yet been conducted. Glutathione-adduct-derived thiol metabolites through the β-lyase pathway is

significant in dog (higher rate of metabolism and lack of N-acetylation detoxification pathway). Preliminary human in vitro and in vivo data suggest similar metabolic pathways but to a much lesser extent. The formation of N-acetylcysteine conjugate was observed in human as evident of N-acetylation detoxification pathway. In rat, however, glucuronidation pathway seems to be predominant.

An assessment of cytochrome P-450 enzyme (CYP) induction was conducted in cultured human hepatocytes, and induction of CYP2B6 and CYP3A4 messenger RNA (mRNA) was observed. Treatment of cultured human hepatocytes with up to 10 µM TAK-041 had little or no effect on CYP1A2 mRNA levels, while treatment with up to 10 µM TAK-041 caused concentration-dependent increases of >2.0-fold and >20% of the positive control in CYP2B6 and CYP3A4 mRNA levels, respectively, in all cultures tested. Thus, TAK-041 was a mild inducer of CYP2B6 and CYP3A4 mRNA in vitro and CYP induction based DDI potential is considered low. TAK-041 showed no reversible inhibition of CYP3A4/5 activities at concentrations ranging up to 100 µM with an IC50 > 100 µM. In the CYP3A4/5 time-dependent inactivation (TDI) study, the percentage of activity remaining in samples preincubated with TAK-041 showed no time-, concentration-, or NADPH-dependent CYP3A4/5 loss of activity. These data suggest that potential reversible inhibition and TDI of CYP3A4/5 by TAK-041 are unlikely.

Urinary excretion of TAK-041 was investigated in dogs after a single IV dose. After IV administration to 3 dogs, TAK-041 was detectable in dog urine, but at low levels. The amount of TAK-041 excreted unchanged into dog urine within 24 hours ranged from approximately 0.009% to 0.0157% with mean recovery of 0.0135% of the given dose.

A comprehensive series of nonclinical safety studies (Good Laboratory Practices [GLP]) have been conducted with TAK-041 to support early human studies including:hERG, electrocardiography in dogs, respiratory and CNS in rats, genetic toxicity studies (Ames, in vitro micronucleus, in vivo micronucleus), and in vitro phototoxicity. An effect of TAK-041 was first observed at 1 µM in the human ether-à-go-go–related gene (hERG) assay (IC_{50} >3 µM); however, no changes in ECG parameters were observed in the in vivo dog cardiovascular (CV) or 4-week repeat-dose toxicity study at 125 mg/kg. In the dog CV study, an increase in systolic blood pressure (10%) resulting in increases in mean arterial and pulse pressures without any associated changes in heart rate at 0.5 to 6.25 hours postdose at 125 mg/kg was observed. A diminished trend not of biological significance occurred at 15 mg/kg with no effect observed at 5 mg/kg. In addition, daily repeat-dose toxicity studies of 4-week and 13-week duration have been conducted in rats and dogs. The oral dose levels in the 4-week toxicity study in rats were 5, 30, and 200 mg/kg/day (males) and 3, 10, and 200 mg/kg/day (females). In the 13-week repeat-dose toxicity study in rats, the oral dose levels were 10, 40 and 200 mg/kg/day in males and 2, 10, and 200 mg/kg/day in females. In the 4- and 13-week toxicity studies in dogs, dosages were 5, 15, 50, and 125 mg/kg/day for the 4-week study and 15, 30 and 60 mg/kg/day in the 13-week study. The no-observed-adverse-effect level (NOAEL) in the rat toxicity studies was the maximum feasible dose of 200 mg/kg/day. The NOAEL in the dog toxicity studies was 15 mg/kg/day in males and 50 mg/kg/day in females for the 4-week study. The NOAEL was 30 mg/kg/day for both males and females in the 13-week dog toxicity study, because of morbidity attributed to hepatic cholestasis and renal tubule degeneration considered secondary to hepatic changes at 60 mg/kg/day, which led

to euthanasia of 2 dogs at Day 85. These animals have elevated ALT, AST, bile acids, BUN, creatinine, GGT, PHOS, and TBILI before euthanasia, and increases in ALP and CHOL as early as Day 14. This finding was monitorable, based on plasma chemistry changes at all dose levels and as early as Day 14 in the high dose group, which preceded clinical signs. After a 4-week treatment-free period, there was no evidence of recovery of biliary hyperplasia, multi-nucleated cells, or mixed cell infiltrate and single cell hepatic necrosis; however, elevations in plasma chemistry values were largely reversible (trending down of elevated liver function tests at all dose levels in the recovery group dogs).

Due to this finding of cholestatic liver injury being monitorable, partially reversible, and observed in dogs but not rats, the selected doses are projected to result in plasma exposures of TAK-041 below those associated with the NOAEL in the dog 13-week toxicology study. Further information from the nonclinical studies, summarized above, can be found in the current Investigator's Brochure. Overall, the nonclinical PK and safety package summarized herein provide support for the clinical evaluation of TAK-041.

4.2 Rationale for the Proposed Study

The nonclinical pharmacology and toxicity data support the proposed study in healthy subjects, which will be the first TAK-041 study in humans. This study will evaluate the safety, tolerability, and PK of TAK-041 following single or multiple oral dose administrations in male and female healthy subjects (Part 1 and Part 2) and as add-on therapy to antipsychotics in subjects with stable schizophrenia (Part 4). In addition, an immediate release tablet formulation for TAK-041 was recently developed. Part 3 of this study is designed to assess the oral bioavailability of TAK-041 in healthy subjects administered as a 40 mg tablet formulation relative to the 40 mg oral suspension formulation in the fasted state, and to assess the effect of a high-fat, high-calorie meal on the pharmacokinetics of a single dose of the 40 mg tablet formulation of TAK-041.

Part 1 Cohorts 1 and 2, which have already been completed, participated in a 2-period, alternating panel, double-blind design to evaluate single-rising doses of TAK-041 or matched placebo with a washout period of at least 7 days between treatment periods. Following single oral dose administrations of TAK-041 over the dose range of 5 to 40 mg under fasted conditions, TAK-041 was rapidly absorbed with a median t_{max} of 1 to 2 hours. Elimination of TAK-041 from plasma was slow (mean $t_{1/2}$ approximately 11 days). Area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}) increased approximately dose proportionally from 1660 ng*hr/mL at 5 mg to 11952 ng*hr/mL at 40 mg. Over this dose range, maximum observed plasma concentration (C_{max}) increased from 140 to 747 ng/mL. The following study safety information is preliminary and based on blinded adverse event data reported by the investigator and blinded safety endpoint data in study TAK-041-1001. Although not expected, these data are subject to change upon finalization following study monitoring, source data verification, and discrepancy query management prior to database lock. Preliminary results indicate that single doses of 5, 10, 20, and 40 mg TAK-041 are well tolerated and safe. Seven AEs were observed in this study, chest pain from acid reflux, deja vu, epistaxis, and fatigue in one subject, tiredness, and upper respiratory infection in one subject, and contact dermatitis from ECG leads in one subject; all seven AEs were mild, were judged by the investigator to be not related to the study drug, and

resolved without treatment. There were no serious AEs or severe AEs. There were no clinically meaningful abnormalities in safety laboratory results (including ALP, AST, ALT, GGT, and TBILI) and no clinically significant abnormalities in physical examination, vital signs, or ECG results were reported for the 16 subjects who received 5 to 40 mg doses of TAK-041 or matching placebo in TAK 041 1001 Cohorts 1 and 2.

Based on the preliminary results from these first 2 cohorts (Cohorts 1 to 2) and due to the unexpected observation of approximately 11 day $t_{1/2}$ of TAK-041, healthy subjects in Part 1 Cohorts 3 to 5 and Part 2 Cohorts 1 onwards will participate in a sequential panel, double-blind design to evaluate single-rising doses (Part 1) or multiple-rising doses (Part 2) of TAK-041. 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.

For the evaluation of the effect of food on the TAK-041 immediate release tablet formulation, since PD or efficacy will not be evaluated, no control group will be used and therefore, an open-label study design will be utilized. A parallel design is selected due to the prolonged $t_{1/2}$ (~11 days) of TAK-041. In accordance to the regulatory guidance on the bioavailability[3] and bioequivalence assessment for drugs with long $t_{1/2}$, a 96-hour PK sampling period is considered adequate to ensure completion of gastrointestinal transit and absorption of TAK-041 after oral administration. Since 96 hours postdose is a common sampling time point in Study TAK-041-1001, along with C_{max}, the PK parameter AUC_{96} can be used to assess the relative bioavailability between the oral suspension formulation and the oral tablet formulation. Based on the preliminary PK analysis, AUC_{96} was approximately 23% of AUC_{∞} following a single 20 or 40 mg dose of TAK-041 via oral suspension, and the corresponding intersubject variability for AUC_{96} ranged from 9.1% to 26.8%.

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5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Primary Objectives

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 of 40 mg immediate release tablet formulation of TAK–041 in healthy subjects (Part 3).

5.1.2 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).

5.1.3 Exploratory Objectives

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[redacted]

5.2 Endpoints for Part 1 and Part 2 and Part 3 (Healthy Subjects) and Part 4 (Subjects with Schizophrenia)

5.2.1 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}).

5.2.2 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.

5.2.3 Exploratory Endpoints

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[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

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. This study design in this amendment reflects a modification of the original design, due to the longer than expected half-life of TAK-041 observed after the single-dose administration of the compound to healthy subjects in the first 2 cohorts. 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 dose 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 (1x 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 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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6.1.1 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 6.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 6.a). Although planned, all subsequent doses after the dose of 80 mg for Cohort 3 will be determined based on the emerging safety, tolerability, and PK data from the preceding cohorts.

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 C_{max} 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 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 6.a.

Table 6.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 6.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 6.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.

6.1.2 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 ($C_{av,ss}$) below the $C_{av,ss}$ 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 6.d.

Table 6.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.

Bond-Lader visual analog scales 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 6.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 (healthy subjects, Cohorts 1-4).

6.1.3 Part 3: Single Dose: Healthy Subjects Relative Bioavailablity 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 6.f.

Table 6.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 6.g.

Table 6.g Part 3 Tablet Formulation / Food Effect Study Schedule (Healthy Subjects)

Pretreatment		Treatment Period			Follow up (a)
Screening	Check-in	Dosing and Study Assessments	Safety and PK Assessments		
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.

6.1.4 Part 4: Single 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. 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 levels 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 escalation 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. The 24 subjects will be randomized with 16 active : 8 placebo.

Overall, Part 4 of the study will consist of a Screening Visit (Days -35 to -3), a predose Check-in Day for all subjects (Days -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 when all subjects will undergo 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.

Bond-Lader visual analog scales 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 6.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 Appendix D/E.

6.1.5 End of Trial

End-of-Trial is defined as the last assessment of the last subject (the Final Study Completion Visit).

6.1.6 Dose Escalation

All decisions concerning dose escalation will be made by Takeda (at a minimum, the clinical science representative(s) and the principal investigator/designee). 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. In addition to this dose escalation review, during the conduct of Part 1, Cohorts 3 to 5, and all cohorts in Part 2, certain sponsor staff not directly involved with the treatment or evaluation may be unblinded to the treatment or intervention. Dose escalation from the previous dose level and will only occur following agreement between the investigator and Takeda. The subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Based on emerging safety, tolerability, and available PK data, the planned dose levels may be modified in accordance with the following:

<u>For Part 1, Cohorts 1 and 2:</u>

- Dose escalations will be limited to an escalated dose that is predicted to give no greater than a 3-fold increase in either C_{max} or AUC. The AUC of the highest planned dose level is predicted not to exceed the mean, male-female combined AUC_{24} (ie, approximately 93,070 ng·hr/mL) for Part 1 or $C_{av,ss}$ (3,878 ng/mL) at the NOAEL of the 13-week toxicity study (the more sensitive species) for Part 2.

For Part 1, Cohorts 3 to 5:

- The highest planned dose is predicted to have C_{max} 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.

For Part 2, All Cohorts:

- Dose escalations will not exceed the highest dose evaluated, deemed safe, and well tolerated in Part 1. The highest proposed weekly dose after the loading dose will have a predicted mean average concentration during a dosing interval, at steady state ($C_{av,ss}$) that is below the $C_{av,ss}$ observed at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study.
- Though modeling will be used to prevent escalation to doses that could exceed these exposures, further escalation will stop if the mean C_{max} or AUC from a cohort exceeds these limits. Lower doses may be explored at that time.
- Additionally, Takeda and the principal investigator/designee may jointly decide to not escalate the dose for a particular period/cohort, but rather administer the same or a lower dose level to the next cohort.

For Part 3:

- The TAK-041 40 mg tablet formulation is designed for immediate drug release and has been manufactured as 40-mg strength for the study, based on safety/tolerability of the same dose in healthy subjects from Part 1 and 2.

For Part 4:

- The dose will not exceed the highest dose evaluated, deemed safe, and well tolerated in Part 1. The highest proposed weekly dose after the loading dose will have a predicted mean average concentration during a dosing interval, at steady state ($C_{av,ss}$) that is below the $C_{av,ss}$ observed at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study.
- 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.

Part 1 Cohorts 1 and 2, there will be a minimum washout period/interval of 7 days between each dose escalation to allow for a full-blinded review of all available safety, tolerability, and PK data. For Part 1 Cohorts 3 to 5, and Part 2, Cohorts 1 to 4, there will be a minimum interval of 21 days between each dose escalation to allow for a sponsor review of all available safety, tolerability, and available PK data. For each dose level administered/completed, the principal investigator and Takeda will determine whether dosing should stop or continue (and, if continue, at what dose, including whether to repeat the previous dose), and whether additional sequential dosing should be implemented in future periods/cohorts.

All adverse events reported during the Treatment Period, both within and across cohorts, up to the time of discharge, will be evaluated to assess the need for subject and/or study termination in accordance with the prespecified criteria for discontinuation/termination (Section 6.3.1).

Following assessment of the adverse event data and predefined criteria for study termination, dose escalation may be interrupted/stopped if these criteria are met. Based on review of study data as outlined above, Takeda in consultation with the principal investigator/designee will decide if and how it is appropriate for the study to proceed.

If agreement regarding a dose escalation decision cannot be reached between the principal investigator/designee and Takeda, the study will be stopped.

The principal investigator or designee will comprehensively examine the blinded safety results (AEs, vital signs, neurological assessments, ECG findings, and records of laboratory tests) obtained at all study examinations after the start of study medication administration and then determine the entry of the next period/cohort after discussion(s) with the sponsor and medical experts, as appropriate.

Other criteria to consider discontinuation of the dose escalation or go to a lower dose cohort are detailed in Section 6.3.2.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

A primary objective of the study is to characterize the safety and tolerability of TAK-041 following oral single and multiple dose administrations in healthy subjects and subjects with stable schizophrenia. As reproductive toxicity studies have not been completed, female subjects of childbearing potential will not be eligible for enrollment and male subjects who are sexually active with a female partner of childbearing potential will be required to use an acceptable form of contraception.

Part 1, 2 and 4 of this study will be double-blind and placebo-controlled to avoid subjective bias in the assessment of the safety, tolerability, and pharmacological effects of TAK-041.

An alternating panel design is proposed for Part 1 SRD Cohorts 1 and 2 because it provides an efficient and robust assessment of within-subject variability on the safety/tolerability and dose proportionality.

Study TAK-041-1001 has enrolled and dosed a total of 16 subjects (12 active and 4 placebo) in an alternating panel design (2 cohorts) at 5, 10, 20 and 40 mg. (Cohort 1 received 5 and 20 mg doses and Cohort 2 received 10 and 40 mg doses) with a washout period of at least 7 days between the 2 treatment periods.

Based on the preliminary results from these first 2 cohorts (Cohorts 1 to 2) and due to the unexpected observation of approximately 11 day $t_{1/2}$, Part 1 Cohorts 3 to 5, Part 2, and Part 4 will participate in a sequential panel, double-blind design to evaluate the safety, tolerability, and PK following single- or multiple-rising doses of TAK-041 or matched placebo. Investigator and

subjects will be kept blinded throughout the study. For Part 2, a weekly dosing regimen with a twice as high loading dose on Day 1, followed by weekly dosing on Days 8, 15, and 22 is planned. The higher loading dose is incorporated to shorten the time necessary to attain steady-state plasma concentrations of TAK-041. A population pharmacokinetic model was developed using the available data from Part 1 Cohorts 1 and 2, and based on modeling and simulations, approximately 92% to 93% of the estimated steady-state C_{max} levels will be attained by the last weekly dose on Day 22.

For Part 1 Cohorts 1 and 2 Period 2, the Follow-up period was extended due to the unexpectedly long half-life of TAK-041. For Part 1 Cohorts 3 through 5, Part 2, and Part 4 of this study, a 6-week Follow-up period (approximately 4 half lives of TAK-041) following the last dose is proposed to fully characterize the single- and multiple -dose PK of TAK-041. It is expected that the population mean plasma concentration at the end of the Follow-up period will be at or below 9% of the corresponding C_{max} value follow a single dose (Part 1) or the last dose on Day 22 (Part 2 and Part 4). All subjects administering placebo will be followed and plasma samples collected identically to subjects administered TAK-041.

The primary objective of Part 3 the study is to determine the oral bioavailability of TAK-041 in healthy subjects administered as a 40 mg immediate release tablet formulation in the fasted state compared to 40 mg oral suspension formulation in the fasted state and to estimate the effect of food on the pharmacokinetics of a single dose of 40 mg immediate release tablet formulation of TAK-041 in healthy subjects.

6.2.2 Dose Selection

A comprehensive series of nonclinical safety studies (GLP) have been conducted with TAK-041 to support early human studies: hERG, electrocardiography in dogs, respiratory and CNS in rats, genetic toxicity studies (Ames, in vitro micronucleus, in vivo micronucleus), or in vivo phototoxicity. An effect of TAK-041 was first observed at 1 μM in the human hERG assay (IC_{50} >3 μM); however, no changes in ECG parameters were observed in the in vivo dog CV or 4-week repeat-dose toxicity study at 125 mg/kg. In the dog CV study, an increase in systolic blood pressure (10% relative to predose values) resulting in increases in mean arterial and pulse pressures without any associated changes in heart rate at 0.5 to 6.25 hours postdose at 125 mg/kg. In addition, daily repeat-dose toxicity studies of up 13-weeks in duration have been conducted in rats and dogs. The maximum oral dose administered in the 4-week toxicity study in rats was the maximum feasible dose of 200 mg/kg/day. Oral doses in dogs were 5, 15, 50, and 125 mg/kg/day in the 4-week study and 15, 30, and 60 mg/kg/day in the 13-week study.

In the recently completed 13-week toxicity studies, there were no pathological findings in rats, and the NOAEL was the highest dose tested of 200 mg/kg/day.

The NOAEL in the dog toxicity studies was 15 mg/kg/day in males and 50 mg/kg/day in females for the 4-week study. The NOAEL was 30 mg/kg/day for both males and females in the 13-week dog toxicity study, due to marked cholestatic liver injury at 60 mg/kg/day, which led to euthanasia of 2 dogs at day 85 due to jaundice and moribundity. This finding was monitorable, based on plasma chemistry changes at all dose levels and as early as Day 14 in the high dose group, which

preceded clinical signs. Elevations in plasma chemistry values were also largely reversible (trending down of elevated liver function tests at all dose levels in the recovery group dogs). Histopathology was not definitively reversible after one month, however given the reduction in plasma hepatobiliary markers (eg, ALP, GGT, TBILI), recovery of histopathological changes might have occurred after a longer recovery period.

Due to this finding of cholestatic liver injury being monitorable, partially reversible, and observed in dogs but not rats, the selected doses are projected to be result in plasma exposures of TAK-041 below those associated with the NOAEL in the dog 13-week toxicology study. Further information from the nonclinical studies, summarized above, can be found in the current Investigator's Brochure. Overall, the nonclinical PK and safety package summarized herein provide support for the clinical evaluation of TAK-041.

Table 6.i Findings above the NOAEL

Species	Study	NOAEL Dose (mg/kg/day)	Day τ Exposure (a) C_{max} (ng/mL)	Day τ Exposure (a) AUC_{0-24} (ng.hr/mL)	Findings above NOAEL
Rat	4-week	200			None of toxicological significance.
	13-week	200	22984	344,644	None of toxicological significance.
Dog	4-week	15 (male) 50 (female)			1 male animal euthanized on Day 24 in moribund condition; blood chemistry elevations consistent with cholestasis and altered renal function
	13-week (b)	30	8528	93,070	2 animals euthanized on Day 85 for jaundice, moribundity; blood chemistry elevations consistent with cholestasis and altered renal function.

(a) Mean of male and female for exposure at the end of the repeat dosing period.
(b) 3 male and 3 female per dosing group in each of the main (13-week) and recovery (4-additional-week) studies

Based on the available data from the completed Part 1 Cohorts 1 and 2, a single dose up to 40 mg TAK-041 was safe and well tolerated, and PK of TAK-041 appeared to be linear over the dose range of 5 to 40 mg. A two-fold dose increment to 80 mg is proposed for Part 1 Cohort 3. Depending on the emerging safety, tolerability and PK data from the completed cohorts, the dose in Part 1 may be further increased to 120 and 160 mg in Cohorts 4 and 5, respectively. At the highest planned dose in Cohort 5 (160 mg), the expected C_{max} is 2903 ng/mL and AUC_{24} 47,828 h.ng/mL, representing a 2.9- and 1.9-fold margin, respectively, compared to the $C_{max,ss}$ and $AUC_{24,ss}$ values at NOAEL of 30 mg/kg/day from the recently completed 13-week toxicology study in dogs.

For Part 2 of this study, the planned starting dose in Cohort 1 is 40 mg on Day 1 followed by weekly doses of 20 mg on Days 8, 15 and 22 (40/20). Although a single dose of 40 mg was shown

to be safe and well tolerated, to further ensure the safety of the subjects following multiple doses of TAK-041, Part 2 Cohort 1 will be initiated after the dose escalation safety review of 21-days of safety, tolerability, and available PK data from Part 1 Cohort 3 (80 mg). The exposure over the 1st week of dosing following the loading dose in Part 2 is expected to be similar to that from Part 1 at the same dose, and the exposure over each subsequent dosing interval is estimated to be lower compared to that in the 1st dosing interval. Due to the different dosing intervals in Part 2 of this study (weekly) and toxicology studies in dogs (daily), $C_{av,ss}$ will be used to compare the estimated clinical exposure and steady-state exposure at NOAEL in dogs. At the planned doses in Cohorts 1 (40/20), 2 (80/40), 3 (120/60), and 4 (160/80) of Part 2, $C_{av,ss}$ is estimated to be 543, 1069, 1594, and 2151 ng/mL, representing a 7.3-, 3.6-, 2.4-, and 1.8-fold margin, respectively, compared to the mean $C_{av,ss}$ at NOAEL (30 mg/kg/day) from the 13-week toxicology study in dogs.

The TAK-041 40 mg tablet formulation is designed for immediate drug release and has been manufactured as 40-mg strength for the study, based on safety/tolerability of the same dose in healthy subjects from Part 1 and 2.

The highest planned loading dose in Part 4 will not exceed the highest dose evaluated, deemed safe, and well tolerated in Part 1 and Part 2. The highest proposed weekly maintenance dose will have a predicted mean average concentration during a dosing interval, at steady state ($C_{av,ss}$) below the $C_{av,ss}$ observed at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study.

Overall, the proposed dose range of TAK-041 to be explored in this FIH study is anticipated to achieve sufficient range of plasma exposures with a margin above and beyond the predicted pharmacologically active exposures/concentrations established in preclinical models. The preliminary safety/tolerability and PK data, as well as PD information will facilitate the design of a proof-of-concept (POC) study in a patient population. Overall, data from this study in conjunction with data from other studies will be used to inform dose selection and regimen for the POC study.

6.2.3 Endpoints

The primary endpoints for this study are 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 secondary endpoints consist of standard PK variables to determine drug exposure at each dose to facilitate dose escalation. The endpoints for evaluation of the TAK-041 tablet formulation (C_{max} and AUC_{96}) in Part 3 are standard exposure metrics to assess the oral bioavailability of TAK-041 and estimate the effect of food on TAK-041 exposures. The use of standard noncompartmental PK parameters are consistent with FDA bioavailability and food effect guidance [3].

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6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

1. New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for TAK-041, such that the risk/benefit profile for TAK-041 is no longer acceptable for subjects participating in the study.
2. Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
3. Two or more subjects in any single cohort or across more than 1 cohort experience any of the Takeda Medically Significant events (as outlined in Table 10.a).*
4. Abnormal liver function:
    a) Two or more subjects at any single dose level or across dose levels experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limit of normal (ULN) in the absence of a concomitant bilirubin increase.*
    b) One or more subjects at any single dose level or across dose levels experience ALT and/or AST elevations >3 × ULN in the presence of a total bilirubin increase >2 × ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternative etiology to explain the elevations (ie, "Hy's Law cases").
    c) Two or more subjects in any single dose level or across dose levels experience ALT and/or AST elevations >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).*
    d) One or more subjects at any single dose level or across dose levels experience ALP elevations >1.5 × ULN in conjunction with elevated total bilirubin >1.5 × ULN or

elevated 5'nucleotidase >2 × ULN or elevated GGT >5 × ULN or elevated AST/ALT >3 × ULN.

e) One or more subjects at any single dose level or across dose levels experience ALP elevations >2 × ULN that persists for longer than 3 days.

f) One or more subjects at any single dose level or across dose levels experience ALP elevations >3 × ULN.

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

6.3.2 Study-Specific Dose Escalation and Stopping Rules

1. Dose escalation between cohorts and within a cohort will be decided after either a full-blinded (Part 1, Cohorts 1 and 2) or a sponsor partial unblinded (Part 1, Cohorts 3 to 5, and Part 2, Cohort 1 onwards, where certain sponsor staff not directly involved with the treatment or evaluation may be unblinded to the treatment or intervention) review of at least 21 days of safety, tolerability, and available PK data from the previous dose. The selection of each subsequent dose will be made jointly and agreed upon by the sponsor and the principal investigator/designee and after careful evaluation of all available data from previous doses.
2. Dose escalation will be stopped at a dose level (ie, one escalation step) below the dose that is predicted to give a TAK-041 AUC24 or Cmax that exceeds the mean AUC24,ss or Cmax,ss (Part 1) or Cav,ss that exceeds Cav,ss (Part 2) at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13 week toxicology study.
3. Escalation will stop once the maximum tolerated dose has been reached or previously defined toxicokinetic exposure limits are met.
4. Dose escalation may not proceed if any of the following occur at the previous dose cohort, although dosing may be resumed at a lower dose in the subsequent cohort:
    a) Significant study drug-related adverse events of severe intensity in ≥3 subjects.
    b) One or more subjects experience clinically significant ECG abnormalities or effects on vital signs indicating dose-limiting intolerance.
    c) One or more subjects experience clinically significant changes in neurological assessments indicating dose-limiting intolerance.
    d) One or more subjects in a cohort experiences a study drug-related serious adverse event (SAE).
    e) One or more subjects has abnormal liver function tests as described in Section 6.3.1 that can be considered related to study drug.
    f) Subject experiences any of the Takeda Medical Significant Events (Table 10.a) that can be considered related to study drug.

5. Within each dose level, if at least 1 subject develops a dose-limiting toxicity (DLT) listed in Table 6.j which is confirmed by repeat test if applicable, no further dosing will occur in that subject if the subject has received TAK-041.

Table 6.j Definition of DLTs

Toxicity	Definition
Leukopenia	Total leukocyte count <2500 cells/mm^3 (2.5 x10^9/L)
Neutropenia	Absolute neutrophil count <1500/mm^3 (1.5 x10^9/L)
Thrombocytopenia	Platelet count <100 x10^9/L
Lymphopenia	Lymphocyte count <1000 cells/mm^3 (1 x10^9/L)
Anemia	Red blood cell count <3.5 x10^{12}/L (men) or <3.0 x10^{12}/L (women)
Low Hemoglobin	Hemoglobin <11 g/dL (men) or <10.5 g/dL (women)
Severe Infection	Serious infection requiring hospitalization, intravenous antibiotics, systemic antifungal or antiviral intervention
QTc	QTc >500 msec

6. After review of the safety data and discussion/agreement between the investigator and Takeda, the same dose may be given again or a lower dose may be given in subsequent periods/cohort to increase data within the dose range.
7. The dose increments and planned doses may be changed as the study progresses dependent upon emerging PK, safety, and tolerability data. Any decision to alter the planned dose scheme and the decision on which doses to use will be made jointly and agreed upon by the investigator and Takeda after careful evaluation of all available data.
8. Should significant adverse events occur, any decision to resume dosing at the current dose level or to escalate the dose will be made jointly by the investigator and Takeda after careful evaluation of all available data and will be communicated to the Institutional Review Board (IRB).

6.3.3 Criteria for Premature Termination or Suspension of Investigational Sites

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

6.3.4 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

7.1.1 Healthy subjects and subjects with schizophrenia

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures including requesting that a subject fast for any laboratory evaluations.
3. The subject is willing to comply with study restrictions (see Sections 7.3 and 7.4 for a summary of restrictions).
4. The subject is an adult man or woman (of non-childbearing potential).*
5. The subject is judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the Screening Visit and prior to administration of the initial dose of study drug.
6. The subject is aged 18 to 55 years, inclusive, at the time of informed consent.
7. The subject weighs at least 45 kg (99 lb) and has a body mass index (BMI) from 18 up to 32 kg/m^2 for healthy subjects and up to 40.5 kg/m^2 for subjects with schizophrenia, inclusive at Screening.
8. A male subject who is non-sterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 145 days (ie, 90 days after 5 half-lives) have elapsed since the last dose of study drug.

*Definitions and acceptable methods of contraception are defined in Section 9.1.10 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11 Pregnancy.

7.1.2 Subjects with schizophrenia only

All entry criteria, including test results, need to be confirmed prior to randomization.

1. The subject is on a stable dose of an antipsychotic medication for at least 2 months as documented by medical history and assessed by site staff (other than those excluded in Table 7.b).

2. The subject meets schizophrenia criteria as defined by the DSM-5 by the Mini International Neuropsychiatric Interview (MINI).
3. The subject has PANSS total score ≤90 and PANSS Negative Symptom Factor Score (NSFS; Sum of PANSS N1, N2, N3, N4, N6, G7, and G16) ≥15 at screening and baseline (Day-1).
4. The subject has stable screening and baseline (Day -1) PANSS and NSFS total scores (<20% change).

7.2 Exclusion Criteria

7.2.1 Healthy subjects

Note: Subjects with schizophrenia who meet any of the criteria listed below with the exception of Number 9, and 14 will also not qualify for entry into the study. For criteria that are also represented in Section 7.2.2 for subjects with schizophrenia, those criteria supersede the criteria in this section (Section 7.2.1).

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

1. The subject has received any investigational compound within 30 days prior to the first dose of study drug, or due to the half-life of the investigational drug is likely to still have detectable plasma levels of that compound.
2. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
3. The subject has a known hypersensitivity to any component of the formulation of TAK-041.
4. The subject has a positive urine/blood drug result for drugs of abuse (defined as any illicit drug use) at Screening or Day -1.
5. The subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications and Dietary Products (Table 7.a for healthy subjects and Table 7.b for subjects with schizophrenia in Section 7.3) or is unable to refrain from or anticipates the use of any medication (except those prescribed) as described in (Table 7.a for healthy subjects and Table 7.b for subjects with schizophrenia in Section 7.3).
6. The subject is lactose intolerant (Part 3 only).
7. If female, the subject is of childbearing potential (eg, premenopausal, not sterilized).
8. If male, the subject intends to donate sperm during the course of this study or for 145 days (ie, 90 days after 5 half-lives) have elapsed since the last dose of study drug.
9. The subject has evidence of current active cardiovascular, central nervous system, hepatobiliary disease including history of biliary tree disorders, gallstones, endoscopic retrograde cholangio pancreatography (ERCP), and/or cholecystectomy, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's

medical history, physical examination, or safety laboratory test results (including elevated ALP, elevated bilirubin, elevated GGT, or elevated 5'-nucleotidase) that in the judgment of the principal investigator represents a reasonable suspicion of a disease that would contraindicate taking TAK-041, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, cholestasis, seizure disorders, and cardiac arrhythmias.

10. The subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
11. Had major surgery, or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to Screening.
12. The subject has a history of cancer, except basal cell carcinoma that has been in remission for at least 5 years prior to Day 1.
13. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody at Screening or a known history of human immunodeficiency virus (HIV) infection.
14. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 21 days prior to Check-in on Day -1. Cotinine test is positive at Screening or Day -1.
15. The subject has poor peripheral venous access.
16. The subject had a transfusion of any blood product within 30 days prior to Day 1.
17. The subject has a Screening or Check-in abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature of the principal investigator or a medically qualified sub-investigator.
18. The subject has a sustained resting heart rate outside the range 40 to 100 beats per minute (bpm), confirmed on repeat testing within a maximum of 30 minutes, at Screening or Check-in.
19. The subject has a QT interval with Fridericia correction method (QTcF) >450 ms or PR outside the range 120 to 220 ms, confirmed on repeat testing within a maximum of 30 minutes, at the Screening Visit or Check-in.
20. The subject has abnormal Screening or Check-in laboratory values (> ULN for the respective serum chemistries) of ALT, AST, TBILI, ALP, GGT, 5'nucleotidase (Screening only) and/or abnormal urine osmolality, confirmed upon repeat testing.
21. The subject has a clinically significant history of head injury or trauma associated with loss of consciousness for > 15 minutes.
22. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or subjects who within the past year prior to Screening have attempted

suicide. Subjects who have positive answers on item 4 or 5 on the C-SSRS (based on the past year) prior to randomization are excluded.

23. The subject has a history of significant skin reactions (hypersensitivity) to adhesives, metals or plastic; this criterion applies only to subjects participating in the study of the two wearable digital devices.
24. The subject is unsuitable for inclusion in the trial in the opinion of the investigator or sponsor.

7.2.2 Subjects with schizophrenia only

Note: Subjects with schizophrenia must not meet any of the criteria listed in Section 7.2.1 for healthy subjects with the exception of Number 9 and 14, as well the criteria listed below. The criteria listed below supersede the criteria in Section 7.2.1.

All entry criteria, including test results, need to be confirmed prior to randomization.

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

1. The subject has an undetectable level of baseline antipsychotic medication at Screening.
2. The subject has a lifetime diagnosis of schizoaffective disorder; a lifetime diagnosis of bipolar disorder; or a lifetime diagnosis of obsessive compulsive disorder based on the MINI combined with the general psychiatric evaluation. As an exception, subjects with a historical prior lifetime diagnosis of schizoaffective disorder may be enrolled in the study with sponsor or designee approval provided that the principal investigator can attest that the subject's overall history and current clinical presentation and history is most consistent with schizophrenia, not schizoaffective disorder.
3. The subject has a recent (within the last 6 months) diagnosis of panic disorder, depressive episode, or other comorbid psychiatric conditions requiring clinical attention based on the MINI for DSM-5 and the general psychiatric evaluation.
4. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as 4 or more alcoholic beverages per day) within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
5. The subject has a diagnosis of substance use disorder (with the exception of nicotine dependence) within the preceding 6 months based on the MINI for DSM-5 and the general psychiatric evaluation.
6. The subject has evidence or history of current clinically significant cardiovascular disease, including uncontrolled hypertension (standing or supine diastolic blood pressure >90 mm Hg and/or standing or supine systolic blood pressure >145 mm Hg, with or without treatment), symptomatic ischemic heart disease, uncompensated heart failure or recent (past 12 months) acute myocardial infarction or bypass surgery. Controlled essential hypertension, non-clinically significant sinus bradycardia and sinus tachycardia will not be considered significant medical illnesses and would not exclude a subject from the study. Other

well-controlled medical illnesses may be permitted that do not increase hepatic risks or other safety risks to the subject's participation in the judgement of the investigator in consultation with the sponsor or designee.

7. The subject has evidence of clinically significant extrapyramidal symptoms as measured by a Simson-Angus Scale (SAS) score >6.
8. The subject has evidence of depression as measured by a Calgary Depression Score (CDSS) score >9.
9. The subject has received TAK-041 in a previous clinical study; or has previously or is currently participating in this study; has received treatment with other experimental therapies within the preceding 60 days or <5 half-lives prior to randomization, whichever is longer; has participated in 2 or more clinical studies within 12 months prior to Screening; or has participated in a clinical study for a psychiatric condition that is exclusionary per this protocol.

7.3 Excluded Medications and Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities (eg, until subject is discharged from the unit).

Table 7.a Excluded Medications and Dietary Products for healthy subjects (Parts 1, 2 and 3)

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

OTC=over-the-counter.
(a) Occasional use of acetaminophen/paracetamol (≤1 g/day) or other medication as approved by Takeda on a case-by-case basis is allowed. Acetaminophen/paracetamol is prohibited on Day 1 in Part 1 and on Days 1, 8, 15 and 22 in Part 2.
(b) Inclusive of, but not limited to, H1N1 and flu vaccinations.
(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine.
(d) atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

Table 7.b Excluded Medications and Dietary Products for Subjects with Schizophrenia (Part 4)

Drug Class	Disallowed (X) During the Study (sections without [X] indicate no restriction)		
	Chronic Use	Episodic Use	Comments or Exceptions
Any investigational drug	X	X	<60 days before Screening or 5 half-lives – whichever is longer
Narcotic analgesics	X	X	
Anorexiants (eg, phentermine, benzphetamine, phendimetrazine, methamphetamine, amphetamine, stimulants, sibutramine, Belviq (lorcaserin), Qsymia (phentermine/topiramate)	X	X	Must be discontinued for ≥30 days prior to Screening
Antiarrhythmics of 1C class, quinidine	X	X	
Antibiotics	X		
Anticholinergics	X	X	Maximum dose of chronic anticholinergic treatment is 2 mg/day of benztropine or equivalent.
Antithrombic agents and anticoagulants (excluding warfarin, which is excluded)		X	
Anticonvulsants	X	X	Exception: gabapentin and pregabalin are permitted if they are prescribed at a stable dose for ≥2 months prior to Screening and throughout study treatment. Subjects taking other anticonvulsants should not be considered for participation in the study, as their discontinuation could lead to symptom instability.
Antidepressants (excluding tricyclic antidepressants, MAOIs, and RIMAs)		X	Tricyclic antidepressants, MAOIs, and RIMAs are excluded, and subjects taking them should not be considered for participation in the study, as their discontinuation could lead to symptom instability. All other antidepressants are allowed with chronic administration
Antihistamines	X	X	Except loratadine, desloratadine, cetirizine, levocetirizine, mizolastine, and fexofenadine.
Antihypertensives			Clonidine NOT allowed.
Antipsoriatic agents	X	X	Topical agents are allowed.
Antipsychotics		X	Phenothiazines (chlorpromazine, perphenazine, prochlorperazine, thioridazine), haloperidol, and clozapine are excluded and must be discontinued 60 days prior to screening; all other treatments must adhere to requirements outlined in the study entry criteria. As an exception, occasional use of an additional dose of the background antipsychotic may be permitted with sponsor or designee approval.

Drug Class		Disallowed (X) During the Study (sections without [X] indicate no restriction)		
		Chronic Use	Episodic Use	Comments or Exceptions
Herbal remedies, which are psychoactive (eg, St Johns Wort, kava kava, valerian, ginkgo biloba, melatonin)		X	X	Must be discontinued ≥7 days prior to Screening.
Sedative hypnotics				Barbituates are excluded. Chronic treatment with BZs is allowed up to 3 mg/day lorazepam or equivalent (BZ equivalence standards will be provided in a site reference document).
Insulin		X	X	
Mood stabilizers		X	X	
Medications that may interfere with cognitive function		X	X	Such as cold medicines containing antihistamine or dextromorphan as a cough suppressant are restricted
Tobacco and Nicotine containing products				Not restricted, except for 2 hours prior to and during baseline assessments and during PD testing (unless the subject exhibits nicotine withdrawal symptoms that pose a risk to the study PD assessments in the judgment of the investigator.
Psychotropic agents known to affect cognition		X	X	Such as long-acting sleep aids, amphetamines, barbiturates, lithium, methylphenidate, anticholinergics, antidepressants
Steroids	Systemic oral or injectable	X	X	As an exception, treatment with local steroid injections for orthopedic conditions may be permitted with sponsor or designee approval.
	Topical			
	Inhalant			
Stimulants		X	X	Must be discontinued for ≥30 days prior to Screening. Does not include substances containing caffeine or nicotine.
UGT enzyme inhibitors (probenecid and valproic acid)				Not within 14 days of dosing.

BZ=benzodiazepine, MAOI=monoamine oxidase inhibitor, RIMA=reversible inhibitor of monoamine oxidase type A, UGT=uridine 5'-diphosphate-glucuronosyltransferase.

Subjects from Parts 1, 2, and 3 must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

7.4 Diet, Fluid, and Activity Control

Subjects will be confined to the unit for the duration of each treatment period in Parts 1, 2, 3 and Part 4 as described in Appendix A, Appendix B, Appendix C, and Appendix D/E respectively. Subjects from Part 1 will be required to remain in the study unit during each treatment period from Check-in, Day 1 for single dose administration, and with Cohorts 1-5 at least 96 hours postdose for a total confinement period for each treatment period of 5 days. Subjects from Part 2 Cohorts 1 to 4, and Part 1 Cohorts 1 and 2, will be required to remain in the study unit from Day -2 to Day 3, Days

7 to 10, Day 14 to Day 17, and Day 21 to Day 24 (48 hours after each dose in Part 2) for safety, PK, and all study assessments before discharge. In addition, subjects will return to the clinic on Days 5, 26, 29, 36, 43, 50, 57, and 64 for safety and PK follow up visits. Subjects with schizophrenia (Part 4) will also undergo part-specific assessments on Days 29 and 43. A Final Visit that completes the study will occur 12 to 16 days after the last safety and PK Follow-up Visit. On the days of dosing, subjects will be administered TAK-041/matched placebo at approximately 0800 hours following a fast of at least 8 hours and will continue to fast for an additional 4 hours postdose.

Subjects from study Parts 1, 2 and 4 may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. The meal start and stop times and the amount consumed will be recorded in the source document and appropriate electronic case report form (eCRF) page for all meals served on the dosing days. During confinement on nondosing days, subjects will be given 3 meals and an evening snack each containing approximately 30% fat (relative to the total calories). Breakfast will not be served on dosing days.

Subjects from all study parts should remain upright (seated, standing, or ambulatory) for 4 hours following dose administration, except as necessitated by the occurrence of an AE /or study procedure (eg, obtaining 12-lead ECG). Subjects should refrain from strenuous exercise from 72 hours before Check-in and throughout the entire course of the study.

7.4.1 Part 3 Diet and Fluid Control

Subjects in Part 3 will be required to remain in the study unit for a confinement period of 3 days. The subjects will be randomized for TAK-041 immediate release tablet administration at approximately 0800 hours either following an overnight fast (no food, no drink other than water, no medications) of at least 10 hours or 30 minutes after starting ingestion of a high-fat, high-calorie breakfast as described in 2002 FDA Food-Effect Guidance (the meal composition should derive of approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively, in total of approximately 800 to 1000 calories).

Per FDA guidance, subjects will be served the standard FDA breakfast to be ingested and completely consumed over 30 minutes. TAK-041 40 mg tablet should be administered immediately after breakfast with a glass of water.

Substitutions to the contents of this high-fat, high-calorie meal can be made as long as the same meal is served to all subjects and a nutritionist at the site ensures that the test meal provides a similar amount of calories from protein, carbohydrates and fat and has comparable meal volume and viscosity. The clinical site will document the amount of protein carbohydrates and fat and total calorie content of the test meal for the study file and provide a copy to the sponsor. The date and time of the meal will also be recorded on the eCRF.

Fasting subjects will also be administered the 40 mg tablet with a glass of water. Both fasting and fed subjects will have no food, no drinks (except water) and no medications for 4 hours after dose administration.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.21.

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

   - Liver Function Test (LFT) Abnormalities

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

     – ALT or AST >8 × ULN.

     – ALT or AST >5 × ULN and persists for more than 2 weeks.

     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5.

     – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

     – ALP elevations >1.5 × ULN in conjunction with elevated total bilirubin >1.5 × ULN or elevated 5'nucleotidase >2 × ULN or elevated GGT > 5 x ULN or elevated AST/ALT >3 × ULN or elevated ALP >2 × ULN, persisting for longer than 3 days.

     – ALP >3 × ULN.

2. Significant protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the unit and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE).
5. Study termination. The sponsor, IRB, independent ethics committee, or regulatory agency terminates the study.
6. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

Note: Skin reactions (cutaneous hypersensitivity) to one of the wearable digital devices will lead to removal of that device for the remainder of the study, and dependent on PI assessment, the subject would not be required to discontinue the study.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Subjects who drop out for nonsafety reasons may be replaced on a case-by-case basis at the discretion of the sponsor in consultation with the investigator. Subjects who drop out for safety reasons will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

The TAK-041 oral crystalline suspension will be used in this study Parts 1, 2 and 4. The TAK-041 crystalline drug substance (milled) will be labeled in an open-label fashion and compounded into oral suspensions that will be labeled in a blinded fashion for third party dispensing. An unblinded pharmacist will manage and prepare doses as needed throughout the study. The oral suspensions will contain 5 to 160 mg of TAK-041 per dose. Compounding instructions will be provided to the clinical site using the compounding worksheet or a similar document.

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

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

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

Table 8.b Composition of Crystalline TAK-041 Oral Suspension

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

(a) Amount shall be in the range of 5 mg to 160 mg, which corresponds to a dose of 5 to 160 mg TAK-041, and a concentration range of 0.07 to 2.29 mg/mL TAK-041.

A placebo suspension will be prepared by weighing an appropriate amount of HPMCAS-M into a dosing bottle. Add 70 mL of 0.5% methylcellulose (MC) vehicle (MC vehicle) and mix well. The composition of the placebo suspension is in Table 8.c.

Table 8.c Composition of Placebo to TAK-041 Oral Suspension

Component	Quantity per Dosing Bottle
Hydroxypropyl methylcellulose acetate succinate-medium grade (HPMCAS-M), NF	(a) mg
0.5% MC vehicle (MC vehicle)	70 mL

(a) Amount determined by the active dose used in the cohort and period. The amount shall be the same as that in the active dose in the same cohort and period, in a range of 5 to 160 mg.

The TAK-041 40 mg tablet will be used in this study for Part 3. The tablet formulation is designed for immediate drug release [redacted] The tablets are round and film coated.

8.1.1.1 Sponsor-Supplied Drug

For Parts 1, 2, and 4, the TAK-041 crystalline drug substance (milled) will be supplied in a powder form, in appropriate packaging, and each container will bear a single panel label that includes all pertinent study information.

The TAK-041 40 mg immediate release tablet will be used in this study for healthy subjects in Part 3. The tablets are packaged in amber glass bottles. Each bottle will contain a label that includes pertinent study information and caution statements.

8.1.2 Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

TAK-041 crystalline drug substance (milled) and 40 mg tablets are stored at controlled room temperature (20°- 25°C with excursions allowed from 15°-30°C).

8.1.3 Dose and Regimen

The planned initial dose of TAK-041 for Part 1 SRD Cohort 1 Period 1 is 5 mg. Doses for subsequent periods/cohorts will be determined based on the available safety, tolerability, and PK data from the preceding period/cohort. The doses will be administered to the subjects by the investigator or the investigator's designee. Subjects will receive the doses by drinking the entire suspension from the dosing bottle. The dosing bottle will then be rinsed with 35 mL of water and the rinse will be administered in the same manner as the suspension. The rinse and administration will be repeated one more time.

Eligible subjects in Part 3 will be randomized to receive a single dose of TAK-041 as one 40 mg tablet administered orally after either an overnight fast of at least 10 hours or 30 minutes after starting ingestion of a high-fat and high-calorie breakfast as recommended in the 2002 FDA Food-Effect Guidance [3] (the meal should derive of approximately 150, 250 and 500 to 600 calories from protein, carbohydrate and fat, respectively, in total of approximately 1000 calories).

The tablet must be administered with a glass of water (approximately 240 mL). It should be swallowed as a whole and not be manipulated in any way.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment according to the randomization schedule allocated to the site. The Randomization Sequence Number will be entered onto the eCRF.

Investigational drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Subjects are to fast overnight for at least 8 hours prior to dosing on Day 1 (in Part 1) and on Days 1, 8, 15 and 22 (in Part 2 and Part 4). Subjects in Part 3 will be randomized to receive TAK-041 as one 40 mg tablet administered orally after at least 10 hours of overnight fast or 30 minutes after starting ingestion of a high-fat, high-calorie breakfast. On all dosing days, subjects in all study parts will be allowed to eat 4 hours postdose. Descriptions of the study supplied meals and dietary fat content, and timing of assessments in relation to dosing can be found in Section 7.4.

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 treatment as the subject they replace. Subjects who drop out for safety reasons will not be replaced.

For each dosing cohort in Parts 1, 2, 3, and 4, randomized subjects will be assigned a 4-digit randomization number in the order they are enrolled. Randomization sequence numbers will be XY01 to XY08 for Parts 1 and 2, XY01 to XY18 for Part 3, and XY01 to XY24 for Part 4, where X refers to study part (1, 2, 3 or 4) and Y refers to cohort number.

For example:

- Subjects in Part 1 Cohort 1 will have randomization sequence numbers 1101 to 1108 and subjects in Part 1 Cohort 2 will have randomization sequence numbers 1201 to 1208.

- Subjects in Part 2 Cohort 1 will have randomization sequence numbers 2101 to 2108, subjects in Part 2 Cohort 2 will have randomization sequence numbers 2201 to 2208, and subjects in Part 2 Cohort 3 will have numbers 2301 to 2308.
- Subjects in Part 3 will have randomization sequence numbers 3101 to 3118.
- Subjects in Part 4 will have randomization sequence numbers 4101 to 4124.

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

If a subject needs to be replaced, the replacement subject will receive the same treatment or treatment sequence of the subject being replaced. The replacement randomization number will be 50 larger than the randomization number of the subject who is being replaced. For example, randomization number 1251 will be used for the subject who replaces the subject who had randomization number 1201, using the same treatment or treatment sequence in Part 1 Cohort 2.

Study drugs will be dispensed in the unit under the supervision of the investigator or designee.

8.3 Randomization Code Creation and Storage

TDC Americas Analytical Sciences Department or designee will generate the randomization schedule and a copy will be provided to the site pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist and the randomization statistician.

8.4.1 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor or designee should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

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

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

No change should be made to any assessment of the subject after unblinding.

8.5 Accountability and Destruction of Sponsor-Supplied Drugs

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

The investigator or designee must ensure that the sponsor-supplied drugs are used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (TAK-041 and matched placebo), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

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

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study.

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative or unblinded pharmacy monitor, otherwise uninvolved with study conduct, will review the randomization schedule and subject dosing log prior to Day 1 for all Cohorts/Periods dosing and following dosing to ensure all subjects received the correct dose of study medication.
- If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (TAK-041 and matched placebo) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry and/or retest dates, date and

amount dispensed, including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

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

In the event of expiry date extension of supplies already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedules of Study Procedures are located in Appendix A, Appendix B, Appendix C and Appendix D and Appendix E for Parts 1, 2, 3, and 4 respectively, of the study.

9.1.1 Informed Consent Procedure

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

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

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

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

9.1.1.1 Pharmacogenomic Informed Consent Procedure

Pharmacogenomics informed consent is a component of the overall study informed consent. The requirements are described in Section 15.2.

The pharmacogenomic sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, and race as described by the subject, alcohol and caffeine history, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease that stopped at or prior to signing of the informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure and Neurological Examination

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

As part of the physical examination, neurological assessments will be included on the Neurological Exam eCRF and include (1) Basic Mental Status; (2) Cranial nerves II-XII; (3) Motor examination; (4) Deep Tendon Reflexes; (5) Sensory examination; (6) Cerebellar function. The Bond-Lader visual analogue scale (VAS) (Section 9.1.13) and the C-SSRS (Section 9.1.14) will also be administered.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as Not Clinically Significant (NCS) or Clinically Significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.8.

On subsequent examinations, any abnormal change from the pretreatment physical examination (including neurological) assessment occurring immediately prior to the start of the investigational drug (Day -1) must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

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

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

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m^2. However, if the BMI is used as entry criteria based on a BMI between 18 and 32 kg/m^2, then this determination must be made after rounding.

9.1.5 Vital Sign Procedure

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 Appendix A, B, C and D/E for the schedules of vital sign assessments in Part 1, 2, 3, and 4 respectively, of the study.

If a vital sign is found to be abnormal postdose, it may be collected every 30 minutes if clinically significant.

Vital signs should be measured at the same time of the day across visits, if possible. When postdose vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.6 Wearable Device Procedure

CCI

[redacted]

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening and/or Baseline (Day -1) examination. The condition (ie, diagnosis) should be described.

9.1.9 Procedures for Clinical Laboratory Samples

All 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 (Appendix A, B, C, and D/E for Part 1, 2, 3 and 4 respectively, of the study.

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

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells (RBC)	ALT	pH
White blood cells (WBC) with differential	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase	Protein
Hematocrit	AST	Glucose
Platelets	Total bilirubin	Blood
PT/INR	Direct bilirubin	Nitrite
aPTT	Total protein	Leucocyte esterase
	Creatinine	Osmolality
	Blood urea nitrogen (BUN)	
	Creatine kinase	Microscopic Analysis^:
	γ-Glutamyl transferase (GGT)	RBC/high power field
	Potassium	WBC/high power field
	Sodium	Epithelial cells, casts, etc.
	Glucose	
	Chloride	^To be performed if abnormal
	Bicarbonate	
	Calcium	
	Total serum cholesterol	
	Triglycerides	
	eGFR	
	5'-nucleotidase	
	Bile acids	

Diagnostic Screening:	
Serum	**Urine/Blood**
Antipsychotic medication level (performed at Screening, Day 21 and Day 50.) Hepatitis panel, including HBsAg and anti-HCV Female subjects only: human chorionic gonadotropin (hCG) for pregnancy Follicle-stimulating hormone (FSH) if menopause is suspected and subject is not surgically sterile	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine

aPTT=activated Partial Thromboplastin Time, eGFR=estimated glomerular filtration rate, PT=prothrombin time, INR=international normalized ratio.

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

If subjects experience any of the following:

1. ALT or AST >3 ×ULN

2. ALP elevations >1.5 × ULN in conjunction with elevated total bilirubin >1.5 × ULN or elevated 5'nucleotidase >1.5 × ULN or elevated GGT > 5 x ULN or elevated AST/ALT >1.5 × ULNALP > 2 × ULN persisting for longer than 3 days
3. ALP > 3 × ULN

follow-up laboratory tests (at a minimum, serum ALP, ALT, AST, total bilirubin, GGT, 5'-nucleotidase, INR, and the specific assessment that meets one of these criteria if not in this list) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

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

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

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

Laboratory reports must be signed and dated by the principal investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator's assessment of not clinically significant before proceeding with enrollment/randomization.

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

9.1.9.1 Renal Function

In addition to the common laboratory tests of kidney function (BUN, creatinine, urinalysis), and eGFR will be determined in all study parts, see Table 9.a. For the Schedule of Procedures, see Appendix A, B, C and D/E for Part 1, 2, 3 and 4, respectively.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for a period of 145 days (ie, 90 days after 5 half-lives) after the last dose of study drug, nonsterilized** male

subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

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

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are barrier methods for male subjects who are sexually active with a female partner of childbearing potential:

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

For female subjects, oral contraceptives are prohibited for 30 days prior to Check-in (Day -2) until 55 days (ie, 5 half-lives) after the last dose of study drug.

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

In addition to a negative serum hCG pregnancy test at Screening, female subjects also must have a negative serum hCG pregnancy test on Day -2 and Study Exit/Early Termination for all study parts.

In addition, male subjects must be advised not to donate sperm from signing of informed consent until 145 days (ie, 90 days after 5 half-lives) have elapsed since the last dose of study drug.

9.1.11 Pregnancy

Women of childbearing potential will not be included in this study.

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

As such, the effect of TAK-041 on fetal development is unknown at this time. TAK-041 has not been administered to women who are pregnant or lactating. No nonclinical reproductive and developmental toxicity studies have been conducted. TAK-041 should not be administered to

pregnant or lactating women at this stage in development. Based on this, it is recommended that women of childbearing potential be excluded from this study. Male subjects who are sexually active with a woman of childbearing potential should use a highly effective method of contraception (<1% failure rate/year), which has low user dependency while participating in this study (see Section 9.1.10). These requirements will apply during treatment and for a period of 145 days (ie, 90 days after 5 half-lives) days after the last dose of study drug.

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or 145 days (ie, 90 days after 5 half-lives) after the last dose of study drug, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, eg, after Day 1 or within 145 days (ie, 90 days after 5 half-lives) have elapsed since the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

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

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

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

9.1.12 ECG Procedure

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 clinically significant, or abnormal and clinically significant. 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 Appendix A, B, C and D/E. Single ECGs will be taken at all time points.

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. A window of ±10 minutes around each scheduled time point can be utilized in order for the central reader to obtain the necessary ECGs. 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.

When an ECG is scheduled at the same time as blood draws or vital signs, then the blood draws and vital signs will take priority and the ECG will be obtained within 0.5 hour before or after the scheduled blood draw/vital sign assessment. If an ECG coincides with a meal, ECG will take precedence followed by the meal.

9.1.12.1 Holter ECG Monitoring (Part 2, Healthy Subject Cohorts)

To ensure high-quality data recording, prior to electrode placement, the anatomical sites must be prepared to allow for proper skin/electrode interface. Any hair on the electrode sites must be shaven. Any oils, lotions, or dead skin should be removed from the electrode sites using an abrasive alcohol prep pad designed for this purpose. An indelible skin marker must be used to mark the exact electrode placement site so that the electrode positions will remain constant throughout each treatment period. The electrodes should always be attached to the Holter connecting cable prior to skin placement.

All Holter recordings will be obtained on 1000 sps flash cards using a 12-lead Holter recorder. The flash cards will be couriered to the central cardiac core laboratory. Alternatively, Holter recordings will be digitally transmitted to the central cardiac core laboratory, as appropriate.

Each 12-lead Holter ECG acquisition window will be approximately 10 minutes in duration, from which cardiac data analysis laboratory will extract 10-second ECGs in triplicate. This window will be preceded by 10 minutes of quiet supine rest.

Subjects will be supervised while remaining at rest, quiet, awake, and in a supine position from at least 10 minutes prior to the beginning of each ECG extraction time point and will remain quiet, awake, motionless, and supine for at least 10 minutes after the beginning of each ECG extraction time point.

ECGs derived from Holter monitoring are not intended to be analyzed for real-time safety monitoring but may be used for future retrospective ECG analyses, unless an earlier analysis is warranted by emerging safety information.

9.1.13 Bond-Lader Visual Analogue Scale

The Bond-Lader VAS will be administered at designated time points shown in Appendix D.

Bond-Lader VAS of Mood and Alertness [13] 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). Nine 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 Bond-Lader VAS is considered a safety measure.

9.1.14 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 (eg, subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency, duration, controllability, deterrents, and reasons for ideation), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) [14].

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 Appendix A, B, C and D/E for Part 1, 2, 3, and 4, respectively.

The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical trial of centrally-acting drugs [14]. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with sub questions assessing the severity. The tool is administered via interview with the subject.

9.1.15 CCI

CCI

[redacted]

CCI

[redacted]

Use

9.1.16 Cognitive Assessments

CCI

[redacted]

Prop

9.1.17 Other Psychiatric/Neurological Rating Scales

Subjects with schizophrenia (Part 4) will also receive the MINI, [redacted]. A trial manual describing the procedures to be used with these assessments will be supplied to the site. These assessments will be administered according to the schedule shown in Appendix D/E. The assessments are briefly described below:

9.1.17.1 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. The clinician responsible for the subject must administer the MINI [20-22].

9.1.17.2 [redacted]

[redacted]

[redacted]

CCI

[redacted]

9.1.18 Pharmacogenomic Sample Collection

CCI

[redacted]

9.1.18.1 DNA Sample Collection

CCI

[redacted]

9.1.18.2 RNA Sample Collection –Part 1

CCI

[redacted]

9.1.18.3 RNA Sample Collection –Part 2, Part 3 and Part 4

CCI

[redacted]

9.1.19 Pharmacokinetic Sample Collection

9.1.19.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (one 4-mL sample per scheduled time) for PK analysis of TAK-041 will be collected into chilled Vacutainers containing anticoagulant K_2EDTA. Placebo samples will not be analyzed by the bioanalytical laboratory except 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 could have been on active treatment. Instructions for sample processing and shipment will be provided in to the site in the Laboratory Manual.

Serial blood samples for determination of TAK-041 in Part 1 will be collected according to Table 9.c, and Table 9.d, and in Appendix A.

Table 9.c 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

Table 9.d 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).

Serial blood samples for determination of TAK-041 in Part 2 and Part 4 will be collected according to Table 9.e and in Appendix B for Part 2 and in Appendix D and Appendix E for Part 4.

Table 9.e Collection of Blood Samples for PK 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 and 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).

Serial blood samples for determination of TAK-041 in Part 3 will be collected according to Table 9.f, and in Appendix C.

Table 9.f 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).

Based on emerging PK data from previous cohorts, the actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. When the timing of safety measurements coincides with a PK

blood collection, the order should be safety assessments followed by PK blood sample collection at the nominal time. The actual times of sample collection will be recorded on the source documents and eCRF.

Sampling time points may be adjusted based on the preliminary emerging PK data collected from prior period/cohort(s), but the total number of samples collected per subject should not exceed the planned number.

9.1.19.2 Collection of Urine for Pharmacokinetic Sampling

Serial urine samples for determination of TAK-041 in Part 1 will be collected according to Table 9.g and in Appendix A.

Table 9.g Collection of Urine Samples for Pharmacokinetic Analysis for 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.

Serial urine samples for determination of TAK-041 in Part 2 will be collected according to Table 9.h and in Appendix B.

Table 9.h Collection of Urine Samples for Pharmacokinetic Analysis for Part 2

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-041	Urine	1	Predose (-12 to 0), and 0 to 6, 6 to12, 12 to 24, 24 to 48 hours postdose.
TAK-041	Urine	22	Predose (-12 to 0), and 0 to 6, 6 to12, 12 to 24, 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.

When Early Termination occurs on a non-PK blood collection day, PK blood and urine samples should be collected.

Urine samples for subjects randomized to placebo will not be analyzed.

Urine volume will be recorded within 2 hours of the end of the collection period. Instructions for sample processing and shipment will be provided to the site in the Laboratory Manual.

CCI [redacted].

9.1.19.3 Bioanalytical Methods

Plasma and urine concentrations of TAK-041 will be measured by high-performance liquid chromatography with tandem mass spectrometry at PPD laboratories.

9.1.20 Pharmacokinetic Parameters

The PK parameters of TAK-041 will be determined from the concentration-time profiles for all evaluable subjects in all study parts. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated for plasma concentration values of TAK-041:

Table 9.i Pharmacokinetic Parameters

Symbol/Term	Definition
Plasma	
AUC_{24}	Area under the plasma concentration-time curve from the time 0 to time 24 hours. 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 the time 0 to time 96 hours.
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval.
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty}=AUC_{t}+C_{last}/\lambda z$
$R_{ac(AUC)}$	Accumulation ratio (based on AUC), calculated as dose normalized AUC_{τ} at steady state/dose normalized AUC_{τ} after a single dose.
$R_{ac(Cmax)}$	Accumulation factor (based on C_{max}), calculated as dose normalized C_{maxss}/dose normalized C_{max} after a single dose.
$C_{av,ss}$	Average plasma concentration at steady state, calculated as AUC_{τ}/τ.
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.
C_{trough}	Trough plasma concentration (measured concentration at the end of a dosing interval at steady state taken directly before next administration.
CL/F	Apparent clearance after extravascular administration, calculated as =Dose/AUC_{∞} after a single dose and as Dose/AUC_{τ} after multiple dosing (at steady state).
$t_{1/2z}$	Terminal elimination half-life, calculated as ln(2)/λz.
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)/λz.

The following urine PK parameters of TAK-041will be derived from urine concentrations of TAK-041:

Table 9.j Urine Parameters Part 1, Part 2 and Part 4

Urine	
Ae_t	Total amount of drug excreted in urine from time 0 to time t.
f_e	Fraction of drug excreted in urine, calculated as (Ae_t/dose)×100. Molecular weight adjustment needed for metabolites.
CL_R	Renal clearance, calculated as Ae/AUC.

9.1.21 Pharmacodynamic Parameters

9.1.21.1 CCI

CCI [redacted]

9.1.22 Exploratory Biomarker Sample Collection

CCI [redacted]

9.1.23 Documentation of Screen Failure

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

The primary reason for screen failure is recorded in the eCRF using the following categories:

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

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

9.1.24 Documentation of Randomization

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

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

9.2 Monitoring Subject Treatment Compliance

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

9.3 Schedule of Observations and Procedures

- The schedules for all study-related procedures in Part 1, Part 2, Part 3 and Part 4 are shown in Appendix A, Appendix B, Appendix C and Appendix D/E, respectively. Assessments should be completed at the designated visit/time point(s).

9.3.1 Discharge

Part 1 Day 5 (Discharge)

- Physical examination and neurological examination.
- Vital signs.
- Weight.
- Concomitant medications.
- 12-Lead ECG.
- Safety laboratory tests.
- Serum pregnancy test (hCG) (female subjects only) (Cohorts 1 and 2 only)
- PK blood collection.
- PK urine collection.
- AE assessment.
- C-SSRS (Since Last Visit).
- Bond-Lader VAS.

Part 2 and Part 4 Days 3, 10, 17, and 24 (Final Discharge)

- Physical examination and neurological examination.
- Vital signs.
- Concomitant medications.
- 12-Lead ECG.
- Safety laboratory tests.
- PK blood collection (Days 3 and 24 only).
- PK urine collection (Days 3 and 24 only).
- AE assessment.
- C-SSRS (Since Last Visit).
- Bond-Lader VAS.

Part 3 Day 19 (Follow-up)

- Physical examination and neurological examination.
- Vital signs.
- Concomitant medications.

- 12-Lead ECG.
- Safety laboratory tests.
- PK blood collection
- AE assessment.
- C-SSRS (Since Last Visit).

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.2 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The following procedures will be performed and documented:

When early termination is within 1 hour of a scheduled PK sample collection and the study drug has been administered, the PK sample should be collected. The site may seek guidance. For example, collect samples if early withdrawal is due to an AE and/or if several hours elapsed since last blood draw.

For all subjects receiving study drug, the investigator must complete the End-of-Study eCRF page. End-of-Study is defined as the Follow-up assessment or Early Termination.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.15, Other Procedures. The genetic material will be preserved and retained at Covance Biorepository for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The samples will be initially stored at Covance Central Laboratory Services, Indianapolis, IN. The Sponsor and researchers working with the Sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the Sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers; the samples are stripped of all personal identifying information but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

9.5 Blood Volume

Total blood sampling volume for an individual subject in Part 1 is shown in Table 9.k.

Table 9.k Approximate Blood Volume for Part 1 Cohort 1

Sample Type	Sample Volume (mL)	Number of Samples							Total Volume (mL)
			Period				Follow-up Visits (a)	Final Visit	
		Screening	1	2	3	4			
Safety laboratory tests	20.2 mL at screening 11.7 mL at other visits	1	3	3	3	3	7	1	**254.2**
5'nucleotidase (a)	3.5 mL	1 (b)	3 (b)	3 (b)	3 (b)	**3 (b)**	7 (b)	1 (b)	**14 (a)**
CCI [redacted]									
PK blood collection	4	0	15	**15**	15	15	7	0	**268**
eGFR (c)	3.5	0	2 (c)	2 (c)	2 (c)	0	0	0	**10.5 (c)**
	Total Approximate Blood Sampling Volume								**562.7**

(a) Number of samples based on 7 weekly safety and PK Follow-up Visits planned.
(b) The blood required for 5'nucleotidase will be collected as part of the safety laboratory samples at Screening, Day 2, Day 5, at the weekly safety Follow-up Visits and at the Final Visit. On Day 1 a separate 3.5 mL sample will be collected.
(c) The blood required for the predose eGFR sample will be collected as part of the safety laboratory samples on Day -1. The postdose eGFR 3.5 mL sample will be collected 6 (±2) hours postdose.

The maximum volume of blood in any single day is approximately 58 mL. The total volume of blood for each subject in Cohort 1 is approximately 562.7 mL. Direct venipuncture or indwelling catheter may be used for blood collection.

Total blood sampling volume for an individual subject in Part 1 Cohort 2 is shown in Table 9.l.

Table 9.l Approximate Blood Volume for Part 1 Cohort 2

Sample Type	Sample Volume (mL)	Number of Samples						Total Volume (mL)
			Period					
		Screening	1	2	3	Follow-up Visits (a)	Final Visit	
Safety laboratory tests	20.2 mL at screening 11.7 mL at other visits	1	3	3	3	7	1	**219.1**
5'nucleotidase (a)	3.5	1 (b)	3 (b)	3 (b)	3 (b)	7 (b)	1 (b)	**10.5 (a)**
CCI								
PK blood collection	4	0	15	15	15	7	0	**208**
eGFR (c)	3.5	0	2 (c)	2 (c)	2 (c)	0	0	**10.5 (c)**
	Total Approximate Blood Sampling Volume							**464.1**

(a) Number of samples based on 7 weekly safety and PK Follow-up Visits planned.
(b) The blood required for 5'nucleotidase will be collected as part of the safety laboratory samples at Screening, Day 2, Day 5, at the weekly safety Follow-up Visits and at the Final Visit. On Day 1 a separate 3.5 mL sample will be collected.
(c) The blood required for the predose eGFR sample will be collected as part of the safety laboratory samples on Day -1. The postdose eGFR 3.5 mL sample will be collected 6 (±2) hours postdose.

Similar to Part 1 Cohort 1, the maximum volume of blood collected for Cohort 2 in any single day is approximately 58 mL. The total volume of blood for each subject in Cohort 2 is approximately 464.1 mL. Direct venipuncture or indwelling catheter may be used for blood collection.

Total blood sampling volume for an individual subject in Part 1 Cohorts 3 to 5 is shown in Table 9.m.

Table 9.m Approximate Blood Volume for Part 1 Cohorts 3 to 5

Sample Type	Sample Volume (mL)	Volume per Subject (mL)										Total Volume per Subject per Cohort (mL)
		Screening Day -21 to -2	Day			Day				Follow-up Visits	Final Visit	
			Day -1	1	2	3	4	5	ET			
Safety laboratory samples	20 mL at screening 12 mL at other visits	20	12		12			12	12	12 (72)(a)	12	140
5'nucleotidase	3.5	(b)			(b)			(b)	(b)	(b)	(b)	0
CCI												
PK samples	4			40	8	4	4	4	4	4 (24)(a)		84
eGFR	3.5		(c)		(c)			(c)		(c)		0
											Total Blood Sampling Volume	245

(a) The numbers represent volume required per visit and in parenthesis, the volume required for 6 visits (Days 8, 15, 22, 29, 36, and 43).
(b) The blood required for 5'nucleotidase will be collected as part of the safety laboratory samples at Screening, Day -1, Day 2, Day 5, at Early Termination, at the weekly safety follow-up visits, and at the Final Visit.
(c) The blood required for eGFR will be collected as part of the safety laboratory samples at Day -1, Day 2, Day 5, and at the weekly safety follow-up visits.

The maximum volume of blood collected for Cohorts 3 to 5 in any single day is approximately 40 mL. The total volume of blood for each subject in Cohorts 3 to 5 is approximately 245 mL. Direct venipuncture or indwelling catheter may be used for blood collection.

Total blood sampling volume for an individual subject in Part 2 is shown in Table 9.n.

Table 9.n Approximate Blood Volume for Part 2 Cohorts 1 to 4

Sample Type	Sample Volume (mL)	Volume per Subject (mL)														Total Volume per Subject per Cohort (mL)
			Day													
		Screening	Day -2	1-3	5	7	8	14	15	21	22	23	Final Discharge Day 24	ET	Follow-up Period Safety PK F/u visits	
Safety laboratory samples	20 mL at screening 12 mL at other visits	20	12	12		12	12	12	12	12	12		12	12	12 (84) (a)	212
5'nucleotidase-(a)	3.5	(b)	(b)			(b)		(b)		(b)			(b)	(b)	(b)	0
CCI																
PK samples	4			44	4		16		16		36	4	4	4	4 (28) (a)	152
eGFR	3.5		(c)	(c)		(c)		(c)		(c)					(c)	0
		Total Blood Sampling Volume														455

The total blood volume of 528.5 ml will be taken over a period of 2.5 months
(a) The numbers represent volume required per visit and in parenthesis, the volume required for 7 visits (Days 26, 29, 36, 43, 50, **57**, and 64).
(b) The blood required for 5'nucleotidase will be collected as part of the safety laboratory samples at Screening, Day -2, Day 7, Day 14, Day 21, Day 24, Early Termination, and at the weekly safety follow-up visits.
(c) The blood required for eGFR will be collected as part of the safety laboratory samples at Days -2, 7, 14, 21, and at the weekly safety follow-up visits.

The maximum volume of blood collected on any single day is approximately 108.5 mL. The total volume of blood to be collected from each subject in Part 2 Cohorts 1 to 4 is approximately 455 mL, and will be taken over a period of 2.5 months. Direct venipuncture or indwelling catheter may be used for blood collection.

Total blood sampling volume for an individual subject in Part 3 is shown in Table 9.o.

Table 9.o Approximate Blood Volume for Part 3

Sample Type	Sample Volume	Number of Samples									Total Volume
		Screening	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	ET	Follow-up Day 19	
Safety Laboratory Samples	20	1	1	-	-	1	-	-	1	1	80
5′ nucleotidase	3.5	(b)	(b)						(b)	(b)	0
PK Samples	4	-	-	11	2	1	1	1	1	1	68
[redacted]											
eGFR	3.5		(c)						(c)	(c)	0
										Total Blood Sampling Volume (ml)	**159**

(a) The numbers represent volume required per visit.
(b) The blood required for 5′nucleotidase will be collected as part of the safety laboratory samples at Screening, Day -1, Early Termination, and at the Follow-up visit.
(c) The blood required for eGFR will be collected as part of the safety laboratory samples at Day -1, ET or Follow-up visit.

The maximum volume of blood collected for a subject in Part 3 in any single day is approximately 55 mL. The total volume of blood for each subject in Part 3 is approximately 159 mL. Direct venipuncture or indwelling catheter may be used for blood collection.

Table 9.p Approximate Blood Volume for Part 4

Sample Type	Sample Volume (mL)	Volume per Subject (mL)														Total Volume per Subject per Cohort (mL)
			Day													
		Screen-ing	Day -2	1-3	5	7	8	14	15	21	22	23	Final Discharge Day 24	ET	Follow-up Period Safety PK F/u visits	
Safety laboratory samples	20 mL at screening 12 mL at other visits	20	12	12		12	12	12	12	12	12		12	12	12 (84) (a)	212
5'nucleotidase-(a)	3.5	(b)	(b)			(b)		(b)		(b)			(b)	(b)	(b)	0
CCI [redacted] CCI																
PK samples	4			44	4		16		16		36	4	4	4	4 (28) (a)	152
eGFR	3.5		(c)	(c)		(c)		(c)		(c)					(c)	0
															Total Blood Sampling Volume	455

(a) The numbers represent volume required per visit and in parenthesis, the volume required for 7 visits (Days 26, 29, 36, 43, 50, 57, and 64).
(b) The blood required for 5'nucleotidase will be collected as part of the safety laboratory samples at Screening, Day -2, Day 7, Day 14, Day 21, Day 24, Early Termination, and at the weekly safety follow-up visits.
(c) The blood required for eGFR will be collected as part of the safety laboratory samples at Days -2, 7, 14, 21, and at the weekly safety follow-up visits.

The maximum volume of blood collected on any single day is approximately 108 mL. The total volume of blood to be collected from each subject in Part 4 is approximately 455 mL, and will be taken over a period of 2.5 months. Direct venipuncture or indwelling catheter may be used for blood collection.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug or due to a study procedure; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug or due to a study procedure, whether or not it is considered related to the study drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

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

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

Events detected by wearable digital devices:

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10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

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

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

10.1.8 Start Date

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

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with or without sequelae or the subject died.

10.1.10 Frequency

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

10.1.11 Action Concerning Study Medication

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

10.1.12 Outcome

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

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

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

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

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until the Follow-up Assessment.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date [and time].
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) as (related or not related) (not completed for PTEs).

6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action taken concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

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

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

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

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

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

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

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT, AST, or ALP elevated >3 ×ULN on 2 consecutive occasions (ie, scheduled visit, repeat test 48 hours apart), the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT, AST, ALP >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.9 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

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

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

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic)

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

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

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

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

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), query responses/ electronic copy of eCRFs, including the audit trail, and detailed records of drug

disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The analysis sets will be defined separately for each part of the study.

Safety Set

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

PK 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.

PD Set

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13.1.2 Analysis of Demographics and Other Baseline Characteristics

For each part of the study, descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, and BMI) for pooled placebo, each TAK-041 dose level, TAK-041 overall, and overall total. For each Part, the number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (sex, ethnicity, and race) will be tabulated for pooled placebo group, each TAK-041 dose level, TAK-041 overall, and overall total. Placebo data will be pooled across the cohorts within each part.

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

13.1.3 Pharmacokinetic Analysis

Concentrations of TAK-041 in plasma will be summarized by dose over each scheduled sampling time using descriptive statistics for each study part. Amount of TAK-041 excreted in urine will be

summarized by dose over each scheduled sampling interval using descriptive statistics for each study part. Individual PK data will be presented in a data listing. PK parameters of TAK-041 will be summarized by dose using descriptive statistics for each study part. Dose proportionality will be assessed graphically (dose-normalized C_{max} and AUC versus dose) in Part 1 and Part 2. To assess dose proportionality of single dosing (Part 1), a power model will be used. The model will include the natural log-transformed AUC and C_{max} as response variable and the natural log-transformed dose [ln(dose)] as a continuous covariate. No formal statistical comparisons will be conducted. For Part 2, dose proportionality will be assessed using an analysis of variance (ANOVA) model separately for dose-normalized AUC and C_{max} on Day 22 with treatment (as a categorical variable) as a fixed effect. The dose-normalized parameters will be natural log-transformed prior to the analysis. All treatment differences and corresponding two-sided 90% CIs will be extracted from the model, back-transformed, and expressed as central value ratios.

The effect of food on TAK-041 exposure will be evaluated in Part 3 using an ANOVA on the natural log-transformed TAK-041 C_{max} and AUC_{96} with regimen (high-fat vs. fasted) as a fixed effect. 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 after the high-fat meal versus the fasted state.

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 using an 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 ANOVA will be performed on the natural log-transformed Day 1 TAK-041 C_{max} and AUC_{96} with regimen as a fixed effect. 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.

13.1.4 Exploratory Analyses

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13.1.5 Safety Analysis

Safety data will be presented by TAK-041 dose and placebo for each part.

TEAEs will be summarized by placebo, each TAK-041 dose level, and TAK-041 overall for each study part.

Clinical laboratory variables, vital signs, and ECG parameters will be summarized with descriptive statistics for baseline, postdose, and change from baseline to postdose values by dose and scheduled time point for each study part. In Part 2, continuous Holter ECG monitoring parameters will be extracted in triplicate and the average of the 3 values at each time point will be calculated and used for all statistical analyses and 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.

Potential QT prolongation will be assessed using the Holter ECG measurements in Part 2. A linear mixed effect model for repeated measures will be used. The response variable in the model will be the change from the time-matched baseline in the average of the triplicate corrected QT intervals (QTc). The time-matched baselines will come from the ECGs taken on Day -1 (23, 22, 20, 16, and 12 hours before dosing). The model will include treatment, time (as a categorical variable), and the treatment-by-time interaction as fixed effects, subject as a random effect, baseline as a covariate, and the baseline-by-time interaction as an additional fixed effect. The LS mean change from time-matched baseline for each treatment and the associated standard error and two-sided 95% CI

will be extracted for each treatment at each timepoint, as well as differences from placebo and associated standard errors, two-sided 95% CIs, and p-values.

A separate linear mixed effects model will be used to assess the relationship between the change from time-matched baseline in QTc and TAK-041 exposure in Part 2. The response variable in the model will be the change from time-matched baseline in QTc. The model will include TAK-041 plasma concentration (as a continuous variable) as a fixed effect and subject as a random effect. Placebo subjects will be included in the analysis with a plasma concentration of 0. The estimated regression line and the 90% confidence band for the regression line will be extracted from the model. The relationship between the change from time-matched baseline in QTc and TAK-041 plasma concentration will also be examined graphically using a scatterplot. The regression line and 90% confidence band for the regression line estimated from the model will be overlaid onto the scatterplot.

The number and percentage of subjects with postdose values meeting Takeda's criteria for markedly abnormal values for clinical laboratory variables, vital signs, and ECG parameters will be presented by dose. Neurological assessments will be judged normal, abnormal, CS or NCS. All summaries will be performed by pooled placebo within cohort and TAK-041 dose level. Physical examination findings will be presented in data listings. Individual results of BL-VAS and the C-SSRS will be listed.

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

13.2 Interim Analysis and Criteria for Early Termination

Section 6.1.6 describes safety, tolerability, and PK reviews that will take place after completion of each cohort/period and prior to the next dose escalation stage in the study. Study-specific dose escalation and stopping rules are described in Section 6.3.2.

An unblinded interim analysis may be performed in Part 4. The purpose of the analysis would be to assess safety and efficacy of TAK-041 in the case of slower than anticipated enrollment of subjects with schizophrenia.

13.3 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.

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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.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

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

14.2 Protocol Deviations

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

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified

immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix F. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of the participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug and notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

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

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

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

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

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing. For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Study Procedures Part 1

Procedure	Screening	Cohort 1 Treatment Periods 1 and 2 Cohort 2 Treatment Periods 1 and 2 Cohorts 3 to 5						ET (b)	Follow-up Period	Final Visit
Study Day	Days -21 to -2	Check-in Day -1	Day 1	Day 2	Day 3	Day 4	Day 5 (Discharge)		Weekly Safety PK Follow-up Visits (a)	Study Completion
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographics (including smoking status) and medical history	X									
Medication history	X									
Physical examination and neurological examination (c)	X		X	X			X	X	X	X
Vital signs (d)	X	X	X	X	X	X	X	X	X	X
Height, weight, and BMI (e)	X						X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X								
12-lead ECG (f)	X	X	X			X	X	X		
Safety laboratory collections (g)	X	X		X			X	X	X	X
eGFR (h)		X		X			X		X	
Urine, cotinine, and drug screen	X	X								
Serum pregnancy test (hCG)(i)	X	X					X (i)	X		X

Footnotes are on last table page.

Appendix A Schedule of Study Procedures Part 1 (continued)

Procedures	Screening	Cohort 1 Treatment Periods 1 and 2 Cohort 2 Treatment Periods 1 and 2 Cohorts 3 to 5						Follow-up Period	Final Visit
Study Days	Days -21 to -2	Check-in Day -1	Day 1	Day 2	Day 3	Day 4	Day 5 (Discharge)	ET (b)	Weekly Safety PK Follow-up Visits (a)	Study Completion
FSH (j)	X									
Hepatitis panel (k)	X									
CCI										
CCI										
PK blood collection (n)			X	X	X	X	X	X	X	
PK urine collection (o)		X	X	X	X	X	X	X		
TAK-041/matching placebo dosing (p)			X							
Confinement (q)		X	X	X	X	X	X			
PTE assessment	X	X	X							
AE assessment (r)			X	X	X	X	X	X	X	
C-SSRS (s)	X	X	X				X	X	X	
Bond-Lader VAS (t)		X	X	X			X	X		
CCI										
CCI										
CCI										

Footnotes are on the following page.

AE=adverse event, BMI=body mass index, C-SSRS=Columbia-Suicide Severity Rating Scale, DNA= deoxyribonucleic acid, eGFR= estimated glomerular filtration rate, ET=Early Termination, ECG=electrocardiogram, FSH= follicle-stimulating hormone, hCG=human chorionic gonadotropin, PK=pharmacokinetics, CCI [redacted], PTE=pretreatment event, RNA= ribonucleic acid, VAS=visual analogue scale.

(a) Weekly safety and PK Follow-up Visits will occur starting from 7 days after dosing (Day 8 ± 2 days) in each Cohort's last treatment period until the concentration of TAK-041 in plasma is not quantifiable in each subject (Cohorts 1 and 2) or 6 weeks after the dose (Cohorts 3 to 5) to assess safety and PK and whether any concomitant medications were used since Discharge on Day 5. 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.

(b) When early termination occurs on a non-PK blood collection day, PK blood and urine samples should be collected.

(c) Physical and neurological examinations will be made at Screening, Day 1, Day 1, Day 2, at Discharge on Day 5 or Early Termination, at each weekly safety and PK Follow-up Visit, and at the Final Visit.

(d) Vital signs will include oral body temperature measurement, 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 will be recorded at Screening, Check-in (Day -1), Day 1 (predose [within 60 minutes prior to dosing]), and at 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours postdose or Early Termination, and at each weekly safety and PK Follow-up Visit, and at the Final Visit.

(e) Height and BMI will be measured at screening only.

(f) For Cohorts 1 and 2, standard 12-lead ECGs will be recorded at Screening, Check-in (Day -1), Day 1 (predose [within 60 minutes prior to dosing]), and at 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours postdose or Early Termination, and at each weekly safety and PK Follow-up Visit. For Cohorts 3 to 5, standard 12-lead ECGs will be recorded at Screening, Day 1 (predose [within 60 minutes prior to dosing]), and at 2, 24, and 96 hours postdose, and at Early Termination. Single ECGs will be taken at these time points.

(g) Collections for hematology, serum chemistry, and urinalysis parameters will occur upon rising after a fast of at least 8 hours at Screening, Check-in (Day -1), Day 2, at Discharge on Day 5, Early Termination, at each weekly safety and PK Follow-up Visit, and at the Final Visit.

(h) eGFR: For Cohorts 1 and 2, the blood required for the Day -1 eGFR sample will be collected as part of the safety laboratory samples on Day -1. For Cohorts 1 and 2, on Day 1, 3.5 mL of blood will be drawn 6 (±2) hours postdose. For Cohorts 3 to 5, the blood required for the Day -1 eGFR sample will be collected as part of the safety laboratory samples on Day -1, Day 2, Day 5, and at each weekly safety and PK follow-up visit.

(i) Serum pregnancy tests for female subjects only will be done at Screening, Day -1 (Check in), and on Discharge on Day 5 (for Cohorts 1 and 2 only), Early Termination, and at the Final Visit.

(j) An FSH level will be obtained for postmenopausal women (defined as continuous amenorrhea of at least 2 years).

(k) Hepatitis panel, including HBsAg and anti-HCV.

(l) CCI [redacted]

(m) CCI [redacted]

(n) PK blood samples for the determination of TAK-041 plasma concentrations will be collected on Day 1 (predose [within 60 minutes prior to dose]) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, 72, and 96 hours postdose, and at each weekly safety and PK Follow-Up Visit (until the concentration of TAK-041 in plasma is not quantifiable in each subject for Period 2 in Part 1 Cohorts 1 and 2, and Days 8, 15, 22, 29, 36, and 43 for Part 1 Cohorts 3 through 5).

(o) Urine samples for the determination of TAK-041 concentrations in urine will be collected predose on Day -1 through Day 1 to just before dosing (-12 to 0 hours)

and at (0 to 6), (6 to 12), (12 to 24), (24 to 48), (48 to 72), and (72 to 96) hour intervals postdose.
(p) Subjects will be administered the TAK-041 or matching placebo at approximately 0800 hours following a 8-hour fast and will continue to fast for an additional 4 hours postdose. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration.
(q) For each treatment period, subjects will be confined to the study unit from Day -1 until discharge on Day 5.
(r) AEs will be captured from the first dose of study drug and will continue until the Final Visit.
(s) C-SSRS: The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered at Check-in on Day -1, Discharge on Day 5 or Early Termination, and Follow-up Visits as appropriate (if clinically significant at Discharge).
(t) Bond-Lader VAS will be administered in on Day -1, Day 1 at 1, 3, 8, and 24 hours postdose (Day 2), Day 5, and (if applicable) at Early Termination.
(u) CCI [redacted]
(v) Optional for subjects in Part 1, Cohorts 1 and 2: The single lead ECG device will be used during the dosing periods and for approximately the first 3 days of the washout period. The subjects will be asked to bring the device to the unit for the next dosing period. CCI [redacted].

Appendix B Schedule of Study Procedures Part 2 Cohorts 1 to 4 (healthy subjects only)

Procedures	Screening		Treatment Period															ET (a)	Follow-up Period	Final Visit
Study Day	Days -21 to -3	Check-in Day -2	Day -1	Day 1	Days 2-3	Day 5	Check-in Day 7	Day 8	Days 9-10	Check-in Day 14	Day 15	Days 16-17	Check-in Day 21	Day 22	Day 23	Day 24	Day 26		Safety PK Follow-up Visits (b)	Study Completion
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		
Demographics (including smoking status) and medical history	X																			
Medication history	X																			
Physical examination and neurological examination (c)	X			X				X			X			X		X	X	X	X	X
Vital signs (d)	X	X	X	X	X			X	X		X	X		X	X	X	X	X	X	X
Height, weight, and BMI (e)	X															X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X																	X	
12-lead ECG(f)	X	X		X	X			X	X		X	X		X	X	X	X			
Holter ECG monitoring (f)			X	X																

Footnotes are on last table page.

Appendix B Schedule of Study Procedures Part 2 Cohorts 1 to 4 (healthy subjects only) (continued)

Procedures	Screening	Treatment Period																	Follow-up Period	Final Visit
Study Day	Days -21 to -3	Check-in Day -2	Day -1	Day 1	Days 2-3	Day 5	Check-in Day 7	Day 8	Days 9-10	Check-in Day 14	Day 15	Days 16-17	Check-in Day 21	Day 22	Day 23	Day 24	Day 26	ET (a)	Safety PK Follow-up Visits (b)	Study Completion
Safety laboratory collections (g)	X	X		X			X	X		X	X		X	X		X	X	X	X	X
eGFR (h)		X		X			X			X			X						X	
Urine, cotinine, and drug screen (i)	X	X																		
Serum pregnancy test (hCG) (j)	X	X	X													X	X	X		X
FSH (k)	X																			
Hepatitis panel (l)	X																			
CCI [redacted]																				
CCI [redacted]																				
CCI [redacted]																				
Fecal collection for microbiome analysis (p)	X		X						X						X			X		
CCI [redacted]																				
PK blood collection (r)				X	X	X		X			X			X	X	X	X	X	X	

Footnotes are on last table page.

Appendix B Schedule of Study Procedures Part 2 Cohorts 1 to 4 (healthy subjects only) (continued)

Procedures	Screening		Treatment Period															Follow-up Period	Final Visit
Study Day	Days -21 to -3	Check-in Day -2	Day -1	Day 1	Days 2-3	Day 5	Check-in Day 7	Day 8	Days 9-10	Check-in Day 14	Day 15	Days 16-17	Check-in Day 21	Day 22	Day 23	Day 24	Day 26	ET (a)	Safety PK Follow-up Visits (b)	Study Comp-letion
PK urine collection (s)			X	X	X								X	X	X	X	X	X		
TAK-041/placebo dosing (t)				X				X			X			X						
Confinement (u)		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X			
PTE assessment	X	X	X																	
AE assessment (v)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS (w)	X	X			X	X	X		X	X		X	X			X	X	X	X	
Bond-Lader VAS (x)			X	X				X			X			X		X	X	X		
Application of single lead ECG device (y)			X										X							
Removal of single lead ECG device (y)								X										X	X	
CCI [redacted]																				
CCI [redacted]																				

Footnotes are on the following page.

AE=adverse event, BMI=body mass index, C-SSRS=Columbia-Suicide Severity Rating Scale, DNA= deoxyribonucleic acid, eGFR= estimated glomerular filtration rate, ET=Early Termination, ECG=electrocardiogram, FSH= follicle-stimulating hormone, hCG=human chorionic gonadotropin, PK=pharmacokinetics, [redacted]
PTE=pretreatment event, RNA= ribonucleic acid, VAS=visual analoque scale.

(a) [redacted]

(b) Safety and PK Follow-up Visits will occur starting from 4 days after dosing (Day 26 ± 2 Days, 29 ± 2 days, 36 ± 2 days, 43 ± 2 days, 50 ± 2 days, 57 ± 2 days, and 64 ± 2 days) for each cohort until 6 weeks after the last dose to assess safety and PK and whether any concomitant medications were used since discharge on Day 24. 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.

(c) Physical examinations and neurological examinations will be made at Screening, Day 1, Days 8, 15, and 22 (predose [within 60 minutes prior to dosing]) and at Study Exit (Day 24) or Early Termination, at each safety and PK Follow-up Visit, and at the Final Visit.

(d) Vital signs will include oral body temperature measurement, 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 will be recorded at Screening, Check-in (Day -2), Day -1, Day 1 (predose [within 60 minutes prior to dosing]), and at 2, 8, 24, 36, and 48 hours postdose), and Days 8, 15, and 22 (predose [within 60 minutes prior to dosing]), and at 2, 8, 24, 36, and 48 hours postdose), at Early Termination, at each safety and PK Follow-up Visit, and at the Final Visit.

(e) Height and BMI will be measured at Screening only.

(f) Standard 12-lead ECGs will be recorded at Screening, Check-in (Day -2); Day 1 (predose [within 60 minutes prior to dosing]), and at 2, 24, and 48 hours postdose), and Days 8, 15, and 22 (predose [within 60 minutes prior to dosing]), and at 2, 24, and 48 hours postdose); and at Early Termination. Single ECGs will be taken at these time points. Continuous Holter ECG monitoring will be conducted 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. A window of ±10 minutes around each scheduled time point can be utilized in order for the central reader to obtain the necessary ECGs.

(g) Collections for hematology, serum chemistry, and urinalysis tests will occur upon rising after an approximate 8-hour overnight fast at Screening, Check-in (Day -2, 7, 14, and 21), Days 1, 8, 15, and 22 (predose [within 60 minutes prior to dosing]), and Day 24 (Study Exit), or Early Termination, at each weekly safety and PK Follow-up Visit, and at the Final Visit.

(h) eGFR: The blood required for the eGFR sample will be collected as part of the safety laboratory samples on Days -2, 1, 7, 14, 21, and at each safety and PK Follow-up Visit.

(i) Urine cotinine and drug screens may be repeated as needed at the investigator's discretion.

(j) Serum pregnancy tests for female subjects only will be done at Screening, Day -2 and on Day 24 (Study Exit), or Early Termination, and at the Final Visit.

(k) An FSH level will be obtained for postmenopausal women (defined as continuous amenorrhea of at least 2 years).

(l) Hepatitis panel, including HBsAg and anti-HCV.

(m) [redacted]

(n) Two 2.5 mL whole blood samples will be collected for RNA pharmacogenomic analysis at each of these timepoints: on Day 1 predose (within 60 minutes prior to dosing), at 24 hours postdose, and on Day 22 (approximately 8 hours postdose) from each subject in Cohorts 1-4.

(o) [redacted]

(p) Feces will collected from subjects in Part 2 Cohorts 1- 4 and for exploratory analysis of gut microbiome approximately 1 week prior to Admission, on Day -1, Day 9 (one day after Day 8 dosing), Day 23 (one day after Day 22 dosing), and at Early Termination if this occurs prior to Day 22. Subjects will be provided with a fecal sample collection kit and instructions at the Screening Visit, sample to be collected approximately 1 week prior to admission to the unit and to be returned when admitted to the unit on Day -1. For the sample

collections scheduled during confinement (Days -1, 9, and 23) a ±1 day window is permitted in order to coincide with the subject's normal pattern of bowel movements or if there is a conflict with other study procedures. The date and approximate time of actual sample collection should be recorded. As subjects' bowel movement patterns show significant inter-subject variability and may be further altered by changes in diet and /or physical activity during the residential stay, if a subject who has consented to this procedure does not provide a sample this will not be considered to be a protocol deviation. The reason for missing the sample should be noted. Full details of sample collection will be provided in the Laboratory Manual. Participation in the collection for fecal samples for exploratory microbiome analysis is voluntary and is subject to separate informed consent.

(q) CCI [redacted]

(r) PK blood samples for the determination of TAK-041 concentrations in plasma will be collected on Day 1 predose (within 60 minutes prior to dose) and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, and 96 hours postdose (on Day 5), Days 8 and 15 predose (within 60 minutes prior to dosing), 1, 2, and 4 hour postdose, and Day 22 predose (within 60 minutes prior to dose) and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours postdose, and at each safety and PK Follow-Up Visit (Days 26, 29, 36, 43, 50, 57, and 64).

(s) Urine samples for the determination of TAK-041 concentrations in urine will be collected predose on Day -1 through Day 3 to just before dosing (-12 to 0 hours) and postdose at (0 to 6 hours), (6 to 12 hours), (12 to 24 hours), (24 to 48 hours) intervals and Day 22 predose (-12 to 0 hours) and postdose at (0 to 6 hours), (6 to 12 hours), (12 to 24 hours), and (24 to 48 hours) intervals. Ten-milliliter aliquots should be taken from the urine collections on Days 1 and 22 (predose and 12-24 hours postdose) for measurement of 6β-hydroxycortisol/cortisol ratio to assess CYP3A4 induction.

(t) Subjects will be administered TAK-041/matching placebo at approximately 0800 hours following a fast of at least 8 hour and will continue to fast for an additional 4 hours postdose. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration.

(u) Subjects will be required to remain in the study unit from Day -2 to Day 3, from Day 7 to Day 10, from Day 14 to Day 17, and from Day 21 to Day 24 (for at least 48 hours after each dose) for safety, PK, and all study assessments before discharge.

(v) AEs will be captured from the first dose of study drug until the Final Visit.

(w) C-SSRS: The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered at Check-in on Day -2; Days 3 (Discharge), 5, 7 (Check-in), 10 (Discharge), 14 (Check-in), 17 (Discharge), 21 (Check-in) and 24 (Final Discharge), Early Termination, and Follow-up Visits as appropriate (if clinically significant at Discharge).

(x) Bond-Lader VAS will be administered 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.

(y) Optional for subjects in Part 2, Cohorts 3 and 4: The single lead ECG device will be worn continuously from Day -1 to Day 8. The devices will be re-applied on Day 21 of the study and will be worn continuously until subjects return to the unit for the first follow-up visit. Devices will be removed if subjects terminate the study early.

(z) CCI [redacted]

Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)

	Screening		Treatment Period																	Early Termination (a)	Follow-up (b)
Study Day	-28 to -2	-1	1 to 5																		19 (±2)
Scheduled Time (h)			Pre-dose Day 1	0	0.25	0.5	1	1.5	2	3	4	6	8	12	24	36	48	72	96		
Administrative Procedures																					
Informed Consent	X																				
Inclusion/Exclusion Criteria	X	X	X																		
Medical History/Demographics	X																				
Prior and Concomitant Medication Review	X	X	----------Continuous Review----------																		
Clinic Procedures/Assessments																					
Full Physical Examination (c)	X	X(c)	X(c)												X				X	X	X
Body Mass Index (d)	X																				

Footnotes are on last table page.

Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect) (continued)

	Screening		Treatment Period																Early Termination (b)	Follow-up (a)
Study Day	**-28 to -2**	**-1**	**1 to 5**																	**19 (±2)**
Scheduled Time			**Pre-dose Day 1**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**		
TAK-041Administration (e)				X																
Semi-recumbent Vital Signs (HR, SBP and DBP) (f)	X		X				X		X					X			X			X	X
Vital Signs (respiratory rate and temperature) (f)	X		X				X		X					X			X			X	X
Standard 12-lead ECGs (g)	X	X	X						X								X			X	X
C-SSRS (h)	X		X														X	X	X	X	X
Adverse Events Monitoring (i)	X	X	X----------Continuous Monitoring----------X																	X	X

Footnotes are on last table page.

Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect) (continued)

	Screening		Treatment Period																Early Termination	Follow-up
Study Day	-28 to -2	-1	1 to 5																	19 (±2)
Scheduled Time (Hours)			Pre-dose Day 1	0	0.25	0.5	1	1.5	2	3	4	6	8	12	24	36	48	72	96		
Laboratory Procedures/Assessments																				
Hematology (j)	X	X(j)															X			X	X
Urinalysis (j)	X	X(j)															X			X	X
Serum Chemistry (j)	X	X(j)															X			X	X
Urine Drug Screen (k)	X	X(k)																	X		
Hepatitis Screen (l)	X																				
Human immunodeficiency virus (HIV) Screen	X																				
βhCG (pregnancy) (m)	X	X																			X
Serum FSH (n)	X																			X	X
CCI	[redacted]																				

Footnotes are on last table page.

Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect) (continued)

	Screening		Treatment Period																Early Termination	Follow-up
Study Day	**-28 to -2**	**-1**	**1 to 5**																	**19 (±2)**
Scheduled Time Hours			**Pre-dose Day 1**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**		
Pharmacokinetics Evaluations																				
Blood Sample for PK TAK-041 (p)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other																				
Confinement (q)		X	----------														X			

AE=adverse event, BMI=body mass index, C-SSRS=Columbia-Suicide Severity Rating Scale, DNA= deoxyribonucleic acid, eGFR= estimated glomerular filtration rate, ET=Early Termination, ECG=electrocardiogram, FSH= follicle-stimulating hormone, hCG=human chorionic gonadotropin, PK=pharmacokinetics, CCI , PTE=pretreatment event, RNA= ribonucleic acid, VAS=visual analogue scale.

(a) When early termination occurs, PK blood samples should be collected.

(b) A Safety and PK Follow-up Visit will 2 weeks days after discharge to assess safety and PK and whether any concomitant medications were used. This will be the final scheduled study visit.

(c) Physical and neurological examinations will be thorough, and subsequent examinations looking for abnormal change from Screening. Predose examinations on Day 1 may be done on Day -1.

(d) Height and BMI will be measured at Screening only.

(e) Subjects will be administered a single TAK-041 40 mg immediate release tablet at approximately 0800 hours, following either a 10-hour fast or 30 min after starting ingestion of a high calorie and high fat meal. Subjects will continue to fast for an additional 4 hours postdose and may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. Standard meals will be administered at approximately Hour 4 (lunch), Hour 7 (snack), Hour 10 (dinner) and Hour 13 (snack) hours post dose.

(f) Vital signs will include oral body temperature measurement, 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.

(g) Standard 12-lead ECGs will be on Day 1 (predose [within 60 minutes prior to dosing]).

(h) C-SSRS: The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered on all other visits.

(i) AEs will be captured from the first dose of study drug and will continue until the Final Visit.

(j) Collections for hematology, serum chemistry, and urinalysis parameters will occur upon rising after a fast of at least 8 hours. Collection on Day 1 prior to dosing can be performed alternatively on Day -1.

(k) Urine cotinine and drug screen may be repeated at the judgement of the investigator.

(l) Hepatitis panel includes HBsAg and anti-HCV

(m) Blood will be collected from female subjects only for pregnancy tests.

(n) An FSH level will be obtained for postmenopausal women (defined as continuous amenorrhea of at least 2 years).

(o) CCI

CCI [redacted]

(p) PK blood samples for the determination of TAK-041 plasma concentrations will be collected on Day 1 (predose [within 60 minutes prior to dose]) and at other scheduled times.
(q) Subjects will be confined to the study unit from Day -1 until 48 hours after dosing. On Day 1, subjects randomized fed will start to ingest a high-fat high calorie breakfast within 30 min prior to dosing, and subjects randomized fasting will continue their minimum 10 hour overnight fast until dose administration. All subjects will have no food, drink (other than water) and no medication after dose administration until lunch 4 hours later.

Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET

Procedures	Screening	ET														
Study Day	Days -35 to -3	Check-in Day -2	Day -1	Day 1	Days 2-3	Day 5	Check-in Day 7	Day 8	Days 9-10	Check-in Day 14	Day 15	Days 16-17	Check-in Day 21	Day 22	Day 23-24	ET (a)
Informed consent	X															
Inclusion/exclusion criteria	X	X														
Demographics (including smoking status) and medical history	X															
Medication history	X															
Physical examination and neurological assessments (b)	X			X				X			X			X	X	X
Vital signs (c)	X	X	X	X	X			X	X		X	X		X	X	X
Height, weight, and BMI (d)	X										X					X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X														
12-lead ECG(e)	X	X		X	X			X	X		X	X		X	X	

Footnotes are on last table page.

Appendix D Schedule of Study Procedures Part 4 : Screening Through Day 24/ET (continued)

Procedures	Screening															
Study Day	Days -35 to -3	Check-in Day -2	Day -1	Day 1	Days 2-3	Day 5	Check-in Day 7	Day 8	Days 9-10	Check-in Day 14	Day 15	Days 16-17	Check-in Day 21	Day 22	Day 23-24	ET (a)
Safety laboratory collections (f)	X	X		X			X	X		X	X		X	X	X	X
Antipsychotic medication level	X												X			
eGFR (g)		X		X			X			X			X			
Urine, and drug screen (h)	X	X		X			X			X			X			
Serum antipsychotic medication level	X												X			
Serum pregnancy test (hCG) (i)	X	X													X	X
FSH (j)	X															
Hepatitis panel (k)	X															
CCI																
CCI																
CCI																
Fecal collection for microbiome analysis (o)	X		X						X						X	X
CCI																
Urine collection for 6β hydroxycortisol / cortisol ratio (q)				X (q)										X(q)		
PK blood collection (r)				X (r)	X (r)	X (r)		X (r)			X (r)			X (r)	X (r)	X

Footnotes are on last table page.

Appendix D Schedule of Study Procedures Part 4: Screening Through Day 24/ET (continued)

Procedures	Screening															
Study Day	Days -35 to -3	Check-in Day -2	Day -1	Day 1	Days 2-3	Day 5	Check-in Day 7	Day 8	Days 9-10	Check-in Day 14	Day 15	Days 16-17	Check-in Day 21	Day 22	Day 23-24	ET (a)
TAK-041/placebo dosing (s)				X				X			X			X		
Confinement (t)		X	X	X	X		X	X	X	X	X	X	X	X	X	
PTE assessment	X	X	X													
AE assessment (u)				X	X	X	X	X	X	X	X	X	X	X	X	X
MINI	X															
PANSS	X		X					X			X			X		
CCI																
CCI																
CCI																
CCI																
CCI																
C-SSRS (v)	X	X			X	X	X		X	X		X	X		X	X
Bond-Lader VAS (w)			X								X (w)					
CCI																

Footnotes are on the following page.

AE=adverse event, CCI , BMI=body mass index, CCI – Severity, C-SSRS=Columbia-Suicide Severity Rating Scale, DNA= deoxyribonucleic acid, eGFR= estimated glomerular filtration rate, ET=Early Termination, ECG=electrocardiogram, FSH= follicle-stimulating hormone, hCG=human chorionic gonadotropin, MINI=Mini International Neuropsychiatric Interview, PANSS=Positive and Negative Syndrome Scale, PK=pharmacokinetics, CCI), PTE=pretreatment event, RNA= ribonucleic acid, CCI , VAS=visual analogue scale.

(a) When early termination occurs on a non-PK blood collection day, PK blood and urine samples should be collected. If early termination occurs on the day of a scheduled exploratory biomarker sample (blood, urine, stool) the sample should be collected

(b) Screening physical and neurological examinations will be thorough. Subjects with evidence of clinically significant extrapyramidal symptoms as measured by a SAS score >6, or evidence of depression as measured by a CDSS score >9 will be excluded from the study. Physical and neurological predose examinations predose examinations will be conducted within 60 minutes prior to dosing on all dosing days, and subsequent examinations looking for abnormal change from Screening.

(c) Vital signs will include oral body temperature measurement, 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 will be recorded on all dosing days within 60 minutes prior to dosing, and at 2, 8, 24, 36, and 48 hours postdose.

(d) Height and body weight and BMI will be measured at Screening only. All other assessments will be body weight only.

(e) Standard 12-lead ECGs will be recorded on all dosing days within 60 minutes prior to dosing and at 2, 24, and 48 hours postdose. Single ECGs will be taken at these time points.

(f) Collections for hematology, serum chemistry, and urinalysis tests will occur upon rising after an approximate 8-hour overnight fast within 60 minutes prior to dosing on all dosing days.

(g) eGFR: The blood required for the eGFR sample will be collected as part of the safety laboratory samples

(h) Urine drug screens may be repeated as needed at the investigator's discretion.

(i) CCI .

(j) An FSH level will be obtained for postmenopausal women (defined as continuous amenorrhea of at least 2 years).

(k) Hepatitis panel, including HBsAg and anti-HCV.

(l) CCI

(m) CCI

(n) CCI .

(o) Feces will be collected from subjects in Part 2 Cohorts 1- 4 for exploratory analysis of gut. Subjects will be provided with a fecal sample collection kit and instructions at the Screening Visit, sample to be collected approximately 1 week prior to admission to the unit and to be returned when admitted to the unit on Day -1. For the sample collections scheduled during confinement (Days -1, 9, and 23) a ±1 day window is permitted in order to coincide with the subject's normal pattern of bowel movements or if there is a conflict with other study procedures. The date and approximate time of actual sample collection should be recorded. As subjects' bowel movement patterns show significant inter-subject variability and may be further altered by changes in diet and /or physical activity during the residential stay, if a subject who has consented to this procedure does not provide a sample this will not be considered to be a protocol deviation. The reason for missing the sample should be noted. Full details of sample collection will be provided in the Laboratory Manual. Participation in the collection for fecal samples for exploratory microbiome analysis is voluntary and is subject to separate informed consent.

(p) CCI

CCI [redacted]

(q) Urine samples will be collected on Day 1 and Day 22 (predose and 12-24 hours postdose) for measurement of 6β hydroxycortisol / cortisol ratio to assess CYP3A4 induction. Ten-milliliter aliquots should be taken from the urine collections.
(r) PK blood samples for the determination of TAK-041 concentrations in plasma will be collected within 60 minutes prior to dose on all dosing days and on Day 1 at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, and 96 hours postdose (on Day 5), at 1,2, and 4 hours postdose on Days 8 and 15, and 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours postdose on Day 22, and on all Follow-up visits.
(s) Subjects will be administered TAK-041/matching placebo at approximately 0800 hours following a fast of at least 8 hours and will continue to fast for an additional 4 hours postdose. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration.
(t) Subjects will be required to remain in the study unit from Day -2 to Day 3, from Day 7 to Day 10, from Day 14 to Day 17, and from Day 21 to Day 24 (for at least 48 hours after each dose) for safety, PK, and all study assessments before discharge.
(u) AEs will be captured from the first dose of study drug until the Final Visit.
(v) C-SSRS: The Screening/Baseline C-SSRS will be administered at Screening and the Since Last Visit C-SSRS will be administered at Check-in on Day -2; Days 3 (Discharge), 7 (Check-in), 10 (Discharge), 14 (Check-in), 17 (Discharge), 21 (Check-in), and 24 (Final Discharge), Early Termination, and Follow-up Visits as appropriate (if clinically significant at Discharge).
(w) VAS is assessed on 1, 8, 15 and 24 hours from dosing on Day 15.
(x) CCI [redacted]

Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Procedures		Follow-Up Period						Final Visit Study Completion
Study Day	**Day 26**	**Day 29**	**Day 36 ±2**	**Day 43 ±2**	**Day 50 ±2**	**Day 57 ±2**	**Day 64 ±2**	**Day 70 ±2**
Concomitant medications	X	X	X	X	X	X	X	X
Physical examination and neurological assessments (a)								X
12-lead ECG						X		
Safety laboratory collections	X	X	X	X	X	X	X	X
Serum antipsychotic medication level					X			
eGFR (b)		X			X			
Urine, and drug screen (c)		X			X			
Serum pregnancy test (hCG)								X
CCI								
CCI								
Fecal collection for microbiome analysis (f)							X	
CCI								
PK blood collection	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X
PANSS		X		X		X		
CCI								
CCI								
CCI								
CCI								
C-SSRS (h)	X	X	X	X	X	X	X	X
Bond-Lader VAS		X						
CCI								

AE=adverse event, CCI , CCI ,
C-SSRS=Columbia-Suicide Severity Rating Scale, eGFR= estimated glomerular filtration rate, ECG=electrocardiogram, hCG=human chorionic gonadotropin, PANSS=Positive and Negative Syndrome Scale, PK=pharmacokinetic, CCI , CCI , VAS=visual analogue scale.

(a) These physical and neurological examinations will look for abnormal change from Screening.

(b) eGFR: The blood required for the eGFR sample will be collected as part of the safety laboratory samples.

(c) Urine drug screens may be repeated as needed at the investigator's discretion.

(d) Two 2.5 mL whole blood samples will be collected for RNA pharmacogenomic analysis from each subject.

(e) CCI .

(f) If a subject who has consented to this procedure does not provide a fecal sample this will not be considered to be a protocol deviation. The reason for missing the sample should be noted. Full details of sample collection will be provided in the Laboratory Manual. Participation in the collection for fecal samples for exploratory microbiome analysis is voluntary and is subject to separate informed consent.

(g) CCI

(h) C-SSRS: The Since Last Visit C-SSRS will be administered at Follow-up Visits as appropriate (if clinically significant at Discharge).

Appendix F Responsibilities of the Investigator

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

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

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

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix G Elements of the Subject Informed Consent

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

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

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

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the unit unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential are excluded from this study. Regular pregnancy tests will be performed throughout the study for all female subjects. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix H Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix I Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 05.

The primary sections of the protocol affected by the changes in Amendment No. 05 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Added Part 3 study design, with population, formulation, dosing, food effect regimen, and confinement

The primary change occurs in Section 6.1.3 Part 3: Single Dose: Healthy Subjects Relative Bioavailablity and Food Effect Study

Added Text and tables:	**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.** **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.** **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.

Rationale for Change: To add to the study design to assess the relative bioavailability and food effect on the PK of the TAK-041 tablet formulation.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 4.2 Rationale for the Proposed Study
- Section 6.1.6 Dose Escalation

Change 2: Added Part 4 study design with stable schizophrenic population, dose levels, dosing days and confinement days.

The primary change occurs in Section 6.1.4 Part 4: Single Dose: Subjects with Schizophrenia

Added text and tables:

Part 4: Single 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. 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 levels 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 escalation 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. The 24 subjects will be randomized with 16 active : 8 placebo.

Overall, Part 4 of the study will consist of a Screening Visit (Days -35 to -3), a predose Check-in Day for all subjects (Days -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 when all subjects will undergo study-specific assessments. After 4 weeks of dosing, subjects will return for follow-up study-specific assessments on Days 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 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.

Bond-Lader visual analog scales 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

CCI

[redacted]

Rationale for Change: To explore the safety, tolerability, and PK of TAK-041 as add-on therapy to antipsychotics in subjects for whom to date there are no approved drugs addressing negative symptoms or cognitive impairment associated with schizophrenia.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 4.2 Rationale for the Proposed Study
- Section 6.1.6 Dose Escalation

Change 3: Added objectives and endpoints for Parts 3 and 4.

The primary change occurs in Section 5.1 Study Objective and Endpoints

Amended or new wording:

Primary Objective

To evaluate the safety and tolerability of TAK-041 ~~following~~

- **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 of 40 mg immediate release tablet formulation of TAK–041 in healthy subjects (Part 3).

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).**

Exploratory Objectives

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[redacted]

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[redacted]

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**Experience** at least 1 treatment-emergent adverse event (TEAE).
- discontinue**Discontinue** due to an adverse event (AE).
- meet**Meet** the markedly abnormal criteria for safety laboratory tests at least once postdose.
- meet**Meet** the markedly abnormal criteria for vital sign measurements at least once postdose.
- meet**Meet** the markedly abnormal criteria for 12-lead ECG parameters at least once postdose.
- experience**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}).

Secondary Endpoints

The secondary ~~endpoints consists~~**endpoint 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_t~~**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 (Part**Parts 2 and 4** only).
- $t_{1/2z}$: terminal disposition phase half-life.

Exploratory Endpoints

[redacted]

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Rationale for Change: to assess the oral bioavailability and food effect on the PK of the 40-mg TAK-041 immediate release tablet and to assess its safety and tolerability as add-on therapy in subjects with stable schizophrenia in Part 4.

The following sections also contain this change:

- Section 5.2 Endpoints for Part 1 and Part 2 and Part 3 (Healthy Subjects) and Part 4 (Subjects with Schizophrenia)
- Section 2.0 STUDY SUMMARY
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 4: Added the justification for the proposed study design dose and endpoints for Part 3.

The primary change occurs in Section 6.2.1 Justification for Study Design, Dose, and Endpoints

Added text: **The primary objective of Part 3 the study is to determine the oral bioavailability of TAK-041 in healthy subjects administered as a 40 mg immediate release tablet formulation in the fasted state compared to 40 mg oral suspension formulation in the fasted state and to estimate the effect of food on the phamacokinetics of a single dose of 40 mg immediate release tablet formulation of TAK-041 in healthy subjects.**

Rationale for Change: to explore the safety, tolerability, and PK of TAK-041 as add-on therapy to stable schizophrenia subjects at doses that will be based on emerging safety/tolerability and available PK data of the same dose in healthy subjects from Part 2. Exploratory endpoints will assess the effect of TAK-041 on improving the negative symptoms, and/or cognitive impairment, and/or anhedonia domains associated with schizophrenia

The following sections also contain this change:

- Section 5.2 Endpoints for Part 1 and Part 2 and Part 3 (Healthy Subjects) and Part 4 (Subjects

with Schizophrenia)

- Section 2.0 STUDY SUMMARY
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)

Change 5: Added the justification for the proposed study design dose and endpoints for Part 4.

The primary change occurs in Section 6.2 Justification for Study Design, Dose, and Endpoints

Added wording: **The highest planned loading dose in Part 4 will not exceed the highest dose evaluated, deemed safe, and well tolerated in Part 1 and Part 2. The highest proposed weekly maintenance dose will have a predicted mean average concentration during a dosing interval, at steady state ($C_{av,ss}$) below the $C_{av,ss}$ observed at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13-week toxicology study.**

Rationale for Change: explore the safety, tolerability, and PK of TAK-041 as add-on therapy to stable schizophrenia subjects at doses that will be based on emerging safety/tolerability and available PK data of the same dose in healthy subjects from Part 2. Exploratory endpoints will assess the effect of TAK-041 on improving the negative symptoms, and/or cognitive impairment, and/or anhedonia domains associated with schizophrenia

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 5.2 Endpoints for Part 1 and Part 2 and Part 3 (Healthy Subjects) and Part 4 (Subjects with Schizophrenia)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 6: Added inclusion and exclusion criteria for Part 3 and 4.

The primary change occurs in Section 7.2 Exclusion Criteria

Amended or new wording: **Note: Subjects with schizophrenia who meet any of the criteria listed below with the exception of Number 9, and 14 will also not qualify for entry into the study. For criteria that are also represented in Section 7.2.2 for subjects with schizophrenia, those criteria supersede the criteria in this section (Section 7.2.1.**

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

1. The subject has received any investigational compound within 30 days prior to the first dose of study drug, or due to the half-life of the investigational

drug is likely to still have detectable plasma levels of that compound.

2. ~~Subject~~**The subject** is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
3. The subject has a known hypersensitivity to any component of the formulation of TAK-041.
4. The subject has a positive urine/blood drug result for drugs of abuse (defined as any illicit drug use) at Screening or Day -1.
5. ~~Subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as 4 or more alcoholic beverages per day) within 1 year prior to the Screening Visit or is unwilling to abstain from alcohol and drugs throughout the study.~~
5. ~~Subject~~ The subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications and Dietary Products **(Table 7a for healthy subjects and Table 7b for subjects with schizophrenia in Section 7.3) or is unable to refrain from or anticipates the use of any medication (except those prescribed) as described in (Table 7a for healthy subjects and Table 7b for subjects with schizophrenia in Section 7.3).**
6. **The subject is lactose intolerant (Part 3 only).**
7. If female, the subject is of childbearing potential (eg, premenopausal, not sterilized).
8. If male, the subject intends to donate sperm during the course of this study or for 145 days (ie, 90 days after 5 half-lives) have elapsed since the last dose of study drug.
9. ~~Subject~~**The subject** has evidence of current **active** cardiovascular, central nervous system, hepatobiliary disease including history of biliary tree disorders, gallstones, endoscopic retrograde ~~cholangio~~cholangio pancreatography (ERCP), and/or cholecystectomy, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory test results (including elevated ALP, elevated bilirubin, elevated GGT, or elevated 5'-nucleotidase) that in the judgment of the principal investigator represents a reasonable suspicion of a disease that would contraindicate taking TAK-041, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, cholestasis, seizure disorders, and cardiac arrhythmias.

10. ~~Subject~~**The subject** has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
11. ~~Subject~~**Had major surgery, or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to Screening.**
12. **The subject** has a history of cancer, except basal cell carcinoma that has been in remission for at least 5 years prior to Day 1.
13. ~~Subject~~**The subject** has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody at Screening or a known history of human immunodeficiency virus (HIV) infection.
14. ~~Subject~~**The subject** has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 21 days prior to Check-in on Day -1. Cotinine test is positive at Screening or Day -1.
15. The subject has poor peripheral venous access.
16. ~~Subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or~~**The subject** had a transfusion of any blood product within 30 days prior to Day 1.
17. ~~Subject~~**The subject** has a Screening or Check-in abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature of the principal investigator or a medically qualified sub-investigator.
18. The subject has a sustained ~~vital signs~~ resting heart rate outside the range 40 to 100 beats per minute (bpm), confirmed on repeat testing within a maximum of 30 minutes, at Screening or Check-in.
19. The subject has a QT interval with Fridericia correction method (QTcF) >450 ms or PR outside the range 120 to 220 ms, confirmed on repeat testing within a maximum of 30 minutes, at the Screening Visit or Check-in.
20. ~~Subject~~**The subject** has abnormal Screening or Check-in laboratory values (> ULN for the respective serum chemistries) of ALT, AST, TBILI, ALP, GGT, 5'nucleotidase **(Screening only)** and/or abnormal urine osmolality, confirmed upon repeat testing.
21. The subject has a clinically significant history of head injury or trauma **associated with loss of consciousness for > 15 minutes.**
22. The subject ~~has a~~**is considered by the investigator to be at** imminent risk of suicide ~~according to the investigator's~~or ~~subinvestigator's clinical~~

~~judgment (eg, per C-SSRS)~~injury to self, others, or ~~has made a suicide attempt in~~property, or subjects who within the past year prior to Screening have attempted suicide. Subjects who have positive answers on item 4 or 5 on the C-SSRS (based on the past year) prior to randomization are excluded.

23. ~~Subject~~The subject has a history of significant skin reactions (hypersensitivity) to adhesives, metals or plastic; this criterion applies only to subjects participating in the study of the two wearable digital devices.
24. The subject is unsuitable for inclusion in the trial in the opinion of the investigator or sponsor.

Subjects with schizophrenia only

Note: Subjects with schizophrenia must not meet any of the criteria listed in Section 7.2.1 for healthy subjects with the exception of Number 9 and 14, as well the criteria listed below. The criteria listed below supersede the criteria in Section 7.2.1.

All entry criteria, including test results, need to be confirmed prior to randomization.

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

1. The subject has an undetectable level of baseline antipsychotic medication at Screening.
2. The subject has a lifetime diagnosis of schizoaffective disorder; a lifetime diagnosis of bipolar disorder; or a lifetime diagnosis of obsessive compulsive disorder based on the MINI combined with the general psychiatric evaluation. As an exception, subjects with a historical prior lifetime diagnosis of schizoaffective disorder may be enrolled in the study with sponsor or designee approval provided that the principal investigator can attest that the subject's overall history and current clinical presentation and history is most consistent with schizophrenia, not schizoaffective disorder.
3. The subject has a recent (within the last 6 months) diagnosis of panic disorder, depressive episode, or other comorbid psychiatric conditions requiring clinical attention based on the MINI for DSM-5 and the general psychiatric evaluation.
4. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as 4 or more alcoholic beverages per day) within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.

5. **The subject has a diagnosis of substance use disorder (with the exception of nicotine dependence) within the preceding 6 months based on the MINI for DSM-5 and the general psychiatric evaluation.**
6. **The subject has evidence or history of current clinically significant cardiovascular disease, including uncontrolled hypertension (standing or supine diastolic blood pressure >90 mm Hg and/or standing or supine systolic blood pressure >145 mm Hg, with or without treatment), symptomatic ischemic heart disease, uncompensated heart failure or recent (past 12 months) acute myocardial infarction or bypass surgery. Controlled essential hypertension, non-clinically significant sinus bradycardia and sinus tachycardia will not be considered significant medical illnesses and would not exclude a subject from the study. Other well-controlled medical illnesses may be permitted that do not increase hepatic risks or other safety risks to the subject's participation in the judgement of the investigator in consultation with the sponsor or designee.**
7. **The subject has evidence of clinically significant extrapyramidal symptoms as measured by a Simson-Angus Scale (SAS) score >6.**
8. **The subject has evidence of depression as measured by a Calgary Depression Score (CDSS) score >9.**
9. **The subject has received TAK-041 in a previous clinical study; or has previously or is currently participating in this study; has received treatment with other experimental therapies within the preceding 60 days or <5 half-lives prior to randomization, whichever is longer; has participated in 2 or more clinical studies within 12 months prior to Screening; or has participated in a clinical study for a psychiatric condition that is exclusionary per this protocol.**

Rationale for Change: select a healthy population consistent with the FDA bioavailability and food effect guidance in Part 3 and to select a stable schizophrenia population to assess safety and tolerability as an add-on therapy to antipsychotics in Part 4

Change 7: Added excluded medications, dietary products and study control of diet, fluid and activity control for Parts 3 and 4.

The primary change occurs in Section 7.4 Diet, Fluid, and Activity Control

Amended or new wording:

Diet, Fluid, and Activity Control

Subjects will be confined to the unit for the duration of each treatment period in Parts 1, 2, 3 and ~~2~~Part 4 as described in Appendix A, **Appendix B, Appendix C, Appendix D and Appendix E respectively.** ~~In~~Subjects from Part 1 ~~subjects~~

~~are~~will be required to remain in the study unit during each treatment period from Check-in, Day 1 for single dose administration, and with Cohorts 1-5 at least 96 hours postdose for a total confinement period for each treatment period of 5 days. Subjects from Part 2 Cohorts 1 to 4, and Part 1 Cohorts 1 and 2, will be required to remain in the study unit from Day -2 to Day 3, Days 7 to 10, Day 14 to Day 17, and Day 21 to Day 24 (48 hours after ~~the~~each dose in Part 2) for safety, PK, and all study assessments before discharge. In addition, subjects will return to the clinic on Days 5, 26, 29, 36, 43, 50, 57, and 64 for safety and PK follow up visits. Subjects with schizophrenia (Part 4) will also undergo part-specific assessments on Days 29 and 43. A Final Visit that completes the study will occur 12 to 16 days after the last safety and PK Follow-up Visit. On the days of dosing, subjects will be administered TAK-041/matched placebo at approximately 0800 hours following a fast of at least 8 hours and will continue to fast for an additional 4 hours postdose.

Subjects from study Parts 1, 2 and 4 may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. The meal start and stop times and the amount consumed will be recorded in the source document and appropriate electronic case report form (eCRF) page for all meals served on the dosing days. During confinement on nondosing days, subjects will be given 3 meals and an evening snack each containing approximately 30% fat (relative to the total calories). Breakfast will not be served on dosing days.

Subjects from all study parts should remain upright (seated, standing, or ambulatory) for 4 hours following dose administration, except as necessitated by the occurrence of an AE /or study procedure (eg, obtaining 12-lead ECG). Subjects should refrain from strenuous exercise from 72 hours before Check-in ~~(Day -2)~~ and throughout the entire course of the study.

Part 3 Diet and Fluid Control

Subjects in Part 3 will be required to remain in the study unit for a confinement period of 3 days. The subjects will be randomized for TAK-041 immediate release tablet administration at approximately 0800 hours either following an overnight fast (no food, no drink other than water, no medications) of at least 10 hours or 30 minutes after starting ingestion of a high-fat, high-calorie breakfast as described in 2002 FDA Food-Effect Guidance (the meal composition should derive of approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively, in total of approximately 800 to 1000 calories).

Per FDA guidance, subjects will be served the standard FDA breakfast to be ingested and completely consumed over 30 minutes. TAK-041 40 mg tablet should be administered immediately after breakfast with a glass of water.

Substitutions to the contents of this high-fat, high-calorie meal can be made

as long as the same meal is served to all subjects and a nutritionist at the site ensures that the test meal provides a similar amount of calories from protein, carbohydrates and fat and has comparable meal volume and viscosity. The clinical site will document the amount of protein carbohydrates and fat and total calorie content of the test meal for the study file and provide a copy to the sponsor. The date and time of the meal will also be recorded on the eCRF.

Fasting subjects will also be administered the 40 mg tablet with a glass of water. Both fasting and fed subjects will have no food, no drinks (except water) and no medications for 4 hours after dose administration.

Rationale for Change: to provide a healthy subject population in Part 3 consistent with FDA bioavailability and food effect guidance in Part 3 on diet, fluid and activity and medication control in Part 4.

The following sections also contain this change:

- Section 7.3 Excluded Medications and Dietary Products
- Section 7.2 Exclusion Criteria
- Section 2.0 STUDY SUMMARY
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 8: Added TAK-041 tablet formulation to study medication for Part 3 and manufacturing, packaging, labeling, dispensing and randomization to include Part 3 and 4.

The primary change occurs in Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Amended or new wording:

The TAK-041 oral crystalline suspension will be used in this study. **Parts 1, 2 and 4**. The TAK-041 crystalline drug substance (milled) will be labeled in an open-label fashion and compounded into oral suspensions that will be labeled in a blinded fashion for third party dispensing. An unblinded pharmacist will manage and prepare doses as needed throughout the study. The oral suspensions will contain 5 to 160 mg of TAK-041 per dose. Compounding instructions will be provided to the clinical site using the compounding worksheet or a similar document.

~~16.1.2.2.1 Investigational Drug~~

The oral suspension containing crystalline TAK-041 (milled) will be prepared at the site by weighing an appropriate amount of crystalline TAK-041 (milled) into a dosing bottle and mixing with 70 mL of 0.5% Tween 80 in 0.5% methylcellulose

vehicle (Tween/MC vehicle). The composition of the Tween/MC vehicle is in Table 8.a. The composition of crystalline TAK-041 oral suspension is listed in Table 8.b.

The TAK-041 40 mg tablet will be used in this study for Part 3. The tablet formulation is designed for immediate drug release [redacted]**. The tablets are round and film coated.**

Sponsor-Supplied Drug

For Parts 1, 2, and 4, the TAK-041 crystalline drug substance (milled) will be supplied in a powder form, in appropriate packaging, and each container will bear a single panel label that includes all pertinent study information.

The TAK-041 40 mg immediate release tablet will be used in this study for healthy subjects in Part 3. The tablets are packaged in amber glass bottles. Each bottle will contain a label that includes pertinent study information and caution statements.

Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

TAK-041 crystalline drug substance (milled) ~~is~~**and 40 mg tablets are** stored at controlled room temperature (20°- 25°C with excursions allowed from 15°-30°C).

Dose and Regimen

The planned initial dose of TAK-041 for Part 1 SRD Cohort 1 Period 1 is 5 mg. Doses for subsequent periods/cohorts will be determined based on the available safety, tolerability, and PK data from the preceding period/cohort. The doses will be administered to the subjects by the investigator or the investigator's designee. Subjects will receive the doses by drinking the entire suspension from the dosing bottle. The dosing bottle will then be rinsed with 35 mL of water and the rinse will be administered in the same manner as the suspension. The rinse and administration will be repeated one more time.

Eligible subjects in Part 3 will be randomized to receive a single dose of TAK-041 as one 40 mg tablet administered orally after either an overnight fast of at least 10 hours or 30 minutes after starting ingestion of a high-fat and high-calorie breakfast as recommended in the 2002 FDA Food-Effect Guidance[3] (the meal should derive of approximately 150, 250 and 500 to 600 calories from protein, carbohydrate and fat, respectively, in total of approximately 1000 calories). The tablet must be administered with a glass of water (approximately 240 mL). It should be swallowed as a whole and not be

manipulated in any way.

Rationale for Change: to provide dosage form, manufacturing, packaging and labeling information and randomization for the TAK-041 immediate release tablet in Part 3

The following sections also contain this change:

! Section 8.2 Investigational Drug Assignment and Dispensing Procedures

Change 9: Added height weight and BMI to Part 3 and 4, with Part 4 subjects have an increased upper limit for BMI of 40.5 kg/m^2.

The primary change occurs in Section 7.1.1 Healthy subjects and subjects with schizophrenia.

Amended or new wording: The subject weighs at least 45 kg (99 lb) and has a body mass index (BMI) from 18 up to 32 kg/m^2 **for healthy subjects and up to 40.5 kg/m^2 for subjects with schizophrenia**, inclusive at Screening.

Rationale for Change: to provide an acceptable BMI range for enrollment of subjects with stable schizophrenia in Part 4

The following sections also contain this change:

Section 2.0 STUDY SUMMARY

! Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET

! Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 10: Added cognitive and other psychiatric/neurological assessments to Part 4.

The primary change occurs in Section 9.1.17 Other Psychiatric/Neurological Rating Scales

New Section: **Subjects with schizophrenia (Part 4) will also receive the MINI,** CCI [redacted] **A trial manual describing the procedures to be used with these assessments will be supplied to the site. These assessments will be administered according to the schedule shown in Appendix D/E. The assessments are briefly described below:**

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. The clinician responsible for the subject must administer the MINI[20-22].

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Rationale for Change: to provide Part 4 assessment of safety and of cognitive function and other psychiatric/neurological rating scales to include measure effect of add-on TAK-041 administration on improving negative symptoms associated with schizophrenia

The following sections also contain this change:

! Section 9.1.13 Bond-Lader Visual Analogue Scale

Section 9.1.15 PANSS

CCI [redacted]

Section 2.0 STUDY SUMMARY

! Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET

! Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 11: Added statistical analysis for Part 3 and Part 4.

The primary change occurs in Section 13.1.3 Pharmacokinetic Analysis

Amended or new wording:

Concentrations of TAK-041 in plasma will be summarized by dose over each scheduled sampling time using descriptive statistics for ~~single (Part1) and multiple doses (Part 2).~~**each study part**. Amount of TAK-041 excreted in urine will be summarized by dose over each scheduled sampling interval using descriptive statistics for ~~single (Part 1) and multiple dose (Part 2).~~**each study part**. Individual PK data will be presented in a data listing. PK parameters of TAK-041 will be summarized by dose using descriptive statistics for single(Part 1) and multiple dose (Part 2). each study part. Dose proportionality will be assessed graphically (dose-normalized C_{max} and AUC versus dose~~).~~ **in Part 1 and Part 2**. To assess dose proportionality of single dosing (Part 1), a power model will be used. The model will include the natural log-transformed AUC and C_{max} as response variable and the natural log-transformed dose [ln(dose)] as a continuous covariate. No formal statistical comparisons will be conducted. For Part 2, dose proportionality will be assessed using an analysis of variance (ANOVA) model separately for dose-normalized AUC and Cmax on Day 22~~. Treatment~~ **with treatment** (as a categorical variable~~, will be~~) **as a** fixed effect. The dose-normalized parameters will be natural log-transformed prior to the analysis. All treatment differences and corresponding two-sided 90% CIs will be extracted from the model, back-transformed, and expressed as central value ratios.

The effect of food on TAK-041 exposure will be evaluated in Part 3 using an ANOVA on the natural log-transformed TAK-041 C_{max} and AUC_{96} with regimen (high-fat vs. fasted) as a fixed effect. 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 after the high-fat meal versus the fasted state.

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 using an 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 ANOVA will be performed on the natural log-transformed Day 1 TAK-041 C_{max} and AUC_{96} with regimen as a fixed effect. 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.

Rationale for Change: to provide statistical analysis for Part 3 effect of food on TAK-041 exposure and the relative bioavailability of TAK-041 administered as a 40 mg immediate release tablet formulation compared to the 40 mg oral suspension in Part 1 and Part 2 (Day 1 only), as well as exploratory analysis in Part 4.

The following sections also contain this change:

Section 13.1.4 Exploratory Analyses

Section 13.1.5 Safety Analysis

! Section 2.0 STUDY SUMMARY

Change 12: Added pharmacogenomic sample collections for Part 3 and 4.

Rationale: to subject DNA and RNA which may provide

The primary change occurs in Section 9.1.18 Pharmacogenomic Sample Collection

Amended or new wording: **Pharmacogenomic Sample Collection**

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[redacted]

CCI [redacted]

Rationale for Change: CCI [redacted]

The following sections also contain this change:

Section 9.1.1.1 Pharmacogenomic Informed Consent Procedure

Section 2.0 STUDY SUMMARY

- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 13: Added PK parameters and PK blood collections for Part 3 and 4 and PK urine collections for Part 4.

The primary change occurs in Section 9.1.19 Pharmacokinetic Sample Collection

Initial wording: Laboratory Manual.

Amended or new wording:

Pharmacokinetic Sample Collection

Collection of Plasma for Pharmacokinetic Sampling

Blood samples (one 4-mL sample per scheduled time) for PK analysis of TAK-041 ~~and its metabolites (if possible)~~ will be collected into chilled Vacutainers containing anticoagulant K_2EDTA ~~according to the schedules for Parts 1 and 2 in Appendix A and Appendix B, respectively~~. Placebo samples will not be analyzed by the bioanalytical laboratory except 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 could have been on active treatment. Instructions for sample processing and shipment will be provided in to the site in the Laboratory Manual.

Serial blood samples for determination of TAK-041 in Part 1 will be collected according to Table 9.c and Table 9.d and in Appendix A.

Serial blood samples for determination of TAK-041 in Part 3 will be collected according to Appendix C.

Based on emerging PK data from previous cohorts, the actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. When the timing of safety measurements coincides with a PK blood collection, the order should be safety assessments followed by PK blood sample collection at the nominal time. The actual times of sample collection will be recorded on the source documents and eCRF.

Sampling time points may be adjusted based on the preliminary emerging PK data

collected from prior period/cohort(s), but the total number of samples collected per subject should not exceed the planned number.

Collection of Urine for Pharmacokinetic Sampling

Serial urine samples for determination of TAK-041 in Part 1 will be collected according to Appendix A.

Serial urine samples for determination of TAK-041 in Part 2 will be collected according to Appendix B.

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.

When Early Termination occurs on a non-PK blood collection day, PK blood and urine samples should be collected.

Urine samples for subjects randomized to placebo will not be analyzed.

Urine volume will be recorded within 2 hours of the end of the collection period. Instructions for sample processing and shipment will be provided to the site in the Laboratory Manual.

CCI [redacted]

Rationale for Change: to add PK collection and parameters for the food effect and bioavailablity comparison in healthy subjects for Part 3 as well as provide PK profile for TAK-041 in the stable schizophrenic subjects in Part 4

The following sections also contain this change:

- Section 9.1.20 Pharmacokinetic Parameters
- Section 2.0 STUDY SUMMARY
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 14: Revised the study-specific dose escalation and stopping rule for Part 1 and Part 2.

The primary change occurs in Section 6.3.2 Study-Specific Dose Escalation and Stopping Rules.

Amended or new wording:

Specific Dose Escalation and Stopping Rules

1. Dose escalation between cohorts and within a cohort will be decided after either a full-blinded (Part 1, Cohorts 1 and 2) or a sponsor partial unblinded (Part 1, Cohorts 3 to 5, and Part 2, Cohort 1 onwards, where certain sponsor

staff not directly involved with the treatment or evaluation may be unblinded to the treatment or intervention) review of at least 21 days of safety, tolerability, and available PK data from the previous dose. The selection of each subsequent dose will be made jointly and agreed upon by the sponsor and the principal investigator/designee and after careful evaluation of all available data from previous doses.

2. Dose escalation will be stopped at a dose level (ie, one escalation step) below the dose that is predicted to give a TAK-041 AUC_{24} or ~~$C_{av,ss}$~~ C_{max} that exceeds the mean $AUC_{24,ss}$ or ~~$C_{av,}$~~$C_{max,ss}$ (Part 1) ~~or Cmax and AUC24~~$C_{av,ss}$ **that exceeds $C_{av,ss}$** (Part 2) at the NOAEL dose of 30 mg/kg/day in the male and female dogs from the 13 week toxicology study.
3. Escalation will stop once the maximum tolerated dose has been reached or previously defined toxicokinetic exposure limits are met.
4. Dose escalation may not proceed if any of the following occur at the previous dose cohort, although dosing may be resumed at a lower dose in the subsequent cohort:
    a) Significant study drug-related adverse events of severe intensity in ≥3 subjects.
    b) One or more subjects experience clinically significant ECG abnormalities or effects on vital signs indicating dose-limiting intolerance.
    c) One or more subjects experience clinically significant changes in neurological assessments indicating dose-limiting intolerance.
    d) One or more subjects in a cohort experiences a study drug-related serious adverse event (SAE).
    e) One or more subjects has abnormal liver function tests as described in Section 6.3.1 that can be considered related to study drug.
    f) Subject experiences any of the Takeda Medical Significant Events (Table 10.a) that can be considered related to study drug.
5. Within each dose level, if at least 1 subject develops a dose-limiting toxicity (DLT) listed in Table 6.j which is confirmed by repeat test if applicable, no further dosing will occur in that subject if the subject has received TAK-041.

Definition of DLTs

Toxicity	Definition
Leukopenia	Total leukocyte count <2500 cells/mm^3 (2.5 x10^9/L)
Neutropenia	Absolute neutrophil count <1500/mm^3 (1.5 x10^9/L)
Thrombocytopenia	Platelet count <100 x10^9/L

Lymphopenia	Lymphocyte count <1000 cells/mm^3 (1 $x10^9$/L)
Anemia	Red blood cell count <3.5 $x10^{12}$/L (men) or <3.0 $x10^{12}$/L (women)
Low Hemoglobin	Hemoglobin <11 g/dL (men) or <10.5 g/dL (women)
Severe Infection	Serious infection requiring hospitalization, intravenous antibiotics, systemic antifungal or antiviral intervention
QTc	QTc >500 msec

6. After review of the safety data and discussion/agreement between the investigator and Takeda, the same dose may be given again or a lower dose may be given in subsequent periods/cohort to increase data within the dose range.
7. The dose increments and planned doses may be changed as the study progresses dependent upon emerging PK, safety, and tolerability data. Any decision to alter the planned dose scheme and the decision on which doses to use will be made jointly and agreed upon by the investigator and Takeda after careful evaluation of all available data.
8. Should significant adverse events occur, any decision to resume dosing at the current dose level or to escalate the dose will be made jointly by the investigator and Takeda after careful evaluation of all available data and will be communicated to the Institutional Review Board (IRB).

Rationale for Change: Updated dose escalation stopping rule updated to incorporate steady state C_{max} and steady state C_{av}

The following sections also contain this change:

- Section 6.1.4 (Dose Escalation)

Change 15: Added exclusion criteria for recent major surgery or donation or loss of blood.

The primary change occurs in Section 7.2 Exclusion Criteria

Amended or new wording: **Had major surgery, or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to Screening.**

Rationale for Change: Now exclude subjects that are recovering from recent major surgery, donated blood or experienced blood loss, as an additional safety measure during screening

Change 16: Revised exclusion for clinically significant history or head injury or trauma to include loss of consciousness for greater than 15 minutes.

The primary change occurs in Section 7.2 Exclusion Criteria

Initial wording:	The subject has a clinically significant history of head injury or trauma.
Amended or new wording:	The subject has a clinically significant history of head injury or trauma **associated with loss of consciousness for > 15 minutes.**

Rationale for Change: Added detail to severity of the head injury or trauma in applying exclusion

The following sections also contain this change:

- SECTION 2.0 STUDY SUMMARY

Change 17: Updated exclusion language on risk of suicide considered by the investigator, including specific C-SSRS results.

The primary change occurs in Section 7.2.1 Healthy subjects

Initial wording:	The subject has a risk of suicide according to the investigator's or sub-investigator's clinical judgment (eg, per C-SSRS) or has made a suicide attempt in the previous 6 months from Screening.
Amended or new wording:	The subject ~~has a~~is **considered by the investigator to be at imminent** risk of suicide ~~according to the investigator's~~ or ~~sub-investigator's clinical judgment (eg, per C-SSRS~~**injury to self, others,** or ~~has made a suicide attempt in~~**property, or subjects who within** the ~~previous six months from~~**past year prior to** Screening **have attempted suicide. Subjects who have positive answers on item 4 or 5 on the C-SSRS (based on the past year) prior to randomization are excluded.**

Rationale for Change: to detail specific answers on the C-SSRS prior to randomization as exclusion criteria and to provide timing of assessments for Part 3 and 4.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 18: Added unsuitable for inclusion in the opinion of the investigator or sponsor as an exclusion criterion.

The primary change occurs in Section 7.2.1 Healthy subjects

Amended or new wording:	Exclusion criteria 24: **The subject is unsuitable for inclusion in the trial in the opinion of the investigator or sponsor.**

Rationale for Change: to ensure in the opinion of the investigator that the subjects are not exposed to an unacceptable level of risk, or if the subject may not be able to follow or complete the study procedures

Change 19: Detailed specific neurological examinations, and combined as part of physical examination, with required assessment as not clinically significant (NCS) or clinically significant (CS).

The primary change occurs in Section 9.1.3 Physical Examination Procedure and Neurological Examination

Initial wording:	A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. Neurological assessments will be included in the 11 system assessments of the physical examination and will mainly consist of tests of sensory and motor functions (eg, reflexes, coordination, and gait). The Bond-Lader visual analogue scale (VAS) (Section 9.1.13) and the C-SSRS (Section 9.1.14) will also be administered. Any abnormal finding on a pretreatment physical examination assessment must be assessed as Not Clinically Significant (NCS) or Clinically Significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.8. On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the investigational drug (Day -1) must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.
Amended or new	Physical Examination Procedure **and Neurological Examination** A physical examination will consist of the following body systems: (1) eyes; (2)

wording: ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

~~Neurological~~ **As part of the physical examination, neurological** assessments will be included ~~in the 11 system asessments of the physical examination~~**on the Neurological Exam eCRF** and ~~will mainly consist of tests of sensory and motor functions (eg, reflexes, coordination, and gait).~~**include (1) Basic Mental Status; (2) Cranial nerves II-XII; (3) Motor examination; (4) Deep Tendon Reflexes; (5) Sensory examination; (6) Cerebellar function.** The Bond-Lader visual analogue scale (VAS) (Section 9.1.13) and the C-SSRS (Section 9.1.14) will also be administered.

Any abnormal finding on a pretreatment physical examination assessment **(including neurological)** must be assessed as Not Clinically Significant (NCS) or Clinically Significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.8.

On subsequent examinations, any abnormal change from the pretreatment physical examination (including neurological) assessment occurring immediately prior to the start of the investigational drug (Day -1) must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

Rationale for Change: To provide clinical assessment of significance of the neurological examinations

The following sections also contain this change:

! Section 13.1.5 Safety Analysis

Change 20: Updated wearable device timing of placement and removal for Part 2 and added to Part 4.

The primary change occurs in Section 9.1.6 Wearable Device Procedure.

CCI

[redacted]

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Rationale for Change: To update the timing of the placement and removal of the wearable devices.

The following sections also contain this change:

- Section 4.2 Rationale for the Proposed Study
- Section 2.0 STUDY SUMMARY
- Appendix B: Schedule of Study Procedures Part 2 Cohorts 1 to 4 (healthy subjects only)
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 21: Added laboratory sample collections and blood sampling volumes for Part 3 and 4

The primary change occurs in Section 9.5 Blood Volume

Amended or new wording:

Approximate Blood Volume for Part 3

The maximum volume of blood collected for a subject in Part 3 in any single day is approximately 55 mL. The total volume of blood for each subject in Part 3 is approximately 159 mL. Direct venipuncture or indwelling catheter may be used for blood collection.

Approximate Blood Volume for Part 4

The maximum volume of blood collected on any single day is approximately 108 mL. The total volume of blood to be collected from each subject in Part 4 is approximately 455 mL, and will be taken over a period of 2.5 months. Direct venipuncture or indwelling catheter may be used for blood collection.

Rationale for Change: to include Part 3 and 4 in clinical laboratory and PK blood sampling procedures, and update blood sampling in Part 1 and 2.

The following sections also contain this change:

- Section 9.1.9 Procedures for Clinical Laboratory Samples
- Section 9.1.19 Pharmacokinetic Sample Collection
- Section 2.0 STUDY SUMMARY
- Appendix A Schedule of Study Procedures Part 1
- Appendix B: Schedule of Study Procedures Part 2 Cohorts 1 to 4 (healthy subjects only)
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 22: Added contraception, avoidance procedures and pregnancy statements to Part 3 and 4.

The primary change occurs in Section 9.1.10 Contraception and Pregnancy Avoidance Procedure

Amended or new wording: In addition to a negative serum hCG pregnancy test at Screening, female subjects also must have a negative serum hCG pregnancy test on Day ~~-1~~ and Study Exit/Early Termination ~~(Parts 1 and 2).~~ **for all study parts.**

Rationale for Change: Update procedures and statements to include Part 3 and 4 subjects.

The following sections also contain this change:

- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 23: Added ECG assessments to Part 3 and 4 and removed triplicate parameter assessments from Holter ECG in part 2.

The primary change occurs in Section 9.1.12 ECG Procedure

Amended or new wording:

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 clinically significant, or abnormal and clinically significant. 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 ~~shown in Table 9.b below, and in Appendix A (Part 1) and Appendix B (Part 2).~~ **in all study parts as shown in Appendix A, B, C and D/E.** Single ECGs will be taken at all time points.

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. A window of ±10 minutes around each scheduled time point can be utilized in order for the central reader to obtain the necessary ECGs. 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

ECG Monitoring (Part 2, Healthy Subject Cohorts)

To ensure high-quality data recording, prior to electrode placement, the anatomical sites must be prepared to allow for proper skin/electrode interface. Any hair on the electrode sites must be shaven. Any oils, lotions, or dead skin should be removed from the electrode sites using an abrasive alcohol prep pad designed for this purpose. An indelible skin marker must be used to mark the exact electrode placement site so that the electrode positions will remain constant throughout each treatment period. The electrodes should always be attached to the Holter connecting cable prior to skin placement.

All Holter recordings will be obtained on 1000 sps flash cards using a 12-lead Holter recorder. The flash cards will be couriered to the central cardiac core laboratory. Alternatively, Holter recordings will be digitally transmitted to the central cardiac core laboratory, as appropriate.

Each 12-lead Holter ECG acquisition window will be approximately 10 minutes in duration, from which cardiac data analysis laboratory will extract 10-second ECGs in triplicate. This window will be preceded by 10 minutes of quiet supine rest.

~~Triplicate parameter estimates will be derived from the ECG traces at each nominal time point, including heart rate, RR interval, PR interval, QT interval, QRS interval, QTcF, QT interval with Bazett correction (QTcB), and T and U wave morphology, as appropriate. Other time points may also be retrospectively assessed if clinical observations or findings require further investigation.~~

Subjects will be supervised while remaining at rest, quiet, awake, and in a supine position from at least 10 minutes prior to the beginning of each ECG extraction time point and will remain quiet, awake, motionless, and supine for at least 10 minutes after the beginning of each ECG extraction time point.

ECGs derived from Holter monitoring are not intended to be analyzed for real-time safety monitoring but may be used for future retrospective ECG analyses, unless an earlier analysis is warranted by emerging safety information.

Rationale for Change: to include Part 3 and 4 in ECG assessments and to update Part 2 Holter ECG assessment (Part 2 (Healthy Subjects)

The following sections also contain this change:

- Section 9.1.12.1 Holter ECG Monitoring (Part 2, Healthy Subject Cohorts)
- Section 2.0 STUDY SUMMARY
- Appendix B: Schedule of Study Procedures Part 2 Cohorts 1 to 4 (healthy subjects only)
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)

- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 24: Added optional exploratory biomarker sample collection to Part 4.

The primary change occurs in Section 9.1.22 Exploratory Biomarker Sample Collection

Amended or new wording: **Exploratory Biomarker Sample Collection**

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[redacted]

Rationale for Change: the biomarker-based deep characterization is exploratory research and will help in the design of future studies

The following sections also contain this change:

- Section 4.2 Rationale for the Proposed Study
- Section 2.0 STUDY SUMMARY
- Section 6.1.2 Part 2 Multiple-Rising Dose: Healthy Subjects
- Section 6.1.4 Part 4: Single Dose: Subjects with Schizophrenia
- Section 9.5 Blood Volume
- Appendix D Schedule of Study Procedures Part 4 Screening Through Day 24/ET
- Appendix E Schedule of Study Procedures Part 4: Follow-Up and Final Visit

Change 25: Updated the nonclinical information on TAK-041

The primary change occurs in Section 4.1.

Amended or new wording:

Behavioral responses were examined in 2 different mouse models exhibiting social interaction deficits: the Balb/c model and the polyinosinic:~~olycytidylic~~**polycytidylic** acid (poly [I:C]) model. In both models, 0.1 mg/kg TAK-041, dosed either acutely or subchronically (15 days of treatment), mitigated the social deficits that were either naturally occurring (Balb/c) or pharmacologically evoked by the inflammatory stimulus (poly [I/C]). Moreover, haloperidol, a dopamine D2 receptor antagonist, did not provide therapeutic benefit as a stand-alone treatment in the poly (I:C) model and did not abrogate the efficacy associated with TAK-041. Furthermore, the cognitive deficits associated with subchronic phencyclidine (PCP) treatment in a rat set shifting task were significantly attenuated by increasing doses of TAK-041 from 0.3 to 3 mg/kg with 4 hours of pretreatment. This result compared favorably to risperidone, a second generation antipsychotic treatment. Accordingly, the available experimental evidence supports the use of TAK-041, a GPR139 agonist, as a potential treatment for the negative symptoms (including amotivation, anhedonia, and asociality) and cognitive impairment associated with schizophrenia, a debilitating disorder with high unmet medical need.

The PK properties of TAK-041 have been characterized in vitro and in Sprague-Dawley rats and beagle dogs after oral (PO) or intravenous (IV) administration. Pharmacokinetic evaluations were conducted in rats and dogs because these were the major species used in the toxicology program.

TAK-041 was absorbed after PO administration to rats and dogs, with peak plasma concentrations generally occurring within 4 to 8 hours postdose in rats and 0.5 to 2 hours postdose in dogs. The plasma clearance of TAK-041 was low in rats and moderate to high in dogs (~4 and ~11 mL/min/kg, respectively). The terminal elimination half-life ($t_{1/2}$) of TAK-041 after PO administration was 1.5 to 2.8 hours in dogs, and undefined in rats because of a poorly defined terminal phase observed in this species. The oral bioavailability of TAK-041 was high (90.8% to 94.2% in rats; in dogs, the dose-normalized PO exposures were greater than observed after IV dosing, resulting in reported bioavailability ~~yp~~**up** to 100% or greater. Absorption was not likely modulated by P-glycoprotein (P-gp), because TAK-041 had a low P-gp efflux ratio (0.4), as demonstrated in LLC-PK1-MDR1 cells, indicating that TAK-041 is not likely a substrate for P-gp. TAK-041 (1 and 10 µM) plasma protein binding was 95.9%, 95.4 to 96.5%, 96.8 to 97.3%, 95.3 to 95.4%, and 96.8 to 97.1% in plasma from mice (tested at 10 µM only), rats, dogs, monkeys, and humans, respectively. Red blood cell: plasma ratios of TAK-041 at 0.1, 1, and 10 µM were approximately 0.8, 0.8, and 1.1 in rats; 0.4, 0.4, and 1.0 in dogs; and 0.7, 0.6, and 0.8 in humans, respectively. TAK-041 showed no inhibitory effect on the Bile Salt Export Pump transporter in rat and human vesicles up to 200

μM and a moderate inhibitory effect in dog vesicles (IC50 ~ 72 μM).

In vitro metabolism studies with hepatic microsomes and hepatocytes from human donors showed trace amounts of a few metabolites including oxidative N-dealkylation to form an amide metabolite and oxidations at the oxobenzotriazine moiety to form positional isomeric structures. Subsequent glucuronidation of these oxidative isomeric structures yielded their corresponding glucuronide conjugate metabolites. In addition to these metabolites, a glutathione conjugate of TAK-041 and one of its downstream metabolites, a cysteine conjugate, were also detected in rat and dog hepatocytes. No human-specific metabolites were observed. An evaluation of the cytochrome P-450 enzymes (CYPs) responsible for the metabolism of TAK-041 has not yet been conducted. Glutathione-adduct-derived thiol metabolites through the β-lyase pathway is significant in dog (higher rate of metabolism and lack of N-acetylation detoxification pathway). Preliminary human in vitro and in vivo data suggest similar metabolic pathways but to a much lesser extent. The formation of N-acetylcysteine conjugate was observed in human as evident of N-acetylation detoxification pathway. In rat, however, glucuronidation pathway seems to be predominant.

An assessment of cytochrome P-450 enzyme (CYP) induction was conducted in cultured human hepatocytes, and induction of CYP2B6 and CYP3A4 messenger RNA (mRNA) was observed. Treatment of cultured human hepatocytes with up to 10 μM TAK-041 had little or no effect on CYP1A2 mRNA levels, while treatment with up to 10 μM TAK-041 caused concentration-dependent increases of >2.0-fold and >20% of the positive control in CYP2B6 and CYP3A4 mRNA levels, respectively, in all cultures tested. Thus, TAK-041 was a mild inducer of CYP2B6 and CYP3A4 mRNA in vitro and CYP induction based DDI potential is considered low. **TAK-041 showed no reversible inhibition of CYP3A4/5 activities at concentrations ranging up to 100 μM with an IC50 > 100 μM. In the CYP3A4/5 time-dependent inactivation (TDI) study, the percentage of activity remaining in samples preincubated with TAK-041 showed no time-, concentration-, or NADPH-dependent CYP3A4/5 loss of activity. These data suggest that potential reversible inhibition and TDI of CYP3A4/5 by TAK-041 are unlikely.**

Urinary excretion of TAK-041 was investigated in dogs after a single IV dose. After IV administration to 3 dogs, TAK-041 was detectable in dog urine, but at low levels. The amount of TAK-041 excreted unchanged into dog urine within 24 hours ranged from approximately 0.009% to 0.0157% with mean recovery of 0.0135% of the given dose.

A comprehensive series of nonclinical safety studies (Good Laboratory Practices [GLP]) have been conducted with TAK-041 to support early human studies including:hERG, electrocardiography in dogs, respiratory and CNS in rats, genetic toxicity studies (Ames, in vitro micronucleus, in vivo micronucleus), and in vitro

phototoxicity. An effect of TAK-041 was first observed at 1 µM in the human ether-à-go-go–related gene (hERG) assay (IC_{50}>3 µM); however, no changes in ECG parameters were observed in the in vivo dog cardiovascular (CV) or 4-week repeat-dose toxicity study at 125 mg/kg. In the dog CV study, an increase in systolic blood pressure (10%) resulting in increases in mean arterial and pulse pressures without any associated changes in heart rate at 0.5 to 6.25 hours postdose at 125 mg/kg was observed. A diminished trend not of biological significance occurred at 15 mg/kg with no effect observed at 5 mg/kg. In addition, daily repeat-dose toxicity studies of 4-week and 13-week duration have been conducted in rats and dogs. The oral dose levels in the 4-week toxicity study in rats were 5, 30, and 200 mg/kg/day (males) and 3, 10, and 200 mg/kg/day (females). In the 13-week repeat-dose toxicity study in rats, the oral dose levels were 10, 40 and 200 mg/kg/day in males and 2, 10, and 200 mg/kg/day in females. In the 4- and 13-week toxicity studies in dogs, dosages were 5, 15, 50, and 125 mg/kg/day for the 4-week study and 15, 30 and 60 mg/kg/day in the 13-week study. The no-observed-adverse-effect level (NOAEL) in the rat toxicity studies was the maximum feasible dose of 200 mg/kg/day. The NOAEL in the dog toxicity studies was 15 mg/kg/day in males and 50 mg/kg/day in females for the 4-week study. The NOAEL was 30 mg/kg/day for both males and females in the 13-week dog toxicity study, because of morbidity attributed to hepatic cholestasis and renal tubule degeneration considered secondary to hepatic changes at 60 mg/kg/day, which led to euthanasia of 2 dogs at Day 85. These animals have elevated ALT, AST, bile acids, BUN, creatinine, GGT, PHOS, and TBILI before euthanasia, and increases in ALP and CHOL as early as Day 14. This finding was monitorable, based on plasma chemistry changes at all dose levels and as early as Day 14 in the high dose group, which preceded clinical signs. After a 4-week treatment-free period, there was no evidence of recovery of biliary hyperplasia, multi-nucleated cells, or mixed cell infiltrate and single cell hepatic necrosis; however, elevations in plasma chemistry values were largely reversible (trending down of elevated liver function tests at all dose levels in the recovery group dogs).

Due to this finding of cholestatic liver injury being monitorable, partially reversible, and observed in dogs but not rats, the selected doses are projected to ~~be~~ result in plasma exposures of TAK-041 below those associated with the NOAEL in the dog 13-week toxicology study. Further information from the nonclinical studies, summarized above, can be found in the current Investigator's Brochure. Overall, the nonclinical PK and safety package summarized herein provide support for the clinical evaluation of TAK-041.

Rationale for Change: To update the nonclinical information related to the study.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 26: Updated PK analysis for all sample parts.

The primary change occurs in Section Part 13.1.3 Pharmacokinetic Analysis

Amended or new wording:

Pharmacokinetic Analysis

Concentrations of TAK-041 in plasma will be summarized by dose over each scheduled sampling time using descriptive statistics for ~~single (Part 1) and multiple doses (Part 2).~~ **each study part.** Amount of TAK-041 excreted in urine will be summarized by dose over each scheduled sampling interval using descriptive statistics for ~~single (Part 1) and multiple dose (Part 2).~~ **each study part.** Individual PK data will be presented in a data listing. PK parameters of TAK-041 will be summarized by dose using descriptive statistics ~~for single (Part 1) and multiple dose (Part 2).~~ **each study part.** Dose proportionality will be assessed graphically (dose-normalized C_{max} and AUC versus dose~~).~~ **in Part 1 and Part 2.** To assess dose proportionality of single dosing (Part 1), a power model will be used. The model will include the natural log-transformed AUC and C_{max} as response variable and the natural log-transformed dose [ln(dose)] as a continuous covariate. No formal statistical comparisons will be conducted. For Part 2, dose proportionality will be assessed using an analysis of variance (ANOVA) model separately for dose-normalized AUC and Cmax on Day 22. Treatment, **with treatment** (as a categorical variable~~, will be~~) **as** a fixed effect. The dose-normalized parameters will be natural log-transformed prior to the analysis. All treatment differences and corresponding two-sided 90% CIs will be extracted from the model, back-transformed, and expressed as central value ratios.

The effect of food on TAK-041 exposure will be evaluated in Part 3 using an ANOVA on the natural log-transformed TAK-041 C_{max} and AUC_{96} with regimen (high-fat vs. fasted) as a fixed effect. 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 after the high-fat meal versus the fasted state.

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 using an 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 ANOVA will be performed on the natural log-transformed Day 1 TAK-041 C_{max} and AUC_{96} with regimen as a fixed effect. 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.

Rationale for Change: to provide statistical analysis of Part 3 primary PK endpoints and Part 4 exploratory PK data

The following sections also contain this change:

Section 2.0 STUDY SUMMARY

Change 27: Added PD analysis set for Part 4 only

The primary change occurs in Section 13.1.4 Exploratory Analyses

Initial wording:	Individual results of BL-VAS, C-SSRS, and CCI assessments will be listed.
Amended or new wording:	~~Individual results of BL-VAS, C-SSRS, and CCI assessments will be listed.~~ CCI [redacted]

CCI

Rationale for Change: To provide statistical basis for the Part 4 exploratory objectives.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Appendix C Schedule of Study Procedures Part 3 (Tablet Formulation – Relative Bioavailability and Food Effect)

Change 28: Updated safety analysis.

The primary change occurs in Section 13.1.5 Safety Analysis

Initial wording:

Safety Analysis

Safety data will be presented by TAK-041 dose and placebo for each part.

TEAEs will be summarized by placebo, each TAK-041 dose level, and TAK-041 overall for Part 1 and Part 2.

Clinical laboratory variables, vital signs, and ECG parameters will be summarized with descriptive statistics for baseline, postdose, and change from baseline to postdose values by dose. In Part 2, continuous Holter ECG monitoring parameters will be extracted in triplicate and the average of the 3 values at each time point will be calculated and used for all statistical analyses and 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 time point. The number and percentage of subjects with postdose values meeting Takeda's criteria for markedly abnormal values for clinical laboratory variables, vital signs, and ECG parameters will be presented by dose. Neurological assessments will be judged normal, abnormal, CS or NCS. All summaries will be performed by pooled placebo within cohort and TAK-041 dose level. Physical examination findings will be presented in

data listings.

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

Amended or new wording:

Safety Analysis

Safety data will be presented by TAK-041 dose and placebo for each part.

TEAEs will be summarized by placebo, each TAK-041 dose level, and TAK-041 overall for ~~Part 1 and Part 2~~**each study part**.

Clinical laboratory variables, vital signs, and ECG parameters will be summarized with descriptive statistics for baseline, postdose, and change from baseline to postdose values by dose**, and scheduled time point for each study part**. In Part 2, continuous Holter ECG monitoring parameters will be extracted in triplicate and the average of the 3 values at each time point will be calculated and used for all statistical analyses and 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.

Potential QT prolongation will be assessed using the Holter ECG measurements in Part 2. A linear mixed effect model for repeated measures will be used. The response variable in the model will be the change from the time-matched baseline in the average of the triplicate corrected QT intervals (QTc). The time-matched baselines will come from the ECGs taken on Day -1 (23, 22, 20, 16, and 12 hours before dosing). The model will include treatment, time (as a categorical variable), and the treatment-by-time interaction as fixed effects, subject as a random effect, baseline as a covariate, and the baseline-by-time interaction as an additional fixed effect. The LS mean change from time-matched baseline for each treatment and the associated standard error and two-sided 95% CI will be extracted for each treatment at each timepoint, as well as differences from placebo and associated standard errors, two-sided 95% CIs, and p-values.

A separate linear mixed effects model will be used to assess the relationship between the change from time-matched baseline in QTc and TAK-041 exposure in Part 2. The response variable in the model will be the change from time-matched baseline in QTc. The model will include TAK-041 plasma concentration (as a continuous variable) as a fixed effect and subject as a random effect. Placebo subjects will be included in the analysis with a plasma concentration of 0. The estimated regression line and the 90% confidence band for the regression line will be extracted from the model. The relationship between the change from time-matched baseline in QTc and TAK-041 plasma concentration will also be examined graphically using a scatterplot. The regression line and 90% confidence band for the regression

line estimated from the model will be overlaid onto the scatterplot.

The number and percentage of subjects with postdose values meeting Takeda's criteria for markedly abnormal values for clinical laboratory variables, vital signs, and ECG parameters will be presented by dose. Neurological assessments will be judged normal, abnormal, CS or NCS. All summaries will be performed by pooled placebo within cohort and TAK-041 dose level. Physical examination findings will be presented in data listings. **Individual results of BL-VAS and the C-SSRS will be listed.**

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

Rationale for Change: to update the safety analysis that will be used for the modified study design.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 29: Updated sample size determination for the study.

The primary change occurs in Section 13.3 Determination of Sample Size.

Initial wording:

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.

CCI

[redacted]

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.

Amended or new wording:

Determination of Sample Size

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) in ~~Parts~~**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.

CCI [redacted]

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.

Rationale for Change: Provided sample size determination for the Part 3 oral bioavailability of the TAK-041 tablet formulation relative to the oral suspension, and the effect of food on the TAK-041 tablet formulation; and for the CCI [redacted]

The following sections also contain this change:

! Section 2.0 STUDY SUMMARY

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	04-Jul-2018 15:19 UTC
	Clinical Pharmacology Approval	05-Jul-2018 18:24 UTC
	Clinical VP Approval	07-Jul-2018 14:18 UTC