



Title: A Randomized, Double-Blind, Placebo Controlled, Two-Period Cross-Over, Proof of Activity Study to Evaluate the Effects of TAK-041 on Motivational Anhedonia as Add-On to Antipsychotics in Subjects With Stable Schizophrenia

NCT Number: NCT03319953

SAP Approve Date: 13 June 2019

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**TAKEDA DEVELOPMENT CENTER
STATISTICAL ANALYSIS PLAN**

STUDY NUMBER: TAK-041-2001

A Randomized, Double-Blind, Placebo Controlled, Two-Period Cross-Over, Proof of Activity Study to Evaluate the Effects of TAK-041 on Motivational Anhedonia as Add-On to Antipsychotics in Subjects with Stable Schizophrenia

**Proof of Activity Study of TAK-041
PHASE 2**

Version: Amendment 1.0

Date: 13 June 2019

Prepared by:

PPD

A large rectangular area of the document is redacted with a solid blue color, covering the names of the individuals who prepared the document.

Based on:

Protocol Version: Amendment 04

Protocol Date: 01 Aug 2018

1.1 APPROVAL SIGNATURES

Study Title: A Randomized, Double-Blind, Placebo Controlled, Two-Period Cross-Over, Proof of Activity Study to Evaluate the Effects of TAK-041 on Motivational Anhedonia as Add-On to Antipsychotics in Subjects with Stable Schizophrenia

Takeda Approvals:

PPD



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3.0 LIST OF ABBREVIATIONS

%CV	percent coefficient of variation
ADaM	Analysis Data Model
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC	area under the concentration-time curve
AUC _t	area under the plasma concentration-time curve from time 0 to last quantifiable concentration
AUC _∞	area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty} = AUC_t + C_{last}/\lambda_z$
CCI	[REDACTED]
BACS	Brief Assessment of Cognition in Schizophrenia
BOLD	blood-oxygen-level dependent contrast imaging
BLQ	below the limit of quantification
BMI	body mass index
CCI	[REDACTED]
CDISC	Clinical Data Interchange Standards Consortium
CCI	[REDACTED]
CI	confidence interval
C _{last}	last observed plasma concentration
C _{max}	maximum observed plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report forms
EEfRT	Effort Expenditure for Rewards Task
fMRI	functional magnetic resonance imaging
LS	least squares
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MID	Monetary Incentive Delay
N	number of subjects
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)

PR interval	The beginning of the P wave to the beginning of the QRS complex
PT	preferred term
PTE	pre-treatment event
QRS	Q, R and S waves
QT interval	Q wave to T wave interval
QTcF	QT interval with Fridericia correction method
RR interval	R wave to R wave interval
rs-fMRI	resting state fMRI
SGA	second-generation antipsychotics
$t_{1/2z}$	terminal elimination half-life, calculated as $\ln(2)/\lambda_z$
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
WHO Drug	World Health Organization Drug Dictionary
λ_z	terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase

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4.0 SUMMARY OF CHANGES

This section describes the changes in reference to the original SAP. The primary purpose of this amendment is to remove the interim analysis. The following is a summary of the changes made in the amendment. Detailed description of amendments to the text is presented in [Appendix F](#).

1. As the program is developing, it was determined that the interim analysis planned in the protocol will not be performed. The section about the interim analysis in the original SAP is removed.
2. Remove the SAS codes in Section 8.11 to allow for flexibility in modeling.
3. More clarifications were added in Section 8.13 on the plots of TAK-041 exposure and PD measures.

5.0 OBJECTIVES

5.1 Primary Objective

- To determine motivation/reward deficits observed in schizophrenia are attenuated by add-on TAK-041 administration to antipsychotics in subjects with stable schizophrenia.
- To determine whether cognitive impairment associated with schizophrenia is improved by add-on TAK-041 administration to antipsychotics in subjects with stable schizophrenia.

5.2 Secondary Objectives

- To determine safety and tolerability of TAK-041 as add-on therapy to SGA in subjects with stable schizophrenia.

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6.0 STUDY DESIGN

TAK-041-2001 is a phase 2, randomized, double-blind, placebo-controlled, two-period cross-over, proof of activity study designed to evaluate the single oral doses of TAK-041, a GPR139 orphan receptor agonist, as an add-on to antipsychotics in attenuating the impairment in motivational anhedonia as well as cognitive function using motivation/reward battery tests as well as brain imaging (CCI) in subjects with stable schizophrenia. A single dose of study drug will be administered in each period. There will be a 35-day (+7 days) washout interval between the 2 doses. Treatment Period 2 begins at the end of the Treatment Period 1 washout.

The trial population will include subjects with stable schizophrenia aged 18-60 years, inclusive, considered eligible on the basis of the trial inclusion and exclusion criteria. The trial will randomize up to 32 subjects to ensure 24 subjects complete. On Day 1 of Period 1, eligible subjects will be randomized in a ratio of 1:1 to 1 of the 2 treatment sequences (Figure 6.a) and will receive each trial drug according to the randomized sequence group. The initial dose of TAK-041 will be 40 mg, but may be adjusted based on emerging safety, tolerability and PK data. A planned unblinded interim analysis (IA) may be conducted when approximately 12 subjects have completed the Day 14 procedures in both periods.

Figure 6.a Sequence Groups

Sequence	Period 1	Period 2
1	TAK-041 + antipsychotic	Placebo + antipsychotic
2	Placebo + antipsychotic	TAK-041 + antipsychotic

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7.0 ANALYSIS ENDPOINTS

7.1 Primary Endpoints

- Change from placebo in the BACS composite score at second testing after TAK-041 administration (Day 14).
- Change from placebo in BOLD signal in the average of left and right ventral striatum activation in the Monetary Incentive Delay (MID) Reward Task at first testing after TAK-041 administration (Day 1).

7.2 Secondary Endpoints

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- Percentage of subjects who meet the markedly abnormal criteria for safety ECG parameters at least once postdose.
- Columbia-Suicide Severity Rating Scale (C-SSRS) at all time points assessed.

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8.0 DETERMINATION OF SAMPLE SIZE

Up to 32 subjects are planned to be randomized equally to the 2 treatment sequences to ensure 24 subjects complete the trial.

Both primary endpoints will be used at the end of the study for decision making. A Bayesian method will be used to calculate the posterior probability of the endpoints meeting predefined criteria using data from TAK-041 and placebo. The criteria for a “Positive” decision is 70% posterior probability (or greater) of a difference between TAK-041 and placebo >0.09 in VS activation in the fMRI MID at 3.5 hours post-dose on Day 1 or 70% (or greater) posterior probability of a difference between TAK-041 and placebo >2 points in the BACS composite score at Day 14.

The probability of declaring “Positive” based on the “Positive” criteria with 24 subjects is at least 70% when the true TAK-041 effect on either endpoint is clinically meaningful, e.g., an increase in VS activation over placebo of 0.19 at 3.5 hours post-dose on Day 1, or an increase in the BACS score over placebo of 4.5 points at Day 14. This sample size will also keep the type 1 error rate no more than 30% when the true drug effect is minimal or the same as placebo. The SD for the BACS composite score is assumed to be 9.30 points⁴. The SD for the VS activation is assumed to be 0.360 based on internal data. Independence between these 2 endpoints was assumed in the sample size calculation.

Non-informative prior distributions were used in the above probability calculation. Allowing for 8 dropouts (due to the long washout interval), up to 32 subjects are planned to be enrolled in order to have 24 completers for this trial.

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9.0 METHODS OF ANALYSIS AND PRESENTATION

9.1 General Principles

This Statistical Analysis Plan (SAP) was developed based on International Conference on Harmonization E3 [2] and E9 [3] Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP was developed using the information provided in Protocol Amendment 03 TAK-041-2001, dated 02 April 2018 [1].

All study-related raw data, including derived data, will be presented in data listings. Continuous data will be summarized using number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum. Where indicated, %CV (arithmetic and/or geometric) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

In following sections, treatment (or study drug) refers to TAK-041 and placebo.

Statistical analysis will be performed using the SAS System[®], Version 9.2 or higher, on a Windows platform.

9.2 Missing Data

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

Plasma concentrations that are below the limit of quantification (BLQ) will be given a value of 0 in the summarization of concentrations and derivation of the PK parameters. These values will be flagged in the data listings, and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

9.3 Derived Datasets and Variables

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

9.4 Definition of Study Days and Baseline

Study Baseline will be defined as the last non-missing measurement prior to first dose of study drug (TAK-041 or placebo) in Period 1.

Baseline of a period will be defined as the last non-missing measurement prior to first dose of study drug (TAK-041 or placebo) in the respective treatment period.

Study day for the entire study duration will be calculated relative to the date of the first dose in Period 1. Study day prior to the first dose of treatment will be calculated as: date of

assessment/event – date of first treatment; study day on or after the date of first dose of treatment will be calculated as: date of assessment/event – date of first treatment + 1.

Period day - study day for a treatment period - will be calculated relative to the date of first dose in the respective treatment period. Period day prior to the first dose of treatment in a treatment period will be calculated as: date of assessment/event – date of first treatment in the respective period; period day on or after the date of first dose of treatment in the respective treatment period will be calculated as: date of assessment/event – date of first treatment in the respective period + 1.

9.5 Analysis Sets

Safety Analysis Set

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

PK Analysis Set

The PK set will consist of all subjects who receive at least 1 dose of trial drug and have at least 1 measurable plasma concentration.

PD Analysis Set

The PD set will consist of all subjects who receive at least 1 dose of trial drug and have at least 1 evaluable primary CC1 measurement.

9.6 Disposition of Subjects

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

Primary reasons for screening failure will be tabulated as entered on the eCRF.

For randomized subjects, the number and percentage of subjects who complete study drugs and study visits, and those who prematurely discontinue study drugs and study visits will be summarized for each treatment sequence and overall. In addition, the number and percentage of subjects will be summarized for reasons of study drug discontinuation and study visit discontinuation for each sequence and overall. Subjects' study completion data, including the dates of the first and last dose, and reasons for premature termination, will be listed.

The number and percentage of subjects comprising each analysis set will be summarized for each sequence and overall.

9.7 Demographic and Baseline Characteristics

For subjects in Safety analysis set, descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, BMI, etc.) by treatment sequence and overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline

characteristics variables (sex, ethnicity, race, etc.) will be tabulated by treatment sequence and overall.

All individual demographic and baseline characteristics will be listed by treatment sequences, study center and subject number. The demographic data listing will include subject identifier, treatment sequence, date of informed consent, date of birth, age at date of informed consent, sex, race, height, baseline weight and baseline BMI and other demographic and baseline information collected in the eCRF.

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 trial. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

9.8 Medical History and Concurrent Medical Conditions

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

Medical history and concurrent medical condition verbatim reported terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No summary statistics for medical history and concurrent medical conditions will be provided. All medical history and concurrent medical conditions will be listed.

9.9 Medication History and Concomitant Medications

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

Medication history and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO Drug). No summary statistics for medication history and concomitant medications will be provided. All medication history and concomitant medications data will be listed.

9.10 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing. Listings and summary statistics for TAK-041 plasma concentrations and pharmacokinetic parameters will be provided. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

9.11 Primary PD Analysis

The average BOLD signal in the left and right ventral striatum in response to the MID Reward Task 3.5 hours post-dose on Day 1 and the BACS composite score on Day 14 are the primary PD measures. The BACS composite score will be calculated as follows:

The BACS consists of items across six subtests: Verbal Memory, Digit Sequencing, Token Motor, Verbal Fluency, Symbol Coding, and Tower of London.

The so-called *subtest scaled score* for each subtest will be computed as follows: Let X_{jkl} be the raw score for subject l on subtest j (1 to 6) at time point k (0 = Day -1; 1 = 2 hours post-dose on Day 1; 2 = Day 14). Assume this subject is of sex m (1=male; 2=female) and in age category n (1=20-39; 2=40-49; 3=50-59; 4=60-69; 5=70-79 years). The scaled score for subtest j will be computed as:

$$C_{jkl} = (X_{jkl} - M_{jmn}) / SD_{jmn},$$

where M_{jmn} and SD_{jmn} are the mean and standard deviation for subtest j , respectively, of the index population for sex m and age category n , the specific values of which can be found in [Appendix D](#). The *subtest T-score* will then be derived as $T_{jkl} = 10 \times C_{jkl} + 50$.

Finally, the BACS *composite score* for subject l at time point k is computed as $T_{kl} = 10 \times AC_{kl} / SD_{mn} + 50$, where AC_{kl} is the sum of the 6 scaled subtest scores for subject l at time k and SD_{mn} is the standard deviation of the sum of the 6 scaled subtest scores for sex m and age category n ([Appendix D](#)).

When up to 2 subtest scores are missing, the sum of the scaled scores will be calculated as (sum of non-missing subtest scaled scores) \times (total number of items) / (number of non-missing subtests). If more than 2 subtests in the BACS assessments are missing, the BACS composite score will be set to missing.

The observed BOLD signal from the left and right ventral striatum (VS) activation, as well as the average of the left and right VS activation, will be summarized (N, mean, median, SD, minimum, and maximum) by treatment [TAK-041 (overall and by dose) and placebo] and time. The BACS composite score will be summarized for baseline, post-dose, and change from baseline by treatment [TAK-041 (overall and by dose) and placebo] and time.

Each of the primary PD endpoints will be analyzed using a Bayesian normal linear model with effects for sequence, period, treatment, time (as a categorical variable), the treatment-by-time interaction, subject within treatment sequence, and baseline (for BACS only). Time is a repeated factor with subject(period) as the subject. For the BOLD fMRI, the observed value will be the response variable in the model. For the BACS, the observed and the change from baseline will be modeled separately. Missing values will not be imputed and will be included in the model under a missing at random assumption. A diffuse normal distribution with mean zero and variance 10^6 will be used as a prior for the regression coefficients and a diffuse inverse gamma with shape and scale parameters of 0.01 for the residual variance.

The posterior mean, standard deviation, and the 90% credible interval (highest posterior density interval) will be extracted for each treatment and time, along with the posterior mean treatment

difference and associated standard deviation and 90% credible interval at each time. In addition, the posterior probability that the treatment difference on BOLD MID fMRI is greater than 0.09 and the posterior probability that the treatment difference on the BACS composite score is greater than 2 points will be derived from the models.

If the posterior probability of the BOLD fMRI MID at 3.5 hours post-dose on Day 1 being higher than placebo by more than 0.09 is at least 70%, or the posterior probability for the BACS composite score on Day 14 (observed value as the response) being higher than placebo by more than 2 is at least 70%, then the “Positive” criteria is achieved.

As a supporting analysis, a linear mixed effects model for repeated measures will be fit to each of the endpoints. For the BOLD fMRI, the observed value will be the response variable in the model. For the BACS, the observed value and the change from baseline will be the response variables. The model will include sequence, period, treatment, time (as a categorical variable), and the treatment-by-time interaction as fixed factors, baseline as a covariate (for BACS only), and subject within sequence as a random factor. Time is a repeated factor with subject within period as the subject. The least square means for each treatment and the associated standard error and 90% confidence interval (CI) for the mean will be extracted from each model for each time, as well as all treatment differences and associated standard errors, two-sided 90% CIs, and p-values.

9.12 Pharmacokinetic Analysis

9.12.1 Plasma Concentrations

TAK-041 plasma concentrations will be tabulated and summarized by descriptive statistics at each scheduled time point (mean, median, SD, percent coefficient of variation [%CV], minimum, and maximum) for each treatment and dose level. Individual subject plasma concentration data will be listed.

9.12.2 Plasma Pharmacokinetic Parameters

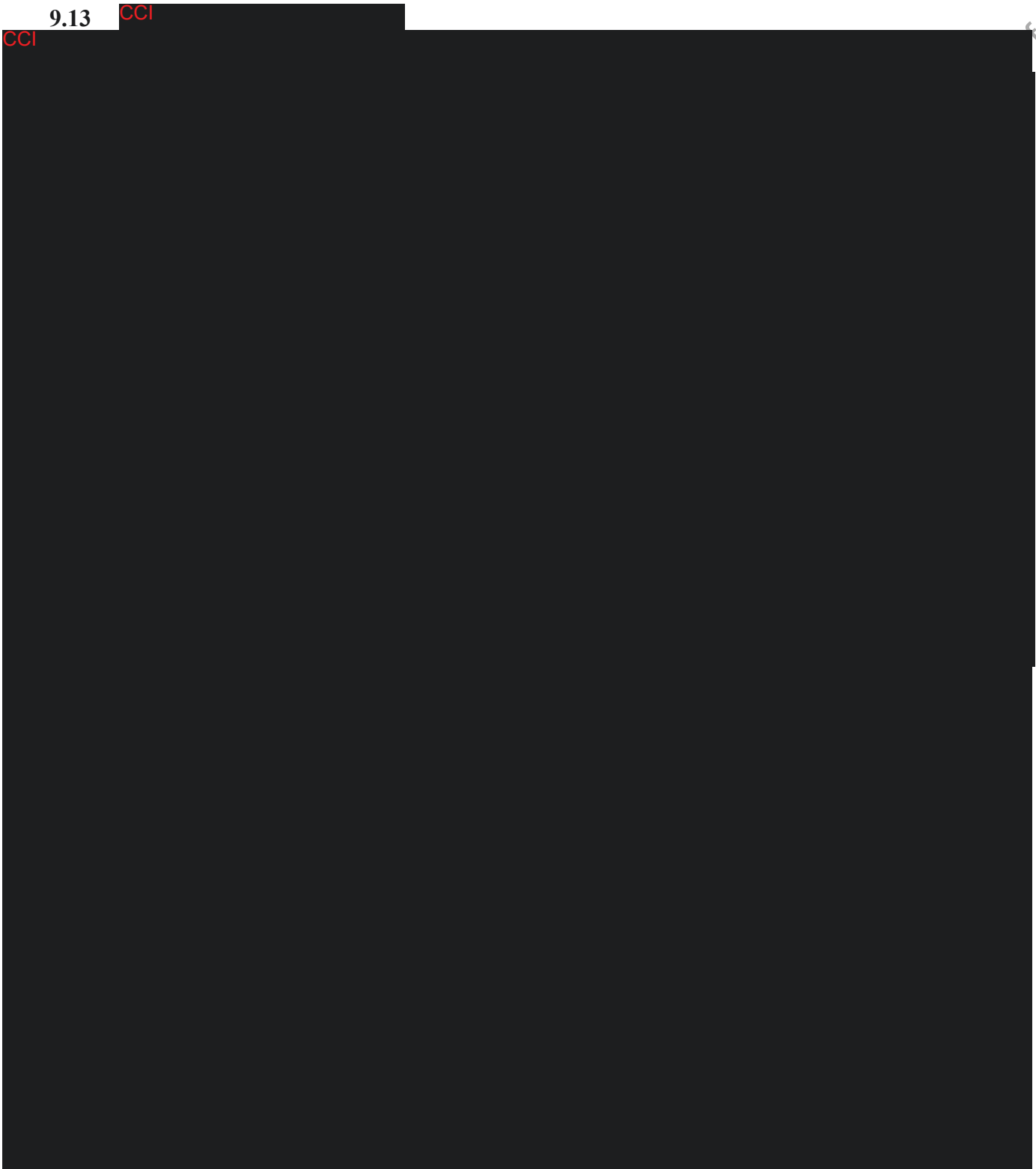
The plasma pharmacokinetic (PK) parameters of TAK-041 will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated using non-compartmental analysis using Phoenix WinNonLin (version 6.3 or higher): AUC_t , AUC_{∞} , C_{max} , t_{max} , and $t_{1/2z}$. Additional PK parameters may be calculated if necessary.

The PK parameter estimates will be tabulated and summarized by descriptive statistics (mean, median, SD, %CV, minimum, and maximum). In addition, geometric means and geometric %CVs will be calculated for C_{max} and AUCs. Individual subject plasma PK parameter data will be listed.

The mean (SD) and individual plasma concentration of TAK-041 will be plotted over time on linear and semi-logarithmic scales.

9.13 CCI

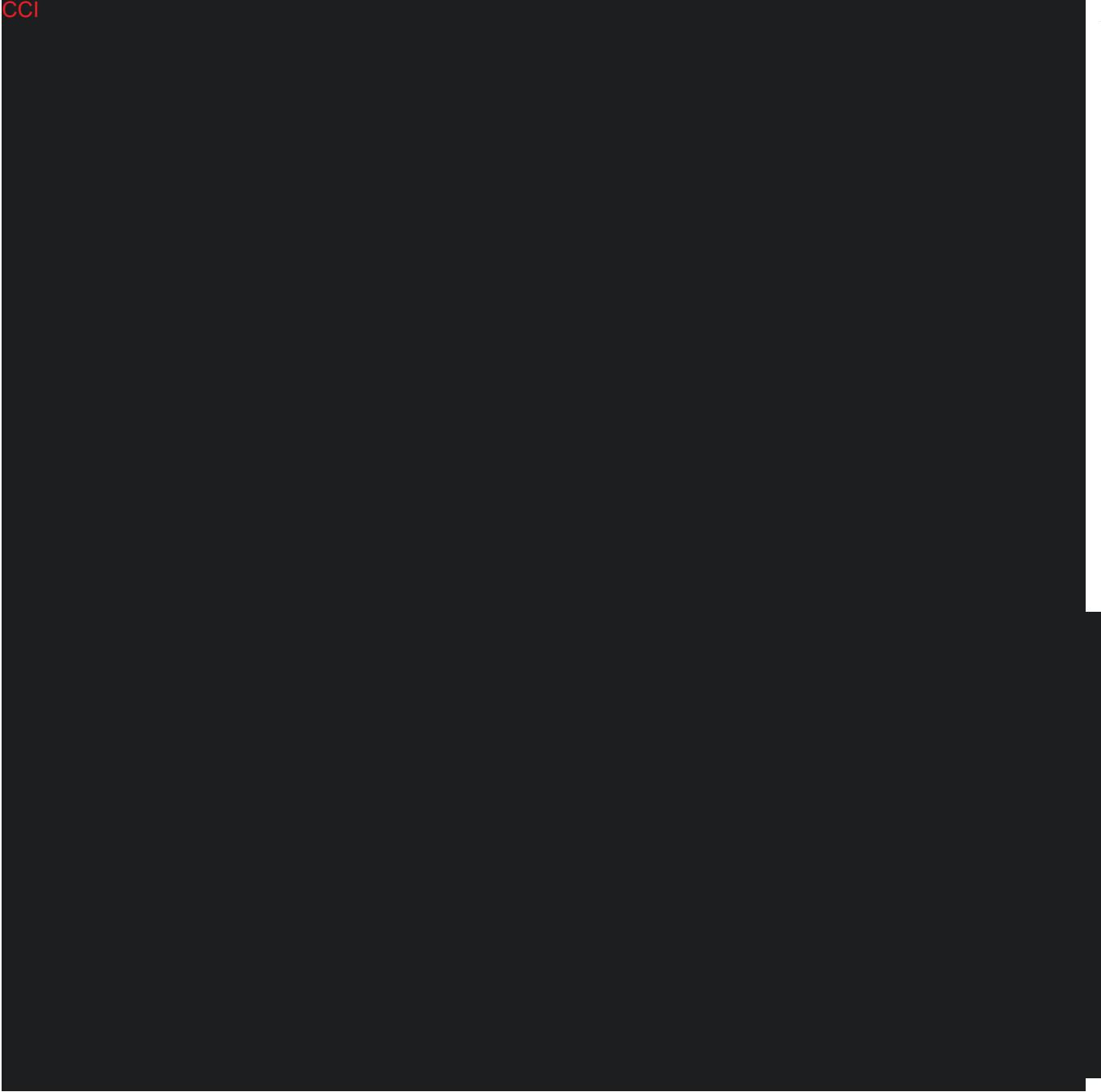
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9.13.1 CCI [Redacted]

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9.13.2 CCI [Redacted]

CCI [Redacted]

9.13.3 CCI [Redacted]

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9.14 Safety Analysis

9.14.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA.

The TEAE summary tables will include numbers and percentages of subjects experiencing at least one TEAE by SOC and PT and will be tabulated by treatment [TAK-041 (overall and by dose) and placebo]. The TEAEs will also be summarized for all subjects in the overview assessment. The following is a list of TEAE summary tables to be generated:

- Overview of TEAEs.
- TEAEs by SOC and PT.
- Subject Mappings for TEAEs.
- TEAEs by PT.
- Most Frequent TEAEs (>2 subjects for any treatment) by PT, sorted by the number of subjects starting from the most frequent.
- Most Frequent Non-Serious (>2 subjects for any treatment) TEAEs by PT, sorted by the number of subjects starting from the most frequent.
- Relationship of TEAEs to Study Drug by SOC and PT (related vs not related).
- Drug-Related TEAEs by SOC and PT.
- Intensity of TEAEs by SOC and PT.
- Intensity of Drug-Related TEAEs by SOC and PT.
- TEAEs leading to study discontinuation by SOC and PT.
- Treatment-emergent SAEs by SOC and PT.

Additional AE summary tables may be added as appropriate.

Data listings will be provided for all AEs including pre-treatment event (PTE), TEAEs, and AEs leading to death, AEs leading to study drug or study visit discontinuation, SAEs, and signs and symptoms of AEs related to increased liver function tests.

9.14.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical laboratory variables will be summarized for baseline, post-dose, and change from baseline to post-dose by treatment and time. The baseline is defined as the last observation prior to the dose of study drug in the corresponding period. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

Individual results for clinical laboratory tests will be evaluated against the Takeda predefined laboratory markedly abnormal values (MAV) criteria ([Appendix A](#)) using the result and criteria in SI units. All subjects with at least 1 post-dose laboratory result that meets the MAV criteria will be presented in a data listing.

The number and percentage of subjects with at least 1 post-dose markedly abnormal laboratory test result will also be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying laboratory result. All post-dose clinical lab MAV results, including scheduled and unscheduled measurements, will be included in the MAV summaries.

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

9.14.3 Vital Signs

Vital sign measurements include body temperature, respiratory rate, blood pressure, and heart rate (beats per minute).

Descriptive statistics (N, mean, median, SD, minimum and maximum) of vital signs in each position (supine, standing, and orthostatic change for blood pressure and heart rate) will be summarized for baseline, post-dose, and change from baseline to post-dose by treatment and time. The baseline is defined as the last observation prior to the dose of study drug in the corresponding period. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

All individual vital signs that meet Takeda's predefined criteria for MAVs ([Appendix B](#)) will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal vital sign measurement will be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying vital sign result. All post-dose MAV vital signs, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

All vital signs data will be presented in both SI and conventional units in data listings.

9.14.4 12-Lead ECGs

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The following parameters will be calculated automatically by the ECG machine: heart rate, RR interval, PR interval, QT interval, QRS interval, and QT interval with Fridericia correction method (QTcF).

Descriptive statistics of the continuous ECG parameters will be summarized for baseline, post-dose, and change from baseline at each post-dose time point by treatment and time. The baseline is defined as the last observation prior to the dose of study drug in the corresponding period. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed ECG parameters.

All individual ECGs that meet Takeda's predefined criteria for MAVs ([Appendix C](#)) will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal ECG measurement will be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying ECG result. All post-dose MAV ECG parameters, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

Individual subject ECGs will be presented in a data listing.

10.0 INTERIM ANALYSIS

There is no interim analysis in this study.

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11.0 CHANGES IN THE STATISTICAL ANALYSIS PLAN FROM THE PROTOCOL

As the program is developing, it was determined that the interim analysis planned in the protocol will not be performed. The section about the interim analysis in the original SAP is removed.

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12.0 REFERENCES

1. Protocol Amendment 03: A Randomized, Double-Blind, Placebo Controlled, Two-Period Cross-Over, Proof of Activity Study to Evaluate the Effects of TAK-041 on Motivational Anhedonia as Add-On to Antipsychotics in Subjects With Stable Schizophrenia, 02 April 2018.
2. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonization, Section ICH E3, 1996.
3. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonization, Section ICH E9, 1998.
4. Clinical Study Report for Study TAK-063_2002, A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-group, 6-Week Study to Evaluate the Efficacy and Safety of TAK-063 in Subjects With an Acute Exacerbation of Schizophrenia.

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Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values
Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	$<0.8 \times \text{LLN}$	$>1.2 \times \text{ULN}$
Hematocrit	Both	$<0.8 \times \text{LLN}$	$>1.2 \times \text{ULN}$
RBC count	Both	$<0.8 \times \text{LLN}$	$>1.2 \times \text{ULN}$
WBC count	Both	$<0.5 \times \text{LLN}$	$>1.5 \times \text{ULN}$
Platelet count	Conventional	$<75 \times 10^3/\mu\text{L}$	$>600 \times 10^3/\mu\text{L}$
	SI	$<75 \times 10^9/\text{L}$	$>600 \times 10^9/\text{L}$

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	$>3x \text{ULN}$
AST	Both	--	$>3x \text{ULN}$
GGT	Both	--	$>3x \text{ULN}$
Alkaline phosphatase	Both	--	$>3x \text{ULN}$
Total bilirubin	Conventional	--	$>2.0 \text{ mg/dL}$
	SI	--	$>34.2 \mu\text{mol/L}$
Albumin	Conventional	$<2.5 \text{ g/dL}$	--
	SI	$<25 \text{ g/L}$	--
Total protein	Both	$<0.8x \text{LLN}$	$>1.2x \text{ULN}$
Creatinine	Conventional	--	$>2.0 \text{ mg/dL}$
	SI	--	$>177 \mu\text{mol/L}$
Blood urea nitrogen	Conventional	--	$>30 \text{ mg/dL}$
	SI	--	$>10.7 \text{ mmol/L}$
Sodium	Conventional	$<130 \text{ mEq/L}$	$>150 \text{ mEq/L}$
	SI	$<130 \text{ mmol/L}$	$>150 \text{ mmol/L}$
Potassium	Conventional	$<3.0 \text{ mEq/L}$	$>6.0 \text{ mEq/L}$
	SI	$<3.0 \text{ mmol/L}$	$>6.0 \text{ mmol/L}$
CPK	Both	--	$>5x \text{ULN}$
Glucose	Conventional	$<50 \text{ mg/dL}$	$>350 \text{ mg/dL}$
	SI	$<2.8 \text{ mmol/L}$	$>19.4 \text{ mmol/L}$

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

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

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

Criteria for Identification of Markedly Abnormal Orthostatic Changes

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

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

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Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

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

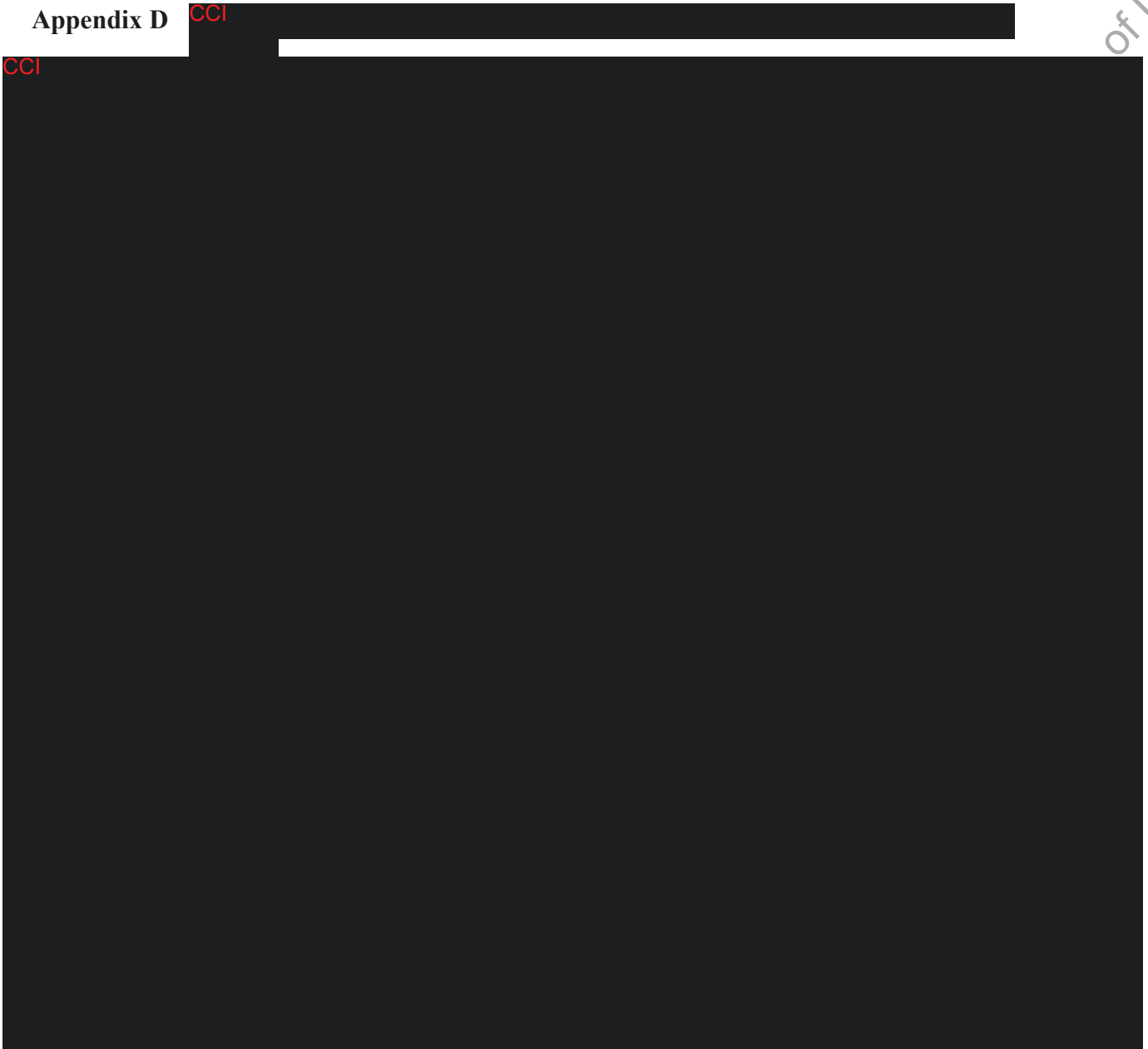
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Appendix D

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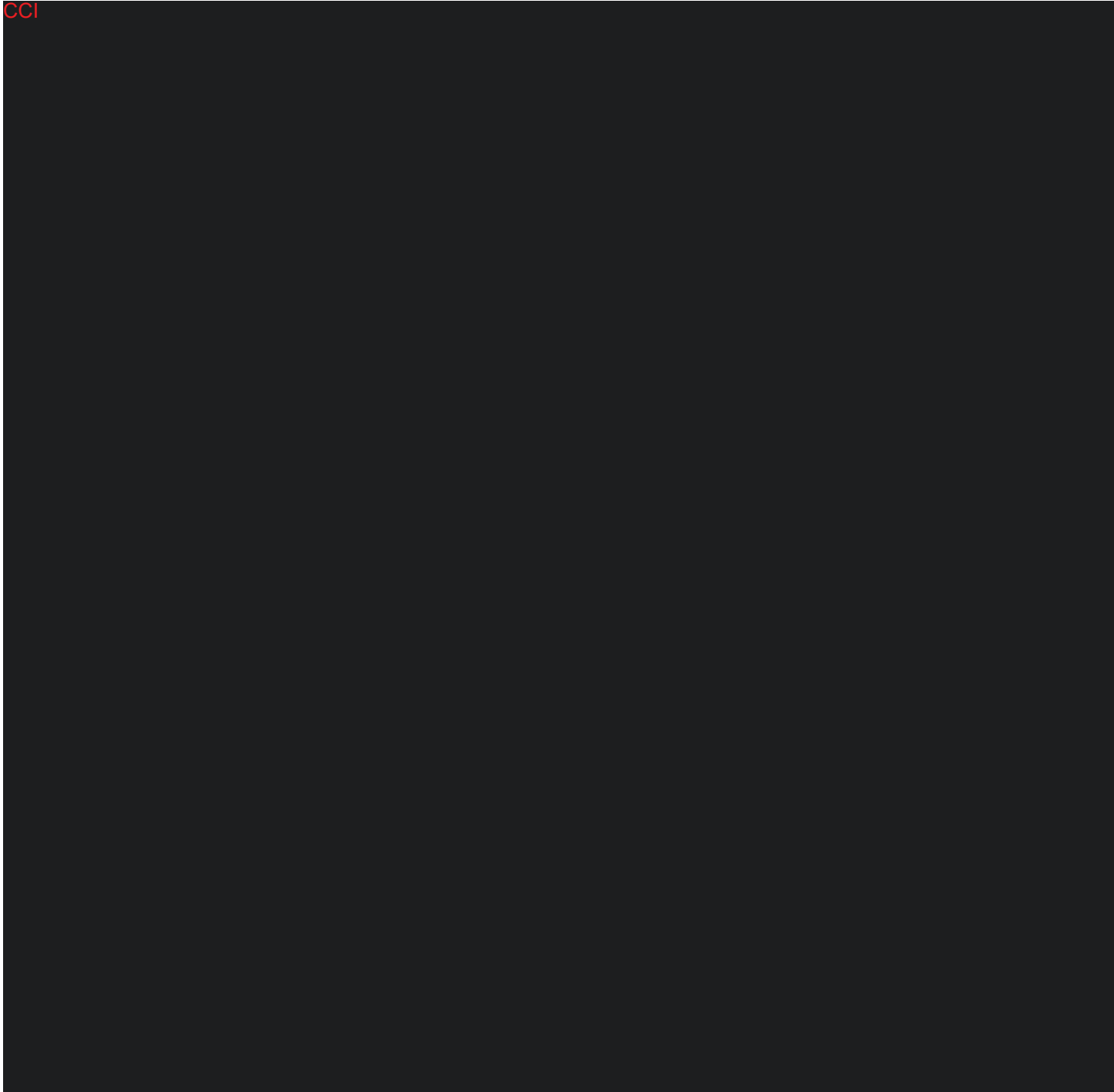
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Appendix F Detailed Descriptions of the Amendments to Text

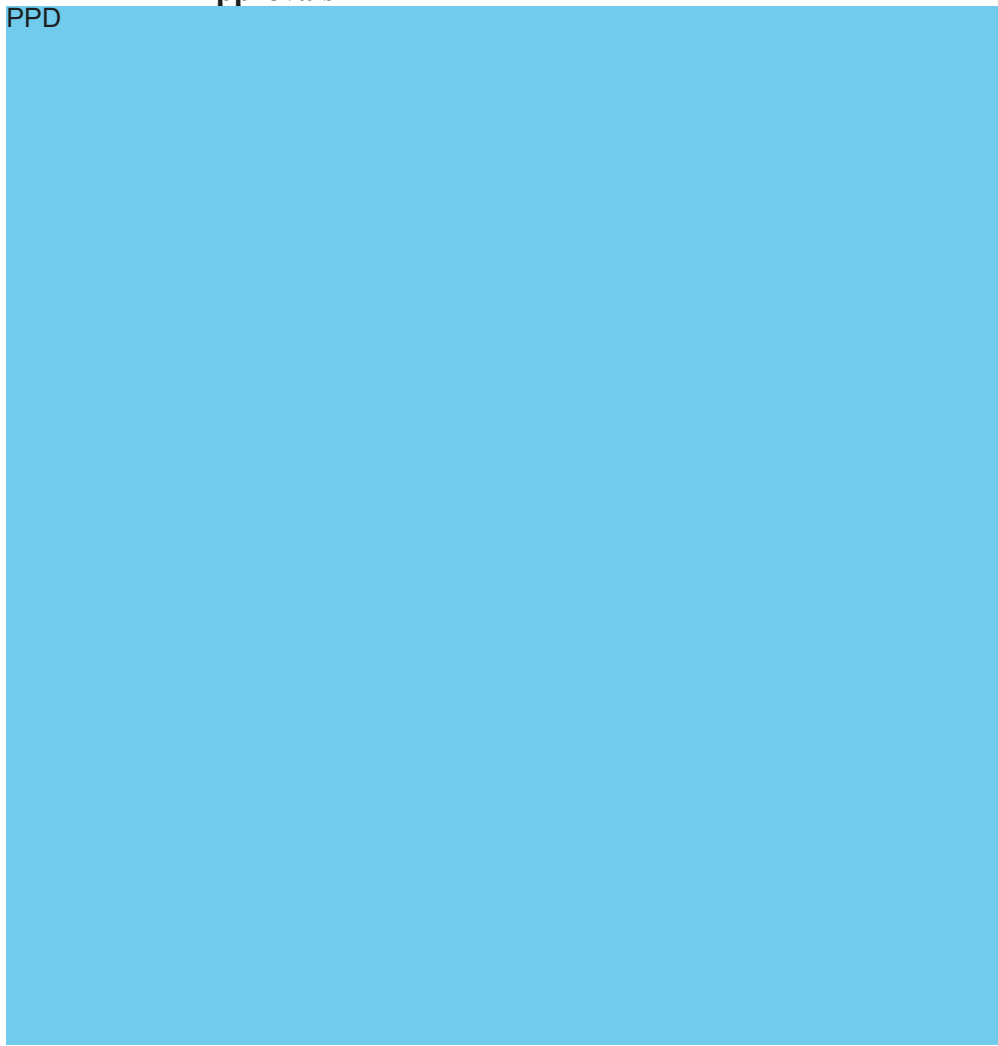
In addition to some minor typo and grammatic changes, changes in reference to SAP are listed below.

Page 2 Section 1.1 Approval Signatures

Existing Text

TAKEDA Approvals

PPD



Date

Date

Date

Date

Date

Date

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Revised Text

TDC Approvals

PPD

Date

Rationale for Amendment

SAP signatories updated in accordance with personnel and SOP changes.

Page 5, Section 3.0 List of Abbreviations

Abbreviations for CDISC, PR, RR, QRS, QT and RR intervals, as well as SGA were added.

Page 11, Section 8.0 Determination of Sample Size

Existing Text

Both primary endpoints will be used at **the IA and** the end of the study for decision making. A Bayesian method will be used to calculate the posterior probability of the endpoints meeting predefined criteria using data from TAK-041 and placebo. The criteria for a 'Positive' decision is **80%** posterior probability (or greater) of a difference between TAK-041 and placebo >0.09 in VS activation in the fMRI MID at 3.5 hours post-dose on Day 1 or **80%** (or greater) posterior probability of a difference between TAK-041 and placebo >2 points in the BACS composite score at Day 14. **The criteria for a 'Negative' decision is less than 10% posterior probability of a difference between TAK-041 and placebo >0.09 in VS activation in the fMRI MID at 3.5 hours post-dose on Day 1 and less than 10% posterior probability of a difference between TAK-041 and placebo >2 points in the BACS composite score at Day 14.**

Revised Text

Both primary endpoints will be used at the end of the study for decision making. A Bayesian method will be used to calculate the posterior probability of the endpoints meeting predefined criteria using data from TAK-041 and placebo. The criteria for a 'Positive' decision is 70% posterior probability (or greater) of a difference between TAK-041 and placebo >0.09 in VS activation in the fMRI MID at 3.5 hours post-dose on Day 1 or 70% (or greater) posterior probability of a difference between TAK-041 and placebo >2 points in the BACS composite score at Day 14.

Rationale for Amendment

Since the interim analysis is removed, corresponding language about decision criteria at the interim analysis is removed.

Page 13, Section 9.4, Definition of Study Days and Baseline

Existing Text

Baseline will be defined as the last non-missing measurement prior to first dose of study drug (TAK-041 or placebo) in the respective treatment period.

Revised Text

Study Baseline will be defined as the last non-missing measurement prior to first dose of study drug (TAK-041 or placebo) in Period 1.

Baseline of a period will be defined as the last non-missing measurement prior to first dose of study drug (TAK-041 or placebo) in the respective treatment period.

Rationale for Amendment

Study baseline definition is added.

Page 16, Section 9.11, Primary PD Analysis

Existing Text

The BOLD signal in the **average of the left and right ventral striatum activation** in the MID Reward Task...

Revised Text

The **average BOLD** signal in the left and right ventral striatum in response to the MID Reward Task...

Rationale for Amendment

Update the description of the endpoint more accurately.

Page 16, Section 9.11, Primary PD Analysis

Existing Text

The observed BOLD signal will be summarized (N, mean, median, SD, minimum, and maximum) by treatment (TAK-041 (overall and by dose) and placebo) and time. The BACS composite score will be summarized for baseline, post-dose, and change from baseline by treatment, dose and time.

Revised Text

The observed BOLD signal from *the left and right ventral striatum (VS) activation, as well as the average of the left and right VS activation*, will be summarized (N, mean, median, SD, minimum, and maximum) by treatment [TAK-041 (overall and by dose) and placebo] and time. The BACS composite score will be summarized for baseline, post-dose, and change from baseline by treatment [*TAK-041 (overall and by dose) and placebo*] and time.

Rationale for Amendment

More clarification was added.

Page 16, Section 9.11, Primary PD Analysis

Existing Text

Each of the primary PD **measures** will be analyzed using a Bayesian normal linear model with effects for sequence, period, treatment, time (as a categorical variable), the treatment-by-time interaction, subject within treatment sequence, and baseline (for BACS only). For the BOLD fMRI, the observed value will be the response variable in the model. For the BACS, ...

Revised Text

Each of the primary PD **endpoints** will be analyzed using a Bayesian normal linear model with effects for sequence, period, treatment, time (as a categorical variable), the treatment-by-time interaction, subject within treatment sequence, and baseline (for BACS only). *Time is a repeated factor with subject(period) as the subject.* For the BOLD fMRI,

Rationale for Amendment

More clarification about the model was added.

Page 16, Section 9.11, Primary PD Analysis

Existing Text

The following code may be used as an example for BOLD fMRI MID:

```
proc genmod data=data;
  class seq per trt time subjid;
  model response = seq per trt time trt*time subjid / dist=Normal link=identity;
  bayes seed=186 coeffprior=normal dispersionprior=igamma(shape=0.01, scale=0.01)
  nmc=10000 maxit=2000 outpost=post diagnostics=all summary=all;
  lsmeans trt*time / pdiff alpha=0.1;
run;
```

The following code may be used with necessary modifications for the change of BACS composite score from baseline:

```
proc genmod data=data;
  class seq per trt time subjid;
  model change = seq per trt time trt*time subjid base / dist=Normal link=identity;
  bayes seed=186 coeffprior=normal dispersionprior=igamma(shape=0.01, scale=0.01)
  nmc=10000 maxit=2000 outpost=post diagnostics=all summary=all;
```

lsmeans trt*time / pdiff alpha=0.1;

run;

Revised Text

Removed the above texts

Rationale for Amendment

To allow flexibility in modeling options.

Page 17, Section 9.11, Primary PD Analysis

Existing Text

If the posterior probability of the BOLD fMRI MID at 3.5 hours post-dose on Day 1 being higher than placebo by **at least 0.09 is greater than 80%**, or the posterior probability for the BACS composite score on Day 14 (observed value as the response) being higher than placebo by **at least 2 is greater than 80%**, then the ‘Positive’ criteria is achieved. **If the posterior probability for both is less than 10%, then the ‘Negative’ criteria will have been met. If neither of these criteria are met, then this will be classified as a ‘Grey’ result,** CCI

Revised Text

If the posterior probability of the BOLD fMRI MID at 3.5 hours post-dose on Day 1 being higher than placebo by **more than 0.09 is at least 70%**, or the posterior probability for the BACS composite score on Day 14 (observed value as the response) being higher than placebo by **more than 2 is at least 70%**, then the “Positive” criteria is achieved.

Rationale for Amendment

Updated the wording based on final analysis and removed the wording about interim analysis.

Page 17, Section 9.11, Primary PD Analysis

Existing Text

... The model will include sequence, period, treatment, time (as a categorical variable), and the treatment-by-time interaction as fixed factors, baseline as a covariate (for BACS only), and subject within sequence as a random factor...

Revised Text

The model will include sequence, period, treatment, time (as a categorical variable), and the treatment-by-time interaction as fixed factors, baseline as a covariate (for BACS only), and subject within sequence as a random factor. *Time is a repeated factor with subject within period as the subject.*

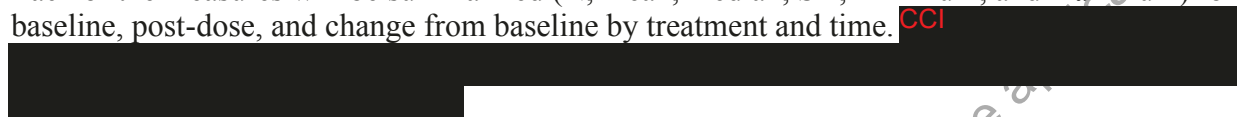
Rationale for Amendment

More clarification on the model was added.

Page 18, Section 9.13, Pharmacodynamic Analysis

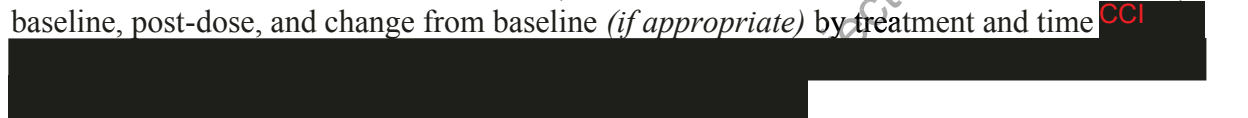
Existing Text

Each of the measures will be summarized (N, mean, median, SD, minimum, and maximum) for baseline, post-dose, and change from baseline by treatment and time. CCI



Revised Text

Each of the measures will be summarized (N, mean, median, SD, minimum, and maximum) for baseline, post-dose, and change from baseline (*if appropriate*) by treatment and time CCI



Rationale for Amendment

More clarification was added.

Page 18, Section 9.13, Pharmacodynamic Analysis

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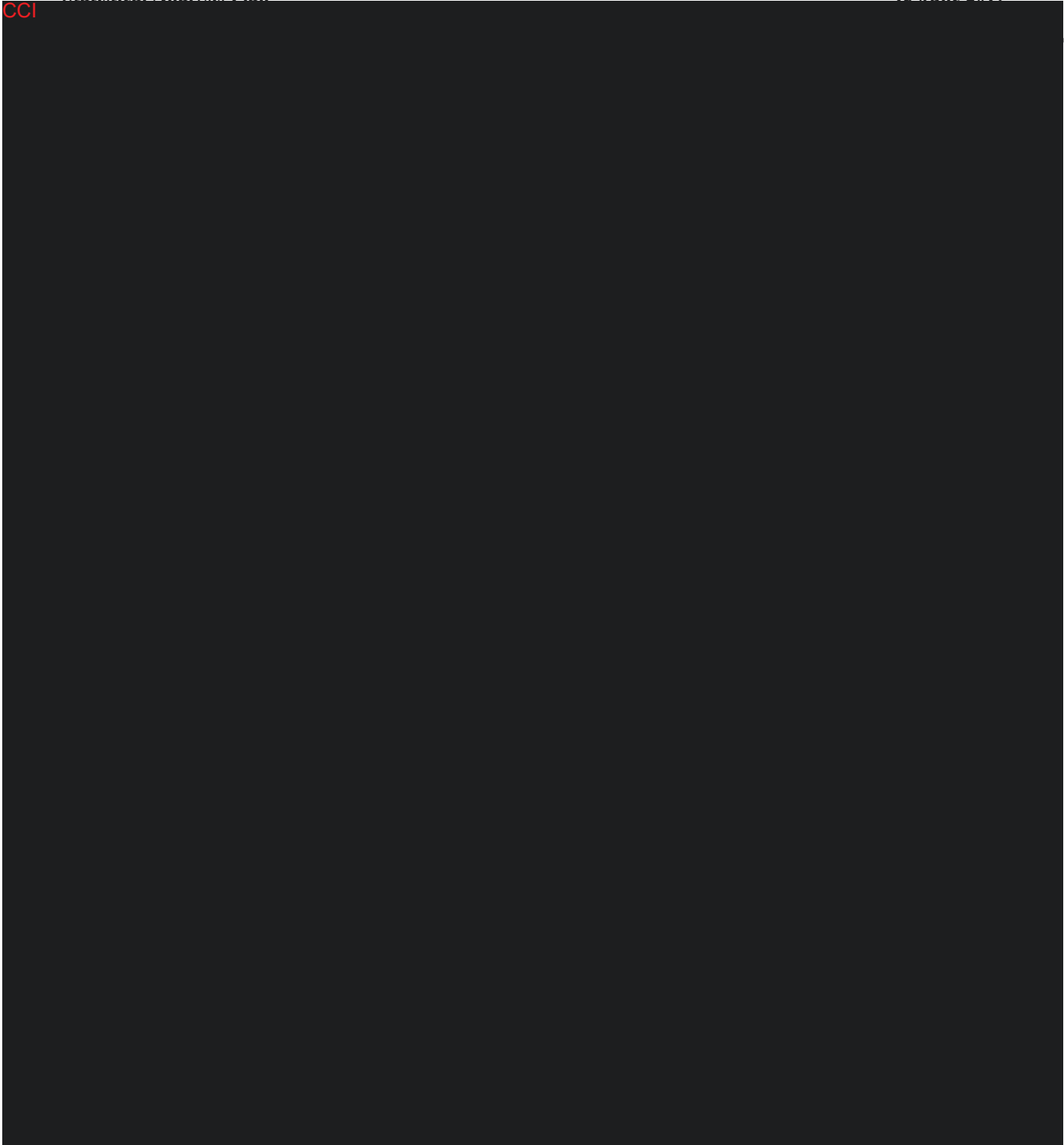


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Rationale for Amendment

More clarification was added.

Pro

Page 21, Section 9.14.1, Adverse Events

Existing Text

... The following is a list of TEAE summary tables to be generated:

- Overview of TEAEs
- TEAEs by SOC and PT
- Subject Mappings for TEAEs
- TEAEs by PT
- Most Frequent TEAEs by PT
- Most Frequent Non-Serious TEAEs by PT
- Drug-Related TEAEs by SOC and PT
- Relationship of TEAEs to Study Drug by SOC and PT (related vs not related)
- Intensity of TEAEs by SOC and PT
- Intensity of Drug-Related TEAEs by SOC and PT

Revised Text

... The following is a list of TEAE summary tables to be generated:

- Overview of TEAEs.
- TEAEs by SOC and PT.
- Subject Mappings for TEAEs.
- TEAEs by PT.
- Most Frequent TEAEs (*>2 subjects for any treatment*) by PT, sorted by the number of subjects starting from the most frequent.
- Most Frequent Non-Serious (*>2 subjects for any treatment*) TEAEs by PT, sorted by the number of subjects starting from the most frequent.
- Relationship of TEAEs to Study Drug by SOC and PT (related vs not related).
- Drug-Related TEAEs by SOC and PT.
- Intensity of TEAEs by SOC and PT.
- Intensity of Drug-Related TEAEs by SOC and PT.
- *TEAEs leading to study discontinuation by SOC and PT.*
- *Treatment-emergent SAEs by SOC and PT.*

Rationale for Amendment

More clarification on the model was added.

Page 22, Section 9.14.4, 12-Lead ECGs

Existing Text

The following parameters will be calculated automatically by the ECG machine: heart rate, RR interval, PR interval, QT interval, QRS interval, and QT interval with **Bazett and Fridericia** correction method (**QTcB** and QTcF, respectively).

Revised Text

The following parameters will be calculated automatically by the ECG machine: heart rate, RR interval, PR interval, QT interval, QRS interval, and QT interval with Fridericia correction method (QTcF).

Rationale for Amendment

QTcB was not measured in this study.

Page 24, Section 10.0, Interim Analysis

Existing Text

An unblinded interim analysis will be performed once the 12th subject finishes the Day 14 procedures in both periods. Patient disposition, demographics, and the following PD measures will be reported at the IA: (1) BOLD fMRI MID, (2) BACS, (3) CCI, and (4) CCI.

The Bayesian analysis and the linear mixed effects model for repeated measures analysis described in Section 8.11 will be performed for BOLD fMRI MID and BACS. The linear mixed effects model for repeated measures analysis will be performed for the CCI and the CCI. Summary tables and data listings of the observed values and the change from baseline (except for BOLD fMRI MID) for each PD measure will be provided.

The criteria for a positive result at the IA is 80% posterior probability (or greater) of a difference between TAK-041 and placebo >0.09 in VS activation in the MID fMRI at 3.5 hours post-dose on Day 1 or 80% (or greater) posterior probability of a difference between TAK-041 and placebo >2 points in the BACS composite score at Day 14.

Revised Text

There is no interim analysis in this study.

Rationale for Amendment

As the program is developing, it was determined that the interim analysis planned in the protocol will not be performed. The section about the interim analysis in the original SAP is removed.

Page 25, Section 11.0, Changes in the Statistical Analysis Plan

Existing Text

Not applicable.

Revised Text

As the program is developing, it was determined that the interim analysis planned in the protocol will not be performed. The section about the interim analysis in the original SAP is removed.

Rationale for Amendment

Changes in the SAP from the protocol was described.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	14-Jun-2019 15:24 UTC

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