



Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Escalating Single and Multiple Doses of TAK-653 in Healthy Subjects

NCT Number: NCT02561156

Protocol Approve Date: 24 March 2017

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## PROTOCOL AMENDMENT

### A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Escalating Single and Multiple Doses of TAK-653 in Healthy Subjects

#### Phase 1 TAK-653 Escalating Single and Multiple Dose Study in Healthy Subjects

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

**Study Number:** TAK-653-1001

**IND Number:** Not Applicable      **EudraCT Number:** 2015-002268-17

**Compound:** TAK-653

**Date:** 24 March 2017      **Amendment Number:** 06

#### Amendment History:

Date	Amendment Number	Amendment Type	Region
23 June 2015	Initial Protocol	Not applicable	United Kingdom
26 August 2015	1	Nonsubstantial	United Kingdom
29 March 2016	2	Substantial	United Kingdom
01 April 2016	3	Substantial	United Kingdom
28 June 2016	4	Substantial	United Kingdom
06 January 2017	5	Substantial	United Kingdom
24 March 2017	6	Substantial	United Kingdom

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## 1.0 ADMINISTRATIVE INFORMATION

### 1.1 Contacts

Investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines should be provided to the site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Centre Europe Ltd. Email: eupv@tgrd.com (preferred method of reporting) Fax: + (44) 207 242 1820
Medical Monitor (medical advice on protocol and compound)	PPD [Redacted] Takeda Development Centre Europe Ltd. Office: PPD Mobile [Redacted] Email: [Redacted]
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD [Redacted] Takeda Development Centre Europe Ltd. Office: PPD Mobile [Redacted] Email: [Redacted]

## 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 Council for Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

### SIGNATURES

The responsible Takeda medical officer and other signatories are shown below. Electronic signatures are located on the last page of the document.

PPD



## INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for 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 D](#) – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix F](#) of this protocol.

PPD



### 1.3 Protocol Amendment 06 Summary of Changes

#### Rationale for Amendment 06

This document describes the changes in reference to the protocol incorporating Amendment No. 06. The primary reasons for Protocol Amendment No.6 are to increase the approximate total number of subjects to be enrolled and to revise the parameters for dose escalation decisions, given the available nonclinical monkey toxicity data and favorable preliminary safety/tolerability and pharmacokinetic (PK) data for cohorts that have completed dosing to date. Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see [Appendix H](#).

#### Changes in Amendment 06

1. The approximate total number of subjects to be enrolled in the study has been increased.
2. The nonclinical basis used to support dose escalation decisions has been revised.
3. The summary of the 13-week repeat-dose monkey toxicity data has been revised.
4. A summary of the 13-week repeat-dose rat toxicity data has been added.
5. A summary of preliminary blinded safety/tolerability and PK data has been added for completed single-rising dose (SRD) Cohorts 1 to 5 and SRD/multiple-rising dose (MRD) Cohorts 1 and 2.
6. The need for an independent medical reviewer from the sponsor to endorse dose escalation decisions has been removed.
7. Text has been added to clarify that study drug-related central nervous system disorders/adverse events may result in the stopping of dose escalation or study drug dosing.
8. Change in peripheral levels of the biomarker CCI [REDACTED] after dosing has been included as an endpoint for all cohorts (rather than just for SRD/MRD Cohort 3).
9. An additional blood sample collection at 168 hours postdose has been included for SRD Cohort 6 onward in Part 1.
10. Text was clarified to indicate that TAK-653 and the CCI [REDACTED] only will be measured in CCI [REDACTED] if feasible.
11. Text has been added to indicate that screening data for subjects who have undergone general screening procedures (ie, panel screening) before the effective date of this protocol amendment may be used to assess subject eligibility for enrollment in this study.
12. The responsibilities of the investigator have been revised to reflect the updated International Council for Harmonisation E6(R2) Good Clinical Practice Consolidated Guideline.
13. Procedures for bioanalytical and pharmacogenomic sample collecting, processing, and shipping have been removed and referenced to the laboratory manual instead.
14. The sponsor signatories for this protocol have been updated.

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## 2.0 STUDY SUMMARY

<b>Name of Sponsor:</b> Takeda Development Centre Europe Ltd.		<b>Compound:</b> TAK-653																																
<b>Title of Protocol:</b> A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Escalating Single and Multiple Doses of TAK-653 in Healthy Subjects		<b>IND No.:</b> not applicable		<b>EudraCT No.:</b> 2015-002268-17																														
<b>Study Number:</b> TAK-653-1001		<b>Phase:</b> 1																																
<p><b>Study Design:</b></p> <p>This first-in-human, double-blind, placebo-controlled, combined single-rising dose (SRD)/multiple-rising dose (MRD) phase 1 study in healthy subjects is designed to assess the safety and tolerability of TAK-653. Approximately 112 healthy male and female volunteers will be enrolled.</p> <p>This study consists of 2 parts: (1) single ascending doses in 5 cohorts (SRD) and (2) single and multiple ascending doses in 4 cohorts (SRD/MRD). Each cohort will consist of 8 subjects (6 active:2 placebo). Subjects will fast for at least 10 hours before dosing. Cohorts may be added or removed.</p> <p>This study will also provide a preliminary assessment of the potential effect of food on TAK-653 PK. Subjects in a selected SRD cohort (fasted conditions) will return to receive the same dose of TAK-653 under fed conditions after safety and tolerability has been established for TAK-653 at a higher dose under fasted conditions.</p> <p>Follow-up assessments will occur approximately 14 days after the last dose of study drug to inquire for any ongoing adverse events (AEs) or serious adverse events (SAEs), new or worsening AEs or SAEs, and concomitant medications taken since final dose. The Follow-up will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. Subjects may then return to the clinic for re-evaluation per investigator's discretion.</p> <p>For all subjects in the SRD and SRD/MRD cohorts [REDACTED]</p> <p><b>SRD Part 1:</b> Subjects will be enrolled in SRD cohorts. Sentinel dosing will be used for each SRD Cohort. The first 2 subjects (1 active: 1 placebo) in each Cohort will receive either TAK-653 or placebo in parallel, followed by a minimum 24-hour gap to ensure adequate evaluation of safety and tolerability prior to administering the same dose of TAK-653 or placebo to the remaining subjects within the Cohort (5 active: 1 placebo). Dosing of the remaining subjects will proceed in a staggered fashion with no more than 3 subjects being dosed at a time and having an approximate 24-hour gap before the next group of subjects is dosed. Each dose cohort will be examined sequentially to ensure adequate evaluation of safety, tolerability, and available PK and PD data prior to administering the next dose level. Administration with food will not occur until safety is established at a higher dose.</p> <p>A schematic of the study design for the SRD study arm is shown below:</p> <table border="1"> <thead> <tr> <th colspan="2">Pretreatment Period</th> <th colspan="4">Treatment Period</th> <th>Follow-up (d)</th> </tr> </thead> <tbody> <tr> <td>Screening</td> <td>Check-in Assessments (a)</td> <td>TAK-653 Dosing Study Assessments (a) (b) (c)</td> <td>Safety/PK/PD Assessments (a) (c)</td> <td>PK Assessments</td> <td>PK Assessments Study Exit (a)</td> <td></td> </tr> <tr> <td>Days -28 to -2</td> <td>Day -1</td> <td>Day 1</td> <td>Days 2-5</td> <td>Day 6 (Cohorts 1-5) Days 6-7 (Cohort 6 onward)</td> <td>Day 7 (Cohorts 1-5) Day 8 (Cohort 6 onward)</td> <td>Day 14 (±2)</td> </tr> <tr> <td colspan="7"> <div style="text-align: center;"> <span>←</span> <span style="border-bottom: 1px dashed black; padding: 0 10px;">-----</span> <span>→</span> </div> <p>Confinement</p> </td> </tr> </tbody> </table> <p>(a) EEG assessments are scheduled on Days -1, 1, 2, and 5, at Study Exit, and at early termination (ET).  (b) Study assessments include PK sample collection throughout.  (c) For SRD Cohort 6 onward, blood samples for [REDACTED] will be collected on Days 1 to 5.  (d) The Follow-up Visit will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In these cases, subjects may then be brought back to the clinic for re-evaluation per investigator's discretion.</p>							Pretreatment Period		Treatment Period				Follow-up (d)	Screening	Check-in Assessments (a)	TAK-653 Dosing Study Assessments (a) (b) (c)	Safety/PK/PD Assessments (a) (c)	PK Assessments	PK Assessments Study Exit (a)		Days -28 to -2	Day -1	Day 1	Days 2-5	Day 6 (Cohorts 1-5) Days 6-7 (Cohort 6 onward)	Day 7 (Cohorts 1-5) Day 8 (Cohort 6 onward)	Day 14 (±2)	<div style="text-align: center;"> <span>←</span> <span style="border-bottom: 1px dashed black; padding: 0 10px;">-----</span> <span>→</span> </div> <p>Confinement</p>						
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Subjects in SRD cohorts will be kept in the study unit for approximately 96 hours after dosing for safety, PK, and PD assessments before discharge. The total confinement period will be 5 days. Subjects in SRD Cohorts 1 to 5 will return to the clinic on Days 6 and 7 for additional PK collections. Subjects in SRD Cohort 6 onward will return to the clinic on Days 6, 7, and 8 for additional PK collections. If the  $t_{1/2}$  of TAK-653 for any cohort differs significantly from what was predicted, the duration of confinement may also be adjusted. Subjects in the food effect cohort will be confined twice for 5 days each for a total of 10 days. For SRD Cohort 6 onward, CCI [REDACTED]. Follow-up assessments for all subjects in the SRD study arm will occur on Day 14 ( $\pm 2$ ).

**SRD/MRD Part 2:** Progression into the SRD/MRD study arm will occur only after review of all safety, tolerability, PK, and PD data collected in at least the first 3 SRD cohorts. All doses used in SRD/MRD Cohorts will be administered only if there is acceptable safety, tolerability, PK, and PD data at the same or higher dose level after a single dose in the SRD Cohorts. The potential for accumulation and its impact on the likelihood of reaching the no-observed-adverse-effect level (NOAEL) exposure cap, will be taken into account when selecting doses for the MRD.

A single dose of TAK-653 or placebo will be administered on Day 1 followed by approximately 120 hours for safety, tolerability, PK, and PD assessments. Once daily (QD) multiple dosing will begin on Day 6 and continue through Day 18 (13 days). Initiation of the multiple-dose phase on Day 6 may be adjusted based on emerging PK data. Subjects in the SRD/MRD Cohorts will be kept in the study unit for at least 72 hours after the last dose for safety assessments before discharge. The total confinement period will be 21 days. For SRD/MRD Cohort 3 only, a CCI [REDACTED] sample will be collected from each subject to measure the concentration of TAK-653 at steady state. CCI [REDACTED] in CCI [REDACTED] (for SRD/MRD Cohort 3 only) or in CCI [REDACTED] only (for SRD/MRD Cohort 4 onward) to investigate the potential biological effects of TAK-653. Concentrations of CCI [REDACTED] in CCI [REDACTED] will also be measured for SRD/MRD Cohort 3, if possible. Follow-up assessments will occur on Day 31 ( $\pm 2$ ).

Each dose cohort will be examined sequentially to ensure adequate evaluation of all available safety, tolerability, PK, and PD data prior to administering the next dose level.

The study schematic for the SRD/MRD study arm is shown below.

Pretreatment Period		Treatment Period					Follow-up (e)
Screening	Check-in Assessments	TAK-653 Single Dose Study Assessments (a) (b) (d)	Safety and PK Assessments (d)	TAK-653 QD dosing Study Assessments (a) (b) (c) (d)	Safety and PK Assessments	Study Exit	
Days -28 to -2	Day -1	Day 1	Days 2-5	Days 6-18	Days 19-20	Day 21	Day 31 ( $\pm 2$ )
← ----- Confinement ----- →							

(a) Study assessments include PK sample collection throughout.

(b) EEG assessments are scheduled on Days 1, 11, 18, and ET.

(c) For SRD/MRD Cohort 3 only, a single CCI [REDACTED] sample will be collected from each subject on Day 12.

(d) For SRD/MRD Cohort 3 onward, blood samples for CCI [REDACTED] will be collected on Days 1 to 5, 18, and 19.

(e) The Follow-up Visit will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In these cases, subjects may then be brought back to the clinic for re-evaluation per investigator's discretion.

All decisions concerning dose escalation will be based on emerging safety, tolerability, and available PK and PD data. The planned dose levels may be modified in accordance with the following parameters:

- Dosing in all Cohorts will be limited to an escalated dose which is predicted to give no greater than ~3-fold increase in either the maximum observed plasma concentration ( $C_{max}$ ) or area under the plasma concentration-time curve (AUC). A smaller increment may be used at higher doses and a larger increment may be used at lower doses if exposures obtained are not sufficiently high, and if it is deemed safe to do so. In the event that the majority of plasma concentrations of TAK-653 are below the limit of detection, the dose will be escalated to a higher dose level, if safety and tolerability are acceptable.
- In the SRD Part 1, following completion of Cohort 1, exposure to TAK-653 in humans compared with what was predicted utilizing nonclinical data will influence the dose to be studied in Cohort 2.
- Administration with food for the food-effect cohort will not occur until safety is established at a higher dose.

- Progression into the SRD/MRD Part 2 will occur only after review of all available safety, tolerability, PK, and PD data collected in SRD Cohorts 1-3. The actual dose used in the SRD/MRD Cohorts will not be administered unless there is adequate safety, tolerability, and PK data at the same or higher dose level from the SRD Cohorts.
- In a 13-week repeat-dose toxicity study conducted with TAK-653 in cynomolgus monkeys, test article-related toxicities occurred around time of first occurrence of  $C_{max}$  ( $t_{max}$ ), typically within the first few days of dosing, and were considered to be related to the  $C_{max}$  rather than to the area under the plasma concentration-time curve from time 0 to 24 hours postdose ( $AUC_{24}$ ). Therefore, the predicted  $C_{max}$  value for the TAK-653 dose selected for any cohort should not exceed 362 ng/mL, the mean  $C_{max}$  value achieved in female monkeys on the first day of dosing at the NOAEL of 3 mg/kg/day. In addition, the predicted AUC value for any TAK-653 dose selected should not exceed CCI, the mean  $AUC_{24}$  value achieved in female monkeys at the end of the 13-week dosing period at the NOAEL of 3 mg/kg/day. If PK data collected during a cohort indicate that exposure to TAK-653 has surpassed the mean CCI at the NOAEL, lower doses will be used in subsequent cohort(s).
- Additionally, Takeda and the principal investigator may jointly decide to not escalate the dose for a particular cohort, but rather administer the same or a lower dose level to the next cohort.

End of trial (study completion date) is based on the final data collection date for the entire study which is the follow-up assessment.

**Primary Objective:**

To determine the safety and tolerability of TAK-653 when administered as single and multiple oral doses at escalating dose levels in healthy subjects.

**Secondary Objectives:**

To determine the PK of TAK-653 when administered as single and multiple oral doses at escalating dose levels in healthy subjects.

**Exploratory/Additional Objectives:**

CCI

**Subject Population:** Healthy male and female subjects aged 18 to 55 years, inclusive, at the time of consent.

**Number of Subjects:**

Per Cohort: 8 (6 active: 2 placebo)  
Estimated total: Up to 112 randomized healthy subjects

**Number of Sites:**

Estimated total: 1 in United Kingdom

**Dose Levels:**

SRD Cohorts: first dose 0.3 mg TAK-653, subsequent dose levels to be determined by emerging safety, tolerability, PK, and PD data in preceding Cohorts.  
SRD/MRD Cohorts: to be determined by emerging safety, tolerability, PK, and PD data in the SRD cohorts and preceding SRD/MRD Cohorts.

**Route of Administration:** Oral

<b>Duration of Treatment:</b> SRD Cohorts: 1 day SRD Food-Effect Cohort: 2 days SRD/MRD Cohorts: 14 days	<b>Period of Evaluation (First dose to Follow-up):</b> SRD Cohorts: 14 days SRD Food-Effect Cohort: 28 days SRD/MRD Cohorts: 31 days
<b>Main Criteria for Inclusion:</b> <ul style="list-style-type: none"> <li>The subject is a healthy male or female adult, aged 18 to 55 years, inclusive, at the time of consent.</li> <li>The subject weighs at least 45 kg (99 lb) and has a body mass index (BMI) between 18.0 and 30.0 kg/m<sup>2</sup>, inclusive, at Screening.</li> </ul>	
<b>Main Criteria for Exclusion:</b> <ul style="list-style-type: none"> <li>Subject has any clinically significant illness, such as cardiovascular, neurologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine, or psychiatric disease or disorder, or other abnormality which may affect safety, increase the risk for seizures, lower the seizure threshold, or potentially confound study results.</li> <li>Subject has a risk of suicide per the Columbia-Suicide Severity Rating Scale (C-SSRS) (a score of 4 or 5 on ideation or any suicidal behavior) or according to the investigator's clinical judgment, has made a suicide attempt in the previous 6 months, or has a history of deliberate self-harm in the past 6 months.</li> <li>Subject has had previous episodes of seizures or convulsion (lifetime), including absence seizure and febrile convulsion.</li> <li>Subject or any immediate family member has a history of epilepsy (including febrile convulsions).</li> <li>Subject has a history of neurological abnormalities including abnormal electroencephalogram (EEG) at Screening or brain injury including traumatic injury, perinatal cerebropathy and postnatal brain damage, blood-brain barrier abnormality, or angioma cavernous.</li> <li>Subject has a history of cerebral arteriosclerosis.</li> <li>Subject has a condition that can potentially reduce drug clearance (eg, renal or hepatic insufficiency).</li> </ul> <p>Additional exclusion criteria for CCI collection in SRD/MRD Cohort 3:</p> <ul style="list-style-type: none"> <li>The subject has had CCI collected within 6 months prior to Check-in (Day -1).</li> <li>The subject has a known hypersensitivity to the anesthetic or its derivatives used during CCI collection or any medication used to prepare the area of lumbar puncture.</li> <li>The subject has any skin condition, abnormality of the lumbar spine, or medical or surgical condition that would preclude lumbar puncture (eg, coagulopathy, local or systemic infection, left ventricular outflow obstruction, aortic stenosis, raised intracranial pressure, previous back surgery).</li> </ul>	
<b>Main Criteria for Evaluation and Analyses:</b> <p><b>Safety:</b> The primary endpoints include AEs, clinical laboratory test results, electrocardiogram (ECG), EEG, vital signs, and suicidality assessments.</p> <p><b>Pharmacokinetics:</b> The following PK parameters of TAK-653 will be determined from plasma: C<sub>max</sub> (Day 1 for all Cohorts and Day 6 for SRD/MRD Cohorts), maximum observed steady-state plasma concentration during a dosing interval (C<sub>max,ss</sub>) (Day 18 for SRD/MRD Cohorts), t<sub>max</sub> (Day 1 for all Cohorts and Day 18 for SRD/MRD Cohorts), area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC<sub>last</sub>) (Day 1 for all Cohorts), area under the plasma concentration-time curve from time 0 to infinity (AUC<sub>∞</sub>) (Day 1 for all Cohorts), area under the plasma concentration-time curve during a dosing interval (AUC<sub>τ</sub>) (Day 6 and Day 18 for SRD/MRD Cohorts).</p> <p><b>Pharmacodynamics:</b> CCI [REDACTED]</p>	



**Statistical Considerations:**

**Safety:**

AEs will be presented in listings, and treatment-emergent adverse events will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis), vital signs, and ECGs will be listed and Baseline, postdose, and changes from Baseline to postdose laboratory, vital signs, and ECG data will be summarized. Physical examination findings and suicidality assessments (C-SSRS) will be presented in data listings.

**Pharmacokinetic Measures:**

For each part of the study, the concentrations of TAK-653 and its metabolites in plasma and urine will be summarized by study Day, period (fasted vs fed), and dose level over each scheduled sampling time using descriptive statistics. Individual plasma concentration data vs time will be presented in a data listing. Descriptive statistics (N, arithmetic mean, SD, median, minimum, maximum and percent coefficient of variation [%CV]) will be used to summarize the plasma and urine PK parameters for TAK-653 and metabolites by study Day, period (fasted vs fed), and dose level. In addition, geometric mean and CV will be computed for  $C_{max}$  and AUCs.

Dose proportionality will be tested for TAK-653  $C_{max}$  and AUCs using a power model. For the SRD part, data from the SRD fed Cohort will not be included in the power model. For the SRD/MRD cohorts, the power model will be run after multiple dosing only.

The concentrations of TAK-653 and CCI in CCI if available, will be presented in a listing for SRD/MRD Cohort 3 only.

Food effect will be assessed for the food-effect SRD cohort subjects using the paired t-test for the natural logarithms of AUCs and  $C_{max}$ .

Additional analyses will be included if appropriate.

**Exploratory PD Endpoints:**

CCI

**Sample Size Justification:** The sample size chosen of 8 subjects in each Cohort (6 active: 2 placebo) is considered to be sufficient for evaluation of safety, tolerability, PK, and PD data of each cohort. The sample size was not based on statistical power considerations.

### **3.0 STUDY REFERENCE INFORMATION**

#### **3.1 Study-Related Responsibilities**

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

#### **3.2 Principal Investigator**

PPD



### 3.3 List of Abbreviations

$\lambda_z$	terminal elimination rate constant
%CV	percent coefficient of variation
AE	adverse event
AESI	adverse event of special interest
$Ae_t$	total amount of drug excreted in urine from time 0 to time t
$Ae_\tau$	total amount of drug excreted in urine during a dosing interval
ALT	alanine aminotransferase
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_\infty$	area under the plasma concentration-time curve from time 0 to infinity
$AUC_{24}$	area under the plasma concentration-time curve from time 0 to 24 hours postdose
$AUC_{last}$	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
$AUC_\tau$	area under the plasma concentration-time curve during a dosing interval
BCRP	breast cancer resistance protein
CCI	CCI
BMI	body mass index
BSA	body surface area
$C_{av,ss}$	average plasma concentration at steady-state
CL/F	apparent clearance after extravascular administration
$CL_R$	renal clearance
$C_{max}$	maximum observed plasma concentration
$C_{max,ss}$	maximum observed steady-state plasma concentration during a dosing interval
CNS	central nervous system
CRO	contract research organization
CS	clinically significant
CCI	CCI
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P-450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
CCI	CCI
EMA	European Medicines Agency
FDA	Food and Drug Administration
$f_e$	fraction of drug excreted in urine
FFT	Fast Fourier transformation

FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GluR1	L-Glutamate type 1 receptor
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IV	intravenous(ly)
K <sub>2</sub> EDTA	potassium ethylenediamine tetraacetic acid
LFT	liver function test
CCI	
MAV	markedly abnormal value
MDD	major depressive disorder
MED	minimally effective dose
MedDRA	Medical Dictionary for Regulatory Activities
MR(AUC <sub>∞</sub> )	metabolite ratio of AUC <sub>∞</sub> values of the metabolite to TAK-653
MR(C <sub>max</sub> )	metabolite ratio of C <sub>max</sub> values of the metabolite to TAK-653
MRD	multiple-rising dose
MRSD	maximum recommended starting dose
mTOR	mammalian target of rapamycin
NCS	not clinically significant
NIMH	National Institute of Mental Health
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
Pgp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PT	preferred term
PTE	pretreatment event
QD	once daily
CCI	
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
R <sub>ac</sub> (AUC)	accumulation ratio based on AUC

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R <sub>ac(C<sub>max</sub>)</sub>	accumulation ratio based on C <sub>max</sub>
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SRD	single-rising dose
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
SUSARs	suspected unexpected serious adverse reactions
t <sub>1/2z</sub>	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TK	toxicokinetic(s)
t <sub>max</sub>	time of first occurrence of C <sub>max</sub>
TRD	treatment-resistant depression
UK-1	unidentified metabolite 1
ULN	upper limit of normal
UV	ultraviolet
WHO	World Health Organization
V <sub>z</sub> /F	apparent volume of distribution during the terminal disposition phase

### **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-653 is a potent and selective potentiator of the L-glutamate type 1 receptor (GluR1), a subunit of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, which is currently in development for treatment-resistant depression (TRD).

Major depressive disorder (MDD) is characterized by a pervasive depressed mood or loss of interest or pleasure (anhedonia) in almost all activities in discrete episodes of at least 2 weeks duration involving clear-cut changes in affect, cognition, and neurovegetative functions and inter-episode remissions [1]. Other features include psychomotor retardation, tearfulness, irritability, anxiety, and slowed thinking. These are typically accompanied by biological symptoms such as sleep disturbances, loss of appetite, and changes in weight (gain/loss), fatigue, and loss of libido. This disorder has been identified as the second leading cause of years lived with disability, designating it as a major public health priority [2]. Up to 86% of subjects who commit suicide were shown to be suffering from depression at the time, based on psychological autopsy studies [3] and up to 15% of patients suffering from MDD commit suicide [4]. MDD is also associated with a significant economic burden. It is estimated that \$210.5 billion in annual costs can be attributable to MDD and approximately 32 workdays per year are lost by the average worker with MDD [5].

While multiple treatments such as medication, psychotherapy, or electroconvulsive therapy exist, a significant proportion of patients do not respond adequately and some do not respond at all. In the National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, only 27.5% of patients with depression responded with up to 14 weeks of treatment [6]. Furthermore, up to one-third of the patients did not achieve remission by the end of the study [7].

Despite years of research and efforts to develop effective treatments, currently available antidepressant medications have serious limitations, among which are low rates of treatment response (30% to 40% of patients with MDD have treatment-resistant depression) [8,9]. TRD by definition is the failure to respond to adequate doses and duration of therapy of 2 different antidepressants from 2 different classes [10]. Moreover, there is a time lag of several weeks to months before a therapeutic effect is observed, a serious problem given the high rate of suicide in depressed patients [2,4,9,11]. Thus, there is a large unmet medical need for novel antidepressant therapies with faster onset of action and efficacy in depression.

Recent findings support the AMPA receptor subunit GluR1 as a potential target for rapid onset of antidepressant action and activity in patients not responding to classical antidepressants [9,12-14]. This antidepressant action appears to be mediated via increased levels of CCI and increased mammalian target of rapamycin (mTOR) signaling [9,14], which is further supported by activity of AMPA receptor potentiators in experimental animal models of depression and cognition.

In nonclinical studies, TAK-653 CCI

CCI [REDACTED] In vivo, TAK-653 was efficacious in animal models of cognition and depression (reduction of submissive behavior), suggesting that it may be efficacious in a variety of psychiatric conditions. In vivo, TAK-653 was able to acutely enhance cognition in normal rats and reduce depression-like symptoms in a rat model of depression. In the novel object recognition model in the rat, TAK-653 at 0.03 and 0.1 mg/kg increased the time that animals spent interacting with a novel object, a result consistent with better remembering of a familiar object, which is indicative of cognitive improvement. At the lower dose of 0.03 mg/kg, TAK-653 was fully active suggesting high in vivo potency of the compound. In the second animal model of depression, the rat dominant-submissive model, TAK-653 at once daily (QD) oral doses of 0.1 and 1 mg/kg during 3 weeks of treatment significantly reduced the dominance score in submissive animals, an antidepressant-like activity. While the overall antidepressant effect was significant at both doses, daily scoring revealed that the 1 mg/kg dose of TAK-653 showed a continuously significant antidepressant effect as of Day 6 of treatment until the end of the treatment period.

TAK-653 was absorbed rapidly after oral administration, with peak plasma concentrations generally occurring within 2 hours postdose in rats and 8 hours postdose in monkeys. The terminal elimination half-life ( $t_{1/2z}$ ) of TAK-653 after intravenous (IV) administration was 1.7 hours in rats and 9.6 hours in monkeys. The predicted oral  $t_{1/2z}$  of TAK-653 in humans is 10 hours based on rat pharmacokinetic (PK) data and 26 hours based on monkey PK data. The oral bioavailability of TAK-653 in animals was high (29.3% in rats and 65.4% in monkeys). CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

Toxicology studies conducted with TAK-653 include a single-dose study in Sprague-Dawley rats; an escalating-dose study in monkeys; repeat-dose toxicity studies up to 13 weeks in duration in rats and monkeys; and in vitro and/or in vivo genotoxicity and phototoxicity studies.

In a Good Laboratory Practice (GLP)-compliant 4-week repeat-dose toxicity study in rats, tonic convulsions were reported in males dosed with 300 mg/kg/day at 4 hours postdose. The dose was subsequently lowered to 100 mg/kg/day for males and no convulsions were reported throughout the remainder of the dosing period. The no-observed-adverse-effect level (NOAEL) in the 4-week rat toxicity study was 100 mg/kg/day for males and  $\geq 200$  mg/kg/day for females.

A 13-week GLP-compliant repeat-dose toxicity study was conducted in rats. Tonic convulsion was observed in 1 female at 200 mg/kg/day; therefore, the highest dose in females was reduced to 100 mg/kg/day beginning on Day 2 of the study. After lowering the dose to 100 mg/kg/day, no convulsions were observed in any group through the end of the dosing period. In addition, there were no test article-related abnormalities observed in clinical signs, body weights, food consumption, ophthalmologic examination, urine output, urinalysis, hematology, coagulation tests, clinical chemistry, necropsy, organ weights, or histopathological examination. The NOAELs in this study were 50 mg/kg/day for males and 100 mg/kg/day for females. CCI

[REDACTED]

In a preliminary 2-week repeat-dose toxicity study in monkeys (2/sex/group), 1 female at 30 mg/kg/day was euthanized moribund on Day 3. This animal demonstrated clonic convulsions, prone position, action tremors, and decreased locomotor activity on Days 1 and 2 and decreased feces on Days 1 to 3. Action/resting tremors, vomiting and marked decreases in feces, food consumption and body weights were seen in all animals postdose at 30 mg/kg/day. Therefore, after a 4-day treatment-free period, the high dose in the study was reduced to 10 mg/kg/day. No additional convulsions were seen; transient tremors, a slight decrease in body weight, and a slight increase in ALT were seen in one female at 10 mg/kg/day.

In the 4-week GLP-compliant repeat-dose toxicity study in monkeys dosed at 0, 0.3, 3, and 10 mg/kg/day, resting and action tremors were noted at  $\geq 3$  mg/kg/day in females and at 10 mg/kg/day in males. Dose-dependent vomiting was reported at 3 and 10 mg/kg/day in both sexes, although this was transient and not considered adverse at 3 mg/kg/day. At 10 mg/kg/day, ptosis, prone position, decreased locomotor activity, and decreased feces were transiently reported in males and/or females. Except for effects on clinical signs, no other adverse effects were seen. As it was unknown if the tremors seen in this study were associated with adverse EEG changes, the assignment of the NOAEL took a conservative approach. Therefore, the NOAELs in the 4-week monkey toxicity study, based on observations of tremor at higher doses, were 3 mg/kg/day for males and 0.3 mg/kg/day for females. CCI

[REDACTED]

A 13-week repeat-dose toxicity study was conducted in cynomolgus monkeys, dosed at 0, 0.3, 3, and 10 mg/kg/day; with some exceptions, the study was GLP-compliant. In this study, monkeys were monitored continuously for EEG and EMG activity and behavior the first 28 days of dosing and for 24-hour periods midstudy and at the end of the study; toxicokinetics were evaluated after the first, 29th, and 90th dose administrations and after a convulsion was observed.

Tremors were seen in all dose groups, including controls, although they occurred with greater frequency in high-dose females. Tremors were not accompanied by underlying changes in EEG activity that were suggestive of seizure episodes (eg, no paroxysmal activity). Dosing of female monkeys with 10 mg/kg/day was associated with EEG paroxysmal activity, repeated sharp waves,



and seizure activity in 2 of 4 animals, first observed after the first or second dose administration. Although tremors were observed 2 to 4 hours before seizure episodes, there was no paroxysmal EEG activity associated with them. Overall, the occurrence of tremors did not reflect an ensuing seizure, and, in fact, the vast majority of tremors were recorded for animals that did not convulse.

Given the apparent intolerability of 10 mg/kg/day in female monkeys, the high dose in this group was reduced to 6 mg/kg/day after a dosing holiday. After the second dosing of 6 mg/kg/day, 1 female showed clinical signs of a convulsion but examination of the EEG, EMG, and video-recorded behavior of the animal indicated that it was likely to be an episode of ataxia rather than a generalized seizure as it was not accompanied by EEG signs of seizure activity (although a partial seizure could not be ruled out). On Day 79 of dosing the same monkey showed clinical signs of a convulsion; as videographic and EEG activity were not being recorded at that time, as per protocol, EEG confirmation of seizure activity was not possible. However, to err on the side of safety, the event was considered to be a seizure.

No adverse effects of treatment were seen in male monkeys at any dose level in the 13-week study.

Overall, the results of the 13-week toxicity study in monkeys indicate no adverse effects of treatment except on clinical signs. There was no adverse effect of treatment on mortality, body weights, or food consumption, electrocardiography, ophthalmology, urinalysis, hematology, clinical chemistry, organ weights, or macroscopic or microscopic observations. Evaluation of videographic recordings of clinical signs throughout the study indicate that tremors occurred in all dose groups, including vehicle controls, although the incidence was increased in females at 10 and 6 mg/kg/day. Tremors were not associated with EEG changes indicative of seizure activity (ie, no synchrony, paroxysmal activity), were not predictive of a seizure, and likely represent an extension of the pharmacology of the compound. The NOAEL in this study was 10 mg/kg/day in males and 3 mg/kg/day in females based on a clinical observation of seizure (unconfirmed by EEG) in 1 female at 6 mg/kg/day. <sup>CCI</sup>

In other studies, TAK-653 was not associated with genotoxic or phototoxic potential examined in vitro and/or in vivo.

#### 4.2 Rationale for the Proposed Study

The ubiquitous expression of AMPA receptors throughout the central nervous system (CNS) makes them central to a multitude of higher neurophysiological processes, including attention, learning, memory, and other cognitive functions. The central role of AMPA receptors in these functions makes them attractive as therapeutic targets for a multitude of diseases. In nonclinical studies, <sup>CCI</sup>

In addition, TAK-653 has shown efficacy in a number of animal models underlining the potential to be efficacious in a variety of psychiatric conditions, including depression. This first-in-human (FIH) study has therefore been designed to evaluate safety, PK, and PD effects of TAK-653 in healthy volunteers before further clinical development.

### 4.3 Risk-Benefit Profile

This FIH phase 1 study has been designed to mitigate the known risks associated with AMPA receptor potentiators as a class and the potential risks based on the nonclinical toxicity data and preliminary clinical data for TAK-653. Descriptions of the risk mitigation measures included in this study are detailed in Section 6.2 and summarized in Section 6.2.4. As this is a study in healthy subjects, there is no expected clinical benefit to the study participants.

To date in this study, a total of 56 subjects have been enrolled and administered study drug (42 active, 14 placebo) in 5 single-rising dose (SRD) cohorts (0.3, 1, 3, 5, and 9 mg) in Part 1 and 2 SRD/multiple-rising dose (MRD) cohorts (0.3 and 1 mg) in Part 2. In addition, dosing in SRD/MRD Cohort 3 (3 mg) has started. A blinded review of the preliminary safety and tolerability data for these completed cohorts indicate that TAK-653 was generally well tolerated at single doses up to 9 mg in Part 1 and multiple doses up to 1 mg QD in Part 2. No serious treatment-emergent adverse events (TEAEs) or CNS-type adverse events (AEs) were reported. No clinically meaningful clinical laboratory, vital sign, electrocardiogram (ECG), or physical examination results were reported. Preliminary PK data from these cohorts indicate that TAK-653 exhibits linear PK across the dose range tested.

## **5.0 STUDY OBJECTIVES AND ENDPOINTS**

### **5.1 Primary Objective**

To determine the safety and tolerability of TAK-653 when administered as oral, single and multiple doses at escalating dose levels in healthy subjects.

### **5.2 Secondary Objective**

To determine the PK of TAK-653 when administered as single and multiple oral doses at escalating dose levels in healthy subjects.

### **5.3 Exploratory/Additional Objectives**

CCI



## **5.4 Endpoints**

### **5.4.1 Primary Endpoints**

- Percentage of subjects who experience at least 1 TEAE.
- Percentage of subjects who discontinue due to an AE.
- 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 electrocardiogram (ECG) parameters at least once postdose.
- Percentage of subjects who experience clinically significant abnormal changes in EEG measurements at least once postdose.

- Columbia-Suicide Severity Rating Scale (C-SSRS):
  - Treatment-emergent suicidal ideation compared to Baseline, as measured by an increase in suicidal ideation category (1-5 on the C-SSRS) during treatment from the maximum suicidal ideation category at Baseline, or any suicidal ideation during treatment if there was none at Baseline.
  - Treatment-emergent suicidal behavior compared to Baseline, as measured by an increase in suicidal behavior category (6-10 on the C-SSRS) during treatment from the maximum suicidal behavior category at Baseline, or any suicidal behavior during treatment if there was none at Baseline.

#### 5.4.2 Secondary Endpoints

Plasma PK parameters of TAK-653:

- $C_{\max}$  (Day 1 for all Cohorts and Day 6 for single-rising dose [SRD]/multiple-rising dose [MRD] Cohorts).
- Maximum observed steady-state plasma concentration during a dosing interval ( $C_{\max,ss}$ ) (Day 18 for SRD/MRD Cohorts).
- Time to reach  $C_{\max}$  ( $t_{\max}$ ) (Day 1 for all Cohorts and Day 18 for SRD/MRD Cohorts).
- Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration ( $AUC_{\text{last}}$ ) (Day 1 for all Cohorts).
- Area under the plasma concentration-time curve from time 0 to infinity ( $AUC_{\infty}$ ) (Day 1 for all Cohorts).
- Area under the plasma concentration-time curve during a dosing interval ( $AUC_{\tau}$ ) (Day 6 and Day 18 for SRD/MRD Cohorts).

#### 5.4.3 Exploratory/Additional Endpoints

CCI



Additional PK endpoints for TAK-653 and metabolites:

CCI



## 6.0 STUDY DESIGN AND DESCRIPTION

### 6.1 Study Design

This FIH, double-blind, placebo-controlled, combined SRD/MRD phase 1 study in healthy subjects is designed to assess the safety and tolerability of TAK-653. Approximately 112 healthy male and female volunteers will be enrolled.

This study consists of 2 parts: (1) single ascending doses in 5 cohorts (SRD) and (2) single and multiple ascending doses in 4 cohorts (SRD/MRD). Each cohort will consist of 8 subjects (6 active:2 placebo). Subjects will fast for at least 10 hours before dosing. Cohorts may be added or removed.

This study will also provide a preliminary assessment of the potential effect of food on TAK-653 PK. Subjects in a selected SRD cohort (fasted conditions) will return to receive the same dose of TAK-653 under fed conditions after safety and tolerability has been established for TAK-653 at a higher dose under fasted conditions.

Follow-up assessments will occur approximately 14 days after the last dose of study drug to inquire for any ongoing AEs or serious adverse events (SAEs), worsening of AEs or SAEs, or development of new AEs or SAEs, and concomitant medications taken since final dose. Follow-up will occur by telephone unless abnormal, clinically significant findings are observed upon discharge or at the investigator's discretion. Subjects should then be brought back to the clinic for re-evaluation.

For all subjects in the SRD and SRD/MRD cohorts, CCI

To assess change from baseline, the last assessment prior to the first dose of the study medication will be used.

#### 6.1.1 Part 1: SRD

Subjects will be enrolled in SRD cohorts. Sentinel dosing will be used for each SRD Cohort. The first 2 subjects (1 active: 1 placebo) in each Cohort will receive either TAK-653 or placebo in parallel, followed by a minimum 24-hour gap to ensure adequate evaluation of safety and tolerability prior to administering the same dose of TAK-653 or placebo to the remaining subjects within the Cohort (5 active: 1 placebo). Dosing of the remaining subjects will proceed in a staggered fashion with no more than 3 subjects being dosed at a time and having an approximate 24-hour gap before the next group of subjects is dosed. Each dose cohort will be examined sequentially to ensure adequate evaluation of all available safety, tolerability, PK, and PD data prior to administering the next dose level.

A schematic of the study design for the SRD Part 1 is presented in [Figure 6.a](#). The schedule of assessments in the SRD Part 1 is in [Appendix A](#) for Cohorts 1 to 5 and in [Appendix B](#) for Cohort 6 onward.

**Figure 6.a SRD Study Schematic**

Pretreatment Period		Treatment Period				Follow up (d)
Screening	Check-in Assessments (a)	TAK-653 Dosing Study Assessments (a) (b) (c)	Safety and PK Assessments (a) (c)	PK Assessments	PK Assessments/ Study Exit (a)	
Days -28 to -2	Day -1	Day 1	Days 2-5	Day 6 (Cohorts 1-5) Days 6-7 (Cohort 6 onward)	Day 7 (Cohorts 1-5) Day 8 (Cohort 6 onward)	Day 14 (±2)
		←----- Confinement -----→				

- (a) CCI [REDACTED]  
(b) Study assessments include PK sample collection throughout.  
(c) CCI [REDACTED]  
(d) Follow-up will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In this case or at investigator's discretion, subjects should return to the clinic for re-evaluation.

The planned first dose level to be studied is 0.3 mg for SRD Cohort 1. The actual choice of the dose levels in subsequent Cohorts will occur after the full review of all available safety, tolerability, PK, and PD data in the preceding cohorts. If necessary, the sponsor team (Takeda only) may unblind the data and perform additional analyses for an informed dose-escalation decision. The next dose level may be higher, lower, or remain the same as the preceding dose level. If the dose is not increased in the next Cohort, staggered dosing is not necessary.

The planned dose cohorts in the SRD study arm are listed in [Table 6.a](#).

**Table 6.a Summary of SRD Dose Cohorts**

Cohort (a)	TAK-653 Single Dose (b) (c)		No. of Subjects
	Planned	Actual	
1	0.3 mg	0.3 mg	6 TAK-653 2 placebo
2	X mg	1.0 mg	6 TAK-653 2 placebo
3 (food-effect cohort) (d)	X mg	3.0 mg	6 TAK-653 2 placebo
4	X mg	5.0 mg	6 TAK-653 2 placebo
5	X mg	9.0 mg	6 TAK-653 2 placebo

(a) Sentinel dosing will occur at the start of each Cohort in the SRD. After the investigator and sponsor review the 24-hour safety and tolerability data, the remaining subjects can be dosed in a staggered fashion (no more than 3 subjects at a time). A 24-hour gap will follow each subsequent administration to evaluate safety and tolerability data.  
(b) Dose escalation to Cohort 2 onward will be based on review of safety, tolerability, and available PK and PD data from the previous cohort(s).  
(c) TAK-653 or placebo will be administered orally to subjects after an overnight fast of at least 10 hours.  
(d) Subjects from SRD Cohort 3 (fasted conditions) will return to the clinic to receive the same dose of TAK-653 following a standard meal.

Subjects in the SRD Cohorts will be kept in the study unit for approximately 96 hours after dosing for safety and PK assessments before discharge. The total confinement period is 5 days. Subjects in Cohorts 1 to 5 will return to the clinic on Days 6 and 7 for additional PK collections. Subjects in Cohort 6 onward will return to the clinic on Days 6, 7, and 8 for additional PK collections. If the  $t_{1/2z}$  of TAK-653 for any cohort differs significantly from what was predicted, the duration of confinement may also be adjusted. Subjects in the food effect cohort will be confined twice for 5 days each for a total of 10 days. For SRD Cohort 6 onward, CCI

Follow-up assessments for all subjects in the SRD study arm will occur on Day 14 ( $\pm 2$ ).

### 6.1.2 Part 2: SRD/MRD

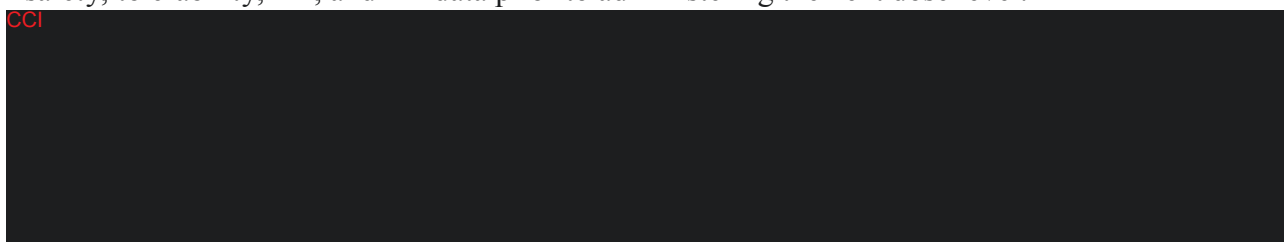
Progression into the SRD/MRD Part 2 will occur only after review of all available safety, tolerability, PK, and PD data collected in at least the first 3 SRD cohorts. The actual dose in the SRD/MRD Cohorts will not be administered unless there is acceptable safety, tolerability, PK, and PD data at the same or higher dose level after a single dose in the SRD Cohorts. If necessary, the sponsor team (Takeda only) may unblind the data and perform additional analyses for an informed dose-escalation decision. The potential for accumulation and its impact on the likelihood of reaching the NOAEL exposure cap, will be taken into account when selecting doses for the MRD.

A single dose of TAK-653 or placebo will be administered on Day 1 followed by approximately 120 hours for safety, tolerability, PK, and PD assessments. Once daily (QD) multiple dosing will begin on Day 6 and continue through Day 18 (13 days). Initiation of the multiple-dose phase on Day 6 may be adjusted based on emerging safety, PK, and/or PD data. Neither sentinels nor



staggered dosing are used in the SRD/MRD. Subjects in the SRD/MRD Cohorts will be kept in the study unit for at least 72 hours after the last dose for safety assessments before discharge. The total confinement period planned is 21 days. Cohort 4 is optional, to be used if emerging safety and/or PK or PD data warrant further study at a different dose. Follow-up assessments will occur on Day 31 ( $\pm 2$ ).

Each dose cohort will be examined sequentially to ensure adequate evaluation of all available safety, tolerability, PK, and PD data prior to administering the next dose level.



The study schematic for the SRD/MRD Part 2 is presented in [Figure 6.b](#). The schedule of assessments in the SRD/MRD Part 2 is in [Appendix C](#).

**Figure 6.b SRD/MRD Study Schematic**

Pretreatment Period		Treatment Period					Follow-up (e)
Screening	Check-in Baseline Assessments	TAK-653 Single Dose Study Assessments (a) (b) (d)	Safety and PK Assessments (d)	TAK-653 QD dosing Study Assessments (a) (b) (c) (d)	Safety and PK Assessments	Study Exit	
Days -28 to -2	Day -1	Day 1	Days 2-5	Days 6-18	Days 19-20	Day 21	Day 31 ( $\pm 2$ )
←----- Confinement-----→							

(a) Study assessments include PK sample collection throughout.

(b) CCI

(c) For SRD/MRD Cohort 3 only, a single CSF sample will be collected from each subject on Day 12.

(d) CCI

(e) The Follow-up assessments will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In this case or per investigator's discretion, subjects should return to the clinic for re-evaluation.

A summary of the SRD/MRD dose cohorts is presented in [Table 6.b](#).

**Table 6.b Summary of SRD/MRD Dose Cohorts**

Cohort	Planned TAK-653 Dose (a) (b) (c)		Subjects
	Planned	Actual	
1	X mg	0.3 mg	6 TAK-653 2 placebo
2	X mg	1.0 mg	6 TAK-653 2 placebo
3	X mg	3.0 mg	6 TAK-653 2 placebo
4	X mg	X mg	6 TAK-653 2 placebo

(a) Dosing for the first SRD/MRD Cohort will not begin until there is acceptable safety, tolerability, and available PK and PD data at the same or higher dose level after a single dose from at least the first 3 SRD Cohorts. Dose escalation to subsequent Cohorts will be based on review of safety, tolerability, and available PK and PD data from previous Cohorts. The subsequent dose level may be higher, lower, or the same as the preceding dose level.

(b) In each Cohort, a single dose will be administered on Day 1 followed by 120 hours of safety, tolerability, PK, and PD assessments. QD multiple doses will proceed from Day 6 through Day 18.

(c) TAK-653 or placebo tablets will be administered orally to subjects after an overnight fast of at least 10 hours.

### 6.1.3 Dose Escalation

All decisions concerning dose escalation will be made by Takeda (at a minimum, the clinical science representative and pharmacovigilance physician, or appropriate delegates) and the principal investigator. The investigator and subjects will remain blinded throughout the study, but at the completion of each cohort, Takeda personnel may be unblinded to analyze data considered necessary to determine subsequent doses.

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

- Dosing in all Cohorts will be limited to an escalated dose which is predicted to give no greater than ~3-fold increase in either  $C_{max}$  or AUC. A smaller increment may be used at higher doses and a larger increment may be used at lower doses if exposures obtained are not sufficiently high, and if it is deemed safe to do so. In the event that the majority of plasma concentrations of TAK-653 are below the limit of detection, the dose will be escalated to a higher dose level, if safety and tolerability are acceptable.
- In SRD Part 1, following completion of Cohort 1, exposure to TAK-653 in humans as compared to what was predicted utilizing nonclinical data will influence the dose to be studied in Cohort 2.
- Progression into SRD/MRD Part 2 will occur only after review of all available safety, tolerability, PK, and PD data collected in SRD Cohorts 1-3. All doses used in the SRD/MRD Cohorts will be administered only if there is adequate safety, tolerability, PK, and PD data at the same or higher dose level from the SRD Cohorts.

- In a 13-week repeat-dose toxicity study conducted with TAK-653 in cynomolgus monkeys, test article-related toxicities occurred around  $t_{\max}$ , typically within the first few days of dosing, and were considered to be related to the  $C_{\max}$  rather than to the  $AUC_{24}$ . Therefore, the predicted exposure for the TAK-653 dose selected for any cohort should not exceed the mean  $C_{\max}$  value (CCl [REDACTED]) achieved in female monkeys on the first day of dosing or the mean  $AUC_{24}$  value (CCl [REDACTED]) achieved in female monkeys at the end of the dosing period at the NOAEL of 3 mg/kg/mL in the 13-week repeat-dose toxicity study. If PK data collected during a cohort indicate that exposure to TAK-653 has surpassed the CCl [REDACTED] [REDACTED] at the NOAEL, lower doses will be used in subsequent cohort(s).
- Administration with food will not occur until safety is established at a higher dose in the fasted state.

Additionally, Takeda and the principal investigator may jointly decide to not escalate the dose for a particular cohort, but rather administer the same or a lower dose level to the next cohort.

In all SRD Cohorts, there will be a minimum period of 24 hours following the dose in the 2 sentinel subjects to allow for collection and review of safety and tolerability data. The remaining 6 subjects in each Cohort will then be dosed in a staggered fashion of no more than 3 subjects at a time, followed by a minimum period of 24 hours for safety assessments.

For each completed dose level Cohort, the principal investigator and Takeda will carefully review all safety, tolerability, PK, and PD data to determine whether dosing should stop or continue (and, if continue, at what dose, including whether to repeat the previous dose), whether additional staggered dosing should be implemented in future cohorts, or whether the blind should be broken to identify whether the subjects received TAK-653 or placebo.

All AEs reported during the Treatment Period, both within and across cohorts, up to the time of discharge (at least 96 hours after dosing for the SRD Cohorts, 72 hours after the last dose for the SRD/MRD Cohorts), will be evaluated to assess the need for subject, Cohort, and/or study termination in accordance with prespecified criteria (Section 6.3.1).

Following assessment of the AE data and predefined criteria for study termination, dose escalation may be interrupted/stopped and the blind broken for further analysis. Based on review of unblinded data, Takeda, in consultation with the principal investigator, will decide if and how it is appropriate for the study to proceed.

Dose escalation and study drug administration will be stopped if an SAE or 2 severe or clinically significant AEs, including CNS disorders/AEs (Section 6.3.1), are observed in a particular cohort and are considered by the investigator to be related to TAK-653.

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

## 6.2 Justification for Study Design, Dose, and Endpoints

### 6.2.1 Study Design

This phase 1 study is randomized, double-blind, and placebo-controlled in order to avoid subjective bias in the assessment of the safety and tolerability of TAK-653. Each cohort dose level in both parts of this study will be examined sequentially prior to administering the next dose level in order to mitigate known risks associated with potentiators of AMPA receptors and potential risks based on nonclinical data for TAK-653. Study-specific eligibility criteria have been added to the standard criteria to ensure that subjects at increased risk of seizures/convulsions are excluded (eg, history of seizures, epilepsy, abnormal screening EEG; and renal and hepatic insufficiency). See Section 7.2.

Additional risk mitigation measures have been incorporated into the first part of this study. Sentinel dosing will be used within each SRD Cohort to evaluate safety and tolerability prior to administering TAK-653 to additional subjects in the same dose Cohort. As a further safety measure, staggered dosing will be employed with only 3 of the remaining 6 subjects in the same Cohort being dosed at one time. All subjects in the SRD cohorts will remain in the phase 1 unit for at least 96 hours after dosing for safety, PK, and PD assessments. The first dose in this study will be 0.3 mg, which represents a 20-fold safety factor. Choosing the dose level for the next Cohort will require review of all available safety, tolerability, PK, and PD data from all subjects in the preceding Cohorts.

This study will also provide a preliminary assessment of the potential effect of food on TAK-653 PK, in which each subject serves as his or her own control when administered TAK-653 under fed and fasted conditions. Subjects in a selected SRD cohort (fasted conditions) will return to receive the same dose of TAK-653 under fed conditions (see Section 7.4) after safety has been established at a higher dose under fasted conditions.

The dose of TAK-653 chosen to be administered to the first SRD/MRD Cohort will be a dose that is equivalent to or lower than the highest dose administered to subjects in at least the first 3 SRD cohorts. The predicted exposure of the selected dose should not exceed the mean  $C_{\max}$  value (CCI [REDACTED]) achieved in female monkeys on the first day of dosing or the mean  $AUC_{24}$  value (CCI [REDACTED]) achieved in female monkeys at the end of the dosing period at the NOAEL of 3 mg/kg/mL in the 13-week repeat-dose toxicity study.

By completing the first 3 SRD Cohorts before starting the first SRD/MRD Cohort, safety, tolerability, and available PK and PD data will have been reviewed from 24 subjects at 3 different dose levels. The SRD/MRD dosing begins with a single dose, followed by safety, PK and PD assessments over 120 hours before the QD multiple dosing commences for 13 days. The PK collected after both single and multiple doses of TAK-653 will allow assessment of time-independence in the PK of TAK-653. PK data collected on Day 1 and Day 6 will provide a preliminary estimate of intrasubject variability.

Based on allometric scaling, the predicted  $t_{1/2z}$  of TAK-653 in humans is 10 hours based on the rat PK data and 26 hours based on monkey PK data. Therefore, 13 days of dosing is sufficient for TAK-653 to reach steady-state based on the current estimates (it takes approximately 4 half-lives

for a drug to reach a concentration that is 90% of the steady-state concentration). Also based on nonclinical data, 13 days of QD multiple dosing is a substantial duration that allows for PD activity and safety events to appear before proceeding with clinical studies of longer duration in a patient population. Subjects in the SRD/MRD Cohorts will be kept in the study unit for 72 hours after the last dose for safety assessments before discharge. The total confinement period for the SRD/MRD Cohorts will be 21 days, with Follow-up safety assessments on Day 31 ( $\pm 2$ ).

Based on the known risks of AMPA receptor potentiators and the potential risks based on TAK-653 nonclinical data, any Cohort may be stopped if a subject experiences tremors with corresponding changes in EEG, QT prolongation, or bradycardia. Dosing may be resumed at lower dose levels in subsequent cohorts.

CCI



### 6.2.2 Dose

The nonclinical toxicity studies conducted to date with TAK-653 provide adequate safety data to support a phase 1 clinical study. The human equivalent doses (HEDs) were derived using the methodology described in the Food and Drug Administration (FDA) Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers [15].

At the time that the starting dose for the current study was selected, the 13-week toxicity studies had not been conducted. The lowest NOAEL in repeat-dose toxicity studies was 0.3 mg/kg/day in the 4-week monkey study, and therefore the monkey is considered the more sensitive species. Allometric scaling (based on body surface area [BSA]) was calculated by multiplying the NOAEL from the 4-week monkey study by a conversion factor of 0.32 in order to obtain the HED of 0.096 mg/kg/day (based on the female monkey), or approximately 5.76 mg/day for a 60 kg human.

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Applying a 10-fold safety factor, the maximum recommended starting dose (MRSD) in humans is 0.6 mg/day for a 60 kg human.

The minimally effective dose (MED) of TAK-653, defined on the basis of the novel object recognition test and reduction of submissive behavior model in rat is considered to be 0.1 mg/kg. AUC<sub>24</sub> at this dose, based on available PK data, would be expected to be 24.5 h\*ng/mL in rats. Utilizing the MED across the rat pharmacology models (TAK-653 0.1 mg/kg), the effective AUC value of TAK-653 in humans is estimated to be approximately 30 h\*ng/mL. The predicted PK profile of TAK-653 in humans was generated utilizing PK parameters of TAK-653 in rat and monkey separately, with allometric scaling based on body weight and plasma protein binding differences between the species. With the assumptions of similar effective concentrations in the rat and humans, PK linearity, and that there is no difference between the animals within a species that were used in the toxicology, PK, and pharmacology studies, the expected effective exposure (AUC) in humans is approximately 3 mg TAK-653 and 0.5 mg TAK-653 based on rat and monkey PK data, respectively. The effective AUC<sub>24</sub> in rat has an 85-fold margin to the NOAEL AUC<sub>24</sub> in the monkey. Based on the current data package and all analyses, the recommended starting dose is 0.3 mg (safety factor 20), which is lower than that which was efficacious in rat (HED utilizing BSA conversion is 1 mg).

In the current study, a blinded review of the preliminary safety and tolerability data for Part 1 SRD Cohorts 1 through 5 and Part 2 SRD/MRD Cohorts 1 and 2 indicate that TAK-653 was generally well tolerated at single doses up to 9 mg and multiple doses up to 1 mg QD. Preliminary PK data from these cohorts indicate that TAK-653 exhibits linear PK across the dose range tested. For SRD Cohort 5 (9 mg), the C<sub>max</sub> (mean [range]=69.5 [55.1-85.8] ng/mL) remained below the mean C<sub>max</sub> value (CCI) in female monkeys at the NOAEL of 3 mg/kg/day in the 13-week repeat-dose toxicity study. CCI

For SRD/MRD Cohort 2 (1 mg), the C<sub>max</sub> (mean [range]=24.9 [14.7-34.9] ng/mL) and AUC<sub>24</sub> (mean [range]=503 [256-741] h\*ng/mL) after multiple-dose administration (on Day 18) remained several fold below the mean C<sub>max</sub> and AUC<sub>24</sub> values in female monkeys at the NOAEL.

In the aforementioned monkey toxicity study, test article-related toxicities occurred around t<sub>max</sub>, typically within the first few days of dosing, and were considered to be related to the C<sub>max</sub> rather than to the AUC<sub>24</sub>. Therefore, given the favorable preliminary safety/tolerability and PK data for the TAK-653 doses administered to date, further dose escalation is considered to be justified. The predicted C<sub>max</sub> value for the TAK-653 dose selected for any cohort should not exceed mean exposures at the monkey NOAEL (Day 1 C<sub>max</sub>=CCI Day 91 AUC<sub>24</sub>=CCI

### 6.2.3 Endpoints

The primary endpoints for this study are the composite of safety variables to determine tolerated doses and dose-limiting effects of TAK-653. The secondary endpoints are standard PK variables of TAK-653 to determine drug exposure at each dose and facilitate dose escalations.

CCI



#### **6.2.4 Risk Mitigation**

TAK-653, like other AMPA receptor potentiators, may induce convulsions through the over activation of AMPA receptors [16]. Other potential risks associated with AMPA receptor potentiators include tremors, anxiety and insomnia. Based on TAK-653 nonclinical findings, the key risks associated with TAK-653 are convulsions, tremors, vomiting, reduced heart rate, and decreased locomotor activity.

Because Study TAK-653-1001 represents the first time that TAK-653 is being administered to humans, anticipated risks are based on the mode of action of TAK-653, nonclinical findings, dose-limiting toxicities, and human experience with other AMPA receptor potentiators. These potential risks have been considered when designing this study by excluding subjects at predictable risk of seizures, minimizing the number of subjects exposed at any one time at each dose level, following strict escalation criteria between Cohorts, and setting conservative stopping rules.

### **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.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a significant change in the known risk/benefit profile for the drug, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Study-specific criteria for terminating the study:
  - a) Subjects in more than 1 cohort have met Cohort Stopping Criteria.
  - b) Any subject in any cohort experiences signs or symptoms of a tremor. (Subjects may not be dosed in this cohort at the same or higher dose level. However, dosing may be resumed at a lower dose level.)

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 that point.



### Cohort Stopping Criteria

If any of the following criteria occur, subsequent subjects in the same Cohort may not be given the same dose or a higher dose although dosing may be resumed at a lower dose.

1. Any subject experiences any of the Takeda Medically Significant events ([Table 10.a](#)).
2. An SAE or 2 severe or clinically significant AEs occur that can be considered related to TAK-653. This includes drug-related CNS disorders/AEs, including but not limited to motor, sensitive, cognitive, or sleep abnormalities detected during the course of the study.
3. Any subject develops a tremor (resting or otherwise) that is associated with EEG changes suggestive of seizures, or more than 1 subject in a Cohort develops a tremor without EEG changes suggestive of seizures.
4. Any subject develops QT prolongation on a postdose ECG, defined as a QT interval with Fridericia correction method (QTcF) > 500 msec or > 60 msec change from baseline.
5. Any subject develops bradycardia (heart rate of  $\leq 40$  bpm) on scheduled assessments only (ie, not on telemetry) or a reduction in heart rate of 30 bpm from baseline.
6. Any subject has abnormal liver function:
  - a) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations  $> 5 \times$  upper limit of normal (ULN) in the absence of a concomitant bilirubin increase.
  - b) ALT and/or AST elevations  $> 3 \times$  ULN in the presence of a total bilirubin increase  $> 2 \times$  ULN or an international normalized ratio (INR)  $> 1.5$  without findings of cholestasis or other alternate etiology to explain the elevations (ie, “Hy’s Law cases”).
  - c) ALT and/or AST elevations  $> 3 \times$  ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ( $> 5\%$ ).

#### 6.3.2 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.

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

In the event that the sponsor, an independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by 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 at Screening and at Check-in (Day -1).

### 7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures including requesting that a subject fast for any laboratory evaluations.
3. The subject is a healthy adult male or female.
4. The subject is aged 18 to 55 years, inclusive at the time of consent.
5. The subject weighs at least 45 kg (99 lb) and has a body mass index (BMI) between 18.0 and 30.0 kg/m<sup>2</sup>, inclusive at Screening.
6. A male subject who is nonsterilized\* and sexually active with a female partner of childbearing potential\* agrees to use adequate contraception\* from signing of informed consent throughout the duration of the study and for 90 days after 5 half-lives have elapsed since last dose of study drug. This should be interpreted as 90 days from the Follow-up Call/Visit unless data indicates otherwise.
7. A female subject of childbearing potential\* who is sexually active with a nonsterilized\* male partner agrees to routinely use highly effective contraception with low user dependency\* from signing of informed consent, throughout the duration of the study, and for 30 days after 5 half-lives have elapsed since the last dose of study drug. This should be interpreted as 30 days from the Follow-up Call/Visit unless data indicates otherwise.

<p>*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.</p>
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### 7.2 Exclusion Criteria

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

1. Subject has received any investigational compound within 90 days prior to the first dose of study drug.
2. 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. Subject has any clinically significant illness, such as cardiovascular, neurologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine, or psychiatric disease or disorder, or other abnormality, which may affect safety, increase risk of seizure or lower the seizure threshold, or potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the Takeda Medical Monitor may be warranted.
4. Subject has a known hypersensitivity to any component of the formulation of TAK-653.
5. Subject has a positive urine/blood result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in (Day -1).
6. Subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
7. Subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications and Dietary Products table (listed in [Table 7.a](#)).
8. Subject is pregnant or lactating or intending to become pregnant before, during, or within 30 days after 5 half-lives have elapsed since the last dose of study drug (ie, 30 days from the Follow-up Call/Visit unless available data indicates otherwise); or intending to donate ova during such time period.
9. If male, subject intends to donate sperm during the course of this study or within 90 days after 5 half-lives have elapsed since the last dose of study drug. This should be interpreted as 90 days from the Follow-up Call/Visit unless data indicates otherwise.
10. Subject has had previous episodes of seizures or convulsion (lifetime), including absence seizure and febrile convulsion.
11. Subject or any immediate family member has a history of epilepsy (including febrile convulsions).
12. Subject has a history of neurological abnormalities including abnormal EEG at screening or brain injury including traumatic injury, perinatal cerebropathy and postnatal brain damage, blood-brain barrier abnormality, and angioma cavernous.
13. Subject has a history of cerebral arteriosclerosis.
14. Subject has a condition that can potentially reduce drug clearance (eg, renal or hepatic insufficiency).
15. 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, any surgical intervention known to impact absorption [eg, bariatric surgery or bowel resection], esophageal reflux, peptic ulcer disease, erosive esophagitis, or frequent [more than once per week] occurrence of heartburn).

16. Subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Check-in (Day 1).
17. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or a known history of human immunodeficiency virus (HIV) infection at Screening.
18. Subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 28 days prior to Check-in Day -1. Cotinine test is positive at Screening or Check-in (Day -1).
19. Subject has poor peripheral venous access.
20. Subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days prior to first dose of study drug.
21. Subject has a Screening or Check-in (Day -1) abnormal (clinically significant [CS]) ECG. Entry of any subject with an abnormal (not clinically significant [NCS]) ECG must be approved, and documented by signature of the principal investigator or medically qualified subinvestigator. In the case of a QTcF interval >450 ms or >480 ms (subjects with Bundle Branch Block) or PR outside the range of 120 to 220 ms, assessment may be repeated once for eligibility determination at the Screening Visit and/or Check-in (Day -1) Visit.
22. Subject has a supine blood pressure outside the ranges of  $\geq 90$  to  $\leq 140$  mm Hg for systolic and  $\geq 50$  to  $\leq 90$  mm Hg for diastolic. If out of range, assessment may be repeated once for eligibility determination at the Screening Visit and/or Check-in (Day -1).
23. Subject has a resting heart rate outside the range of 50 to 90 bpm (not on ECGs). If out of range, the assessment may be repeated once for eligibility determination at the Screening Visit and/or Check-in (Day -1).
24. Subject has abnormal Screening or Check-in (Day -1) laboratory values that suggest a clinically significant underlying disease or subject has the following lab abnormalities: ALT and/or AST >1.5 ULN.
25. Subject has a risk of suicide per the C-SSRS (a score of 4 or 5 on ideation or any suicidal behavior) or according to the investigator's clinical judgment, has made a suicide attempt in the previous 6 months, or has a history of deliberate self-harm in the past 6 months.

Additional exclusion criteria for CCI collection in SRD/MRD Cohort 3:

26. The subject has had CCI collected within 6 months prior to Check-in (Day -1).
27. The subject has a known hypersensitivity to the anesthetic or its derivatives used during CCI collection or any medication used to prepare the area of lumbar puncture.
28. The subject has any skin condition, abnormality of the lumbar spine, medical or surgical condition that would preclude lumbar puncture (eg, coagulopathy, local or systemic infection,

left ventricular outflow obstruction, aortic stenosis, raised intracranial pressure, previous back surgery).

### 7.3 Excluded Medications, Dietary Products

Use of the agents in [Table 7.a](#) (prescription or nonprescription) is prohibited from the time points specified until subject is discharged from the unit.

**Table 7.a Prohibited Medications and Dietary Products**

28 days prior to Check-in (Day -1)	7 days prior to Check-in (Day -1)	72 hours prior to Check-in (Day -1)
Prescription medications	OTC medications (a)	Products containing caffeine or xanthine
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	poppy seeds
Immunization/Vaccines (b)	Foods or beverages containing grapefruit or grapefruit juice, star fruit or star fruit juice, 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)		

OTC=over-the-counter.

(a) Occasional use of acetaminophen/paracetamol ( $\leq 1$  g/day) or other medication as approved by Takeda on a case-by-case basis is allowed. Prohibition and approval on case-by-case basis may both be acceptable terms.

(b) Inclusive of but not limited to H1N1 and other flu vaccinations.

(c) Omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine. Subjects 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 clinic for the duration of each treatment period (see SRD [Figure 6.a](#) and SRD/MRD [Figure 6.b](#)).

During the confinement period, subjects will be given a menu for the dosing period that includes 3 meals and an evening snack, each containing approximately 30% fat (relative to the total calories). The meals served on the PK assessment days should be identical for each cohort in the study. The study menu should be recorded and submitted to the study file with a copy provided to

the sponsor prior to the start of the study. Record whether the meal was fully consumed, or, if not, record the percentage consumed (0, 25%, 50%, 75%).

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

During the SRD Cohorts, except the fed portion of the food effect study, TAK-653 and placebo will be administered on Day 1 with 240 mL of water after a fast of at least 10 hours. Subjects will continue to fast for an additional 4 hours after dosing. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. Subjects do not have to fast on days when no dosing is scheduled.

During the food effect phase of the study, subjects should fast overnight for at least 10 hours and should start the recommended high-fat, high-calorie meal 30 minutes prior to administration of the drug. Subjects should complete the meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. The recommended high-fat, high-calorie meal will consist of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. The clinical site may make minor modifications to the high-fat, high-calorie meal as long as the same meal is served to all subjects and the meal meets the high-fat criteria together with comparable meal volume and viscosity. The clinical site will document the amount of protein, carbohydrate, 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, whether fully consumed or, if not, what percentage was consumed will also be recorded on the electronic case report form (eCRF).

For single and multiple dosing in the SRD/MRD Cohorts, TAK-653 and placebo will be administered in the morning on Day 1 and Days 6 through 18 with 240 mL of water after a fast of at least 10 hours. Food may be consumed approximately 2 hours after dosing. Subjects may consume water ad libitum with the exception of 1 hour before and 1 hour after drug administration. Subjects do not have to fast when no dosing is scheduled.

#### collection - SRD/MRD Cohort 3 only

On SRD/MRD Day 12, the 1-hour predose vitals will be collected supine and standing. The vitals at 15 minutes, 30 minutes, and 1 hour post-lumbar puncture will be collected supine only. After the procedure, the subject will be observed by staff and will preferably lie in the supine position for 1 hour—at the investigator's discretion for up to 4 hours if necessary. Subjects may also rest comfortably in a seated or semirecumbent position at the investigator's discretion.

#### All Cohorts

Subjects will remain upright (seated, standing, or ambulatory) for 4 hours following dose administration, except as necessitated by the occurrence of an AE/or study procedures (eg, obtaining 12-lead ECG). Subjects will refrain from strenuous and/or unaccustomed exercise throughout the entire course of the study.

## 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 drug should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.19.

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

Study drug 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 9.1.8), if any of the following circumstances occur at any time during study drug treatment:

- ALT or AST  $>8 \times$  ULN.
  - ALT or AST  $>5 \times$  ULN and persists for more than 2 weeks.
  - ALT or AST  $>3 \times$  ULN in conjunction with elevated total bilirubin  $>2 \times$  ULN or INR  $>1.5$ .
  - ALT or AST  $>3 \times$  ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ( $>5\%$ ).
3. Significant protocol deviation. The discovery after randomization or after the first dose of study drug 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.
  4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
  5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) 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. Withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category.

6. Study termination. The sponsor, IEC, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

8. Other. The specific reason(s) should be recorded in the "specify" field of the eCRF.

## **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. Discontinued or withdrawn subjects may be replaced (see Section 8.2).

## **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**

In this protocol, the term study drug refers to all or any of the drugs defined below.

TAK-653 tablets will be provided in the following strengths:

- 0.1 mg.
- 0.25 mg.
- 1 mg.
- 5 mg.
- Matching placebo tablets.

##### *8.1.1.1 Sponsor-Supplied Drug*

TAK-653 study drug will be supplied as 0.1, 0.25, 1, and 5 mg, and matching placebo as round, yellow-red film-coated tablets. TAK-653 drug product is manufactured by Takeda Pharmaceutical Company Ltd., Osaka, Japan.

TAK-653 tablets will be supplied in amber glass bottles with metal screw caps. Each bottle will contain 50 tablets.

Each bottle of TAK-653 active or placebo will bear a single-panel label that includes pertinent study information.

#### **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. A daily temperature log of the drug storage area must be maintained every working day.

#### **8.1.3 Dose and Regimen**

The planned initial dose of TAK-653 for SRD Cohort 1 is 0.3 mg. Doses for subsequent cohorts will be determined based on the safety, tolerability, and available PK and PD data of previous cohorts. The doses will be administered to the subjects by the investigator or investigator's designee.



#### 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 tear-off portion of the medication label will be affixed to the Dispensing Log. The Randomization Sequence Number will be entered onto the eCRF.

For each dosing cohort in both SRD and SRD/MRD parts, randomized subjects will be assigned a 4-digit randomization number in the order which they are enrolled. Randomization sequence numbers will be XY01 to XY08, where X refers to SRD (part 1) or SRD/MRD (part 2) and Y refers to Cohort number.

For example:

- Subjects in SRD Cohort 1 will have randomization sequence numbers 1101 to 1108 and subjects in SRD Cohort 2 will have numbers 1201 to 1208.
- Subjects in SRD/MRD Cohort 1 will have randomization sequence numbers 2101 to 2108 and subjects in SRD/MRD Cohort 2 will have numbers 2201 to 2208.

In case a subject needs to be replaced, the replacement subject should receive the same treatment that the subject being replaced would have received. The replacement randomization numbers will be XX1X. For example, subject 1211 will replace subject 1201 with the same treatment. No replacement randomization schedule will be generated.

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

### **8.3 Randomization Code Creation and Storage**

The randomization schedule will be generated by Takeda's Analytical Sciences Department and 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.

At the completion of SRD/MRD Cohort 3 onward, Takeda nonstudy personnel may be unblinded (with the exception of the site monitor) for a preliminary review of the safety, PK, and PD data. The investigator and subjects will remain blinded until the completion of the study.

### **8.5 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 should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by contacting the dispensing pharmacist. Code break envelopes will be supplied for emergency unblinding when the pharmacist is unavailable.

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.

### **8.6 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 drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to 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 faxing 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. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry dates 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(s) 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 dosing for SRD portion and Days 1 and 4 to 16 dosing for MRD portion, and following dosing to ensure all subjects received the correct dose of study drug.

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 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 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, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

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 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 Schedule of Study Procedures for SRD Part 1 Cohorts 1 to 5 is located in [Appendix A](#), for SRD Part 1 Cohort 6 onward is located in [Appendix B](#), and for SRD/MRD Part 2 is located in [Appendix C](#).

#### 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.

A unique subject identification number (subject ID=site + 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

CCI

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#### 9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include age, sex, race as described by the subject, height, weight, caffeine consumption, 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 under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see [Section 9.1.7](#)).

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

#### 9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) lymph nodes; (10) genitourinary, and (11) a complete neurological examination (details are provided in [Appendix G](#)).

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 9.1.7.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the first dose of the investigational drug in each cohort 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 is kilograms (kg) with 1 decimal place. BMI should be derived as:

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

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

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<sup>2</sup>. However, if the BMI is used as entry criteria, then this determination must be made after rounding.

#### 9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral), supine blood pressure (resting more than 5 minutes), respiration rate, and heart rate. Heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing. Vital signs will be collected according to the schedule shown in Table 9.a. When 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.

Vital signs may be repeated. All measurements will be recorded on the source documents and in the eCRF. Vital signs taken as safety measures (not protocol-specified) will be recorded as unscheduled.

**Table 9.a Schedule for Vital Signs Assessments**

Vital Signs	Day	Schedule of Assessments
<b>SRD</b>		
Oral temperature, respiration, heart rate (a, b), and blood pressure (a)	Screening, Check-in (Day -1)	
	1	Predose (within 50 minutes prior to dosing), and at 1, 2, 4, 6, 8, 10, 12, and 16 hours postdose.
	2-6, ET, Day 7 (Study Exit)	On rising or early termination
	14 ( $\pm 2$ )	As appropriate, if the subject must return to the site for a follow-up visit.
<b>SRD/MRD</b>		
Oral temperature, respiration, heart rate (a, c), and blood pressure (a)	Screening, Check-in (Day -1)	As appropriate
	1, 6-18	Predose (within 30 minutes prior to dosing), and at 1, 6, and 12 hours postdose.
	2-5, 19-20, ET, 21 (Study Exit)	As appropriate
	31 ( $\pm 2$ )	As appropriate, if the subject must return to the site for a follow-up visit.

(a) Heart rate and blood pressure will be measured after 5 minutes supine and again 1 and 3 minutes after standing.

(b) SRD heart rate will also be obtained on dosing Day 1 at 0.5 and 1.5 hours postdose.

(c) SRD/MRD heart rate will also be obtained on the days of dosing (Day 1 and Days 6-18) at 0.5, 1.5, and 2 hours postdose.

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

#### 9.1.6 Documentation of Concomitant Medications

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

#### 9.1.7 Documentation of Concurrent Medical Conditions

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

### 9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken following a minimum 10-hour overnight fast on the days stipulated in the Schedule of Study Procedures for SRD Part 1 ([Appendix A](#) and [Appendix B](#)) and SRD/MRD Part 2 ([Appendix C](#)).

[Table 9.b](#) lists the tests that will be obtained for each laboratory specimen.

**Table 9.b Clinical Laboratory Tests**

Hematology	Serum Chemistry	Urinalysis
Red blood cells (RBC)	ALT	pH
White blood cells (WBC)	Albumin	Specific gravity
with differential (absolute counts)	Alkaline phosphatase	Protein
Hemoglobin	AST	Glucose
Hematocrit	Total bilirubin	Blood
Platelets	Direct bilirubin	Nitrite
PT/INR	Total protein	Leukocyte esterase
aPTT	Creatinine	Ketones
	Blood urea nitrogen	Bilirubin
	Creatine kinase	Urobilinogen
	$\gamma$ -Glutamyl transferase (GGT)	
	Potassium	
	Sodium	
	Glucose	
	Chloride	
	Bicarbonate	
	Calcium	
<b>Diagnostic Screening:</b>		
<b>Serum</b>	<b>Urine/Blood</b>	
HIV test	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine. (c)	
Hepatitis panel, including HBsAg and anti-HCV		
Female subjects: serum hCG (a)		
Female subjects, if menopause is suspected and not surgically sterile: FSH (b)	Female subjects: urine hCG (a).	

aPTT=activated partial thromboplastin time, FSH=follicle-stimulating hormone, hCG=human chorionic gonadotropin.

(a) Serum hCG pregnancy test will be done at Screening and Study Exit/Early termination, and at the Follow-up Visit if the subject is brought back to the clinic for re-evaluation. Urine hCG pregnancy test will be done at Check-in (Day -1).

(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (ie, no menses for 12 months without an alternative medical cause) and not surgically sterile. The result must be >40 IU/L for the subject to be enrolled.

(c) To be performed at Screening and Check-in Day -1.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to Takeda or designee in the format requested by Takeda.



If subjects experience ALT or AST  $>3 \times \text{ULN}$ , follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST  $>3 \times \text{ULN}$  in conjunction with total bilirubin  $>2 \times \text{ULN}$ .)

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

The investigator or designee is responsible for transcribing or attaching laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the 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 Telemetry

In the SRD Part 1, continuous cardiac monitoring (telemetry) will be performed from dosing on Day 1 through to approximately 36 hours postdose.

#### 9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 90 days after 5 half-lives have elapsed since the last dose of study drug (ie, 90 days from the Follow-up Call/Visit unless data indicates otherwise), 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.

From signing of informed consent, throughout the duration of the study, and for 30 days after 5 half-lives have elapsed since the last dose of study drug (ie, 30 days from the Follow-up Call/Visit unless data indicates otherwise), female subjects of childbearing potential\* who are sexually active with a nonsterilized male partner\*\* must use highly effective contraception ( $<1\%$

failure rate/year), which has low user dependency. In addition they must be advised not to donate ova during this period.

\*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study drug 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.

A highly effective method of contraception for women of child bearing potential is defined as one that has no higher than a 1% failure rate per year. The acceptable methods of contraception are:

- Intrauterine device (IUD).
- Bilateral tubal occlusion.
- Vasectomized partner (provided that the partner is the sole sexual partner of the trial participant and that the absence of sperm in the ejaculate has been confirmed).
- Sexual abstinence if it is the preferred and usual lifestyle of the subject. Subjects practicing abstinence as a method of contraception must refrain from heterosexual intercourse throughout the duration of the study and for 30 days (females) or 90 days (males) after 5 half-lives have elapsed since the last dose of the study drug. This should be interpreted as 30 days (females) or 90 days (males) from the Follow-up Call/Visit unless available data indicates otherwise.

The use of hormonal contraceptives is not recommended for TAK-653 studies as there is currently no data on possible drug-drug interactions between TAK-653 and hormonal contraceptives.

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

Serum hCG pregnancy tests must be conducted for all female subjects at Screening and Study Exit/Early Termination. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study drug (eg, at Check-in Day -1).

During the course of the study, subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures.

See [Appendix A](#) and [Appendix B](#) (SRD cohorts) and [Appendix C](#) (SRD/MRD cohorts) for the schedules for these procedures.

#### 9.1.11 Pregnancy

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 for 12 weeks after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, eg, within 12 weeks of the last dose of active study drug, 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 subject or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/male partner of the subject was participating in a clinical study at the time the woman 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

Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF. QTcF may also be calculated manually by the site.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position and should have an approximate 10-minute rest period prior to ECG recordings. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

ECGs will be read automatically and the investigator or subinvestigator will also manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source.

The schedule for ECG assessments in the SRD part of the study is shown in [Appendix A](#) and [Appendix B](#) and in the SRD/MRD part of the study is shown in [Appendix C](#). When an ECG is scheduled at the same time as blood draws or vital signs, the blood draws and vital signs will take priority and the ECG will be obtained within 0.5 hours 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.

Additional unscheduled ECGs may be recorded where clinically necessary for subject safety. For eligibility determination, ECGs may be repeated once at Screening and/or Day -1.

#### 9.1.13 Safety EEG Procedure

EEG data will be collected in a resting state with eyes open and closed, with photic stimulation, and with 3 minutes hyperventilation. EEG time may be adjusted in consultation with the PI and sponsor, and based on emerging PK or other data. When an EEG is scheduled at the same time as blood draws, the blood draws will take priority and the EEG will be obtained within 2 hours before or after the scheduled blood draw and/or vital sign assessment.

EEGs will be evaluated by a qualified individual for clinically significant abnormalities. Findings will be categorized as (1) within normal limits, (2) abnormal but not clinically significant, or (3) clinically significant abnormal. Abnormal EEG findings should be described. If a subject has a tremor during the study, an EEG must be conducted as soon as possible.

Prior to randomization, EEG reports must be reviewed by the investigator. Descriptive text reports will be provided for all screening and postdose EEGs. A subject with an EEG categorized as significantly abnormal during screening will not be eligible for randomization. To aid with EEG interpretation, video recordings and live streams of the volunteers' faces may be done during the EEG, at the investigator's and/or qualified individual's discretion.

A study manual of EEG assessments will be prepared and provided to the site before the start of the study. The EEG study manual will be stored with the study file.

#### 9.1.14 CCI

CCI

CCI

9.1.14.1 CCI

CCI

9.1.14.2 CCI

CCI

9.1.14.3 CCI

CCI

Instructions for collecting, processing, and shipping of samples are provided in the laboratory manual.

### 9.1.15 Pharmacokinetic Sample Collection

#### 9.1.15.1 Collection of Plasma and Urine for Pharmacokinetic Sampling

Blood and urine samples will be collected for the determination of concentrations of TAK-653, CCI Urine samples will only be collected for the SRD/MRD Cohorts. The

sampling schedule may change based on emerging data but will not exceed the number of planned samples.

Serial blood and urine samples for determination of plasma and urinary concentrations of TAK-653 and its metabolites will be collected according to [Table 9.c](#). The actual time of sample collection will be recorded on the source document and eCRF.

**Table 9.c Collection of Blood and Urine Samples for Pharmacokinetic Analysis**

Sample Type	Dosing Day	Time Postdose (hours)
<b>SRD (Cohorts 1-5)</b>		
Plasma	1	Predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours postdose.
<b>SRD (Cohort 6 onward)</b>		
Plasma	1	Predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose.
<b>SRD/MRD (All cohorts)</b>		
Plasma	1	Predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 (a) hours postdose.
Plasma	6	0.5, 1, 2, 4, 6, 8, 12, 16, and 24 (b) hours postdose.
Plasma	12,14, 16	Predose (within 15 minutes of dosing) (and following <b>CCI</b> collection procedure on Day 12, SRD/MRD Cohort 3 only).
Plasma	18	Predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose.
Urine	1	Predose (-12 to 0 hours) and at (0 to 6), (6 to 12), (12 to 24), (24 to 48), and (48 to 72) hour intervals postdose.
Urine	18	(0 to 6), (6 to 12), and (12 to 24) hour intervals postdose.

(a) The 120-hour sample must be collected before dosing on Day 6.

(b) The 24-hour sample must be collected before dosing on Day 7.

Blood samples (one 4-mL sample per scheduled time) for PK analysis will be collected into chilled Vacutainers containing anticoagulant (K<sub>2</sub>EDTA) according to the schedules in [Appendix A](#), [Appendix B](#), and [Appendix C](#).

Blood samples for placebo will not be analyzed by the bioanalytical laboratory except for 2 samples per subject receiving placebo, 1 predose and the other around the expected time at which C<sub>max</sub> 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.

Urine samples will not be collected for the SRD cohorts. Urine samples in the SRD/MRD for subjects randomized to placebo will not be analyzed.

Instructions for collecting, processing, and shipping of samples are provided in the laboratory manual.

9.1.15.2

CCI

CCI

9.1.15.3 *Bioanalytical Methods*

Plasma and urine concentrations of TAK-653 and CCI and CCI concentrations of TAK-653 and CCI, if feasible, will be measured by high-performance liquid chromatography with tandem mass spectrometry.

Part of the archival plasma and urine samples will be sent to Takeda Pharmaceutical Company Limited (Japan) for potential analysis of unknown metabolite characterization, if appropriate.

**9.1.16 Pharmacokinetic Parameters**

The PK parameters of TAK-653, CCI 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 for plasma concentration values of TAK-653, CCI ( ):

Symbol/Term	Definition
<b>Plasma</b>	
$AUC_{24}$	Area under the plasma concentration-time curve from time 0 to 24 hours postdose.
$AUC_{\tau}$	Area under the plasma concentration-time curve during a dosing interval, where tau ( $\tau$ ) 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.
$AUC_{\infty}$	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty} = AUC_{last} + C_{last}/\lambda_z$
CCI	
CCI	
$C_{av,ss}$	Average plasma concentration at steady state, calculated as $AUC_{\tau}/\tau$ .
$C_{max}$	Maximum observed plasma concentration.
$C_{max,ss}$	Maximum observed steady-state plasma concentration during a dosing interval.
CCI	
$\lambda_z$	Terminal disposition phase 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.
$\tau$	Dosing interval.
CI	
$t_{max}$	Time of first occurrence of $C_{max}$ .
CCI	
CCI	
<b>Urine</b>	
CCI	



### 9.1.17 Pharmacodynamic Sample Collections

9.1.17.1 CCI

CCI

9.1.17.2 CCI

CCI

**Table 9.e Collection of Blood Samples for Analysis** CCI

Study Day	Time Points
SRD (Cohort 6 onward) and SRD/MRD (Cohort 3 onward)	
1	Predose and 4, 8, 12 hours postdose
2-5	24, 48, 72, 96 hours postdose
SRD/MRD (Cohort 3 onward)	
18	Predose and 4, 8, and 12 hours postdose
19	24 hours postdose

CCI

Note: A single dose is administered on Day 1. No additional doses are administered until Day 6 when QD dosing begins from Day 6 through 18.

CCI

he subjects will be required to consent to this additional analysis.

### 9.1.18 Pharmacodynamic Parameters

9.1.18.1 CCI

CCI

9.1.18.2 CCI

#### 9.1.19 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. If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were 2 separate subjects. Therefore the data should be entered as follows:

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

#### 9.1.20 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.

#### 9.1.21 Assessment of Suicidal Ideation and Behavior

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. The C-SSRS is composed of 3 questions addressing suicidal behavior and

5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject.

### **SRD**

The Screening/Baseline C-SSRS will be administered at Screening and Check-in (Day -1) and the Since Last Visit C-SSRS will be administered on discharge Day 5 and Study Exit Day 7 or Early Termination.

### **SRD/MRD**

The Screening/Baseline C-SSRS will be administered at Screening and Check-in (Day -1) and the Since Last Visit C-SSRS will be administered on Day 11, and Study Exit (Day 21) or Early Termination.

## **9.2 Monitoring Subject Treatment Compliance**

Study drug will be administered while subjects are under observation in the clinical research unit. Following administration of the study drug, 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 drug 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 schedule for all study-related procedures for all evaluations is shown in [Appendix A](#). Assessments should be completed at the designated visit/time point(s). Additional assessments may be conducted or timing of existing assessments may be amended based on emerging safety, PK or PD data.

### **9.3.1 Screening**

Subjects will be screened within 28 days prior to randomization, in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.19 for procedures for documenting screening failures.

Procedures to be completed at Screening (all cohorts) include the following:

- Informed consent.
- Inclusion/exclusion criteria.
- Demographics, medical history, and medication history.
- Physical examination (including a comprehensive neurological examination-details in [Appendix G](#)).

- Vital signs.
- Weight, height, and BMI.
- Concurrent medical conditions.
- Screening clinical laboratory tests.
- Hepatitis panel.
- FSH (postmenopausal women).
- Serum pregnancy test (hCG) (all female subjects).
- Pregnancy avoidance counseling.
- Urine drug screen and alcohol breathalyzer.
- ECG procedure.
- EEG assessments.
- C-SSRS (Baseline/Screening version).
- PTE assessment.

In the event that subjects have undergone general screening assessments (ie, panel screening) before the effective date of this protocol amendment, the data from this general screening may be used to assess subject eligibility for enrollment in this study, provided that the procedures were performed within the protocol-defined Screening Period window.

### 9.3.2 Check-In Procedures

Procedures to be completed at Check-in (Day -1) include the following:

#### SRD Cohorts

- Inclusion/exclusion criteria assessments.
- Physical examination, including complete neurological examination (see [Appendix G](#)).
- Vital signs.
- Weight.
- Concomitant medications.
- Concurrent medical conditions.
- Clinical Laboratory tests.
- Urine pregnancy test (hCG) (all female subjects).
- Urine drug screen.
- Alcohol breathalyzer.

- ECG.
- EEG.
- C-SSRS (Baseline/Screening version).
- PTE assessments.

#### **SRD/MRD Cohorts**

- Inclusion/exclusion criteria assessments.
- Physical examination, including complete neurological examination (see [Appendix G](#)).
- Vital signs.
- Weight.
- Concomitant medications.
- Concurrent medical conditions.
- Clinical laboratory tests.
- Urine pregnancy test (hCG) (all female subjects).
- Urine drug screen.
- Alcohol breathalyzer.
- ECG.
- C-SSRS (Baseline/Screening version).
- PK urine collection.
- PTE assessments.

#### **9.3.3 Treatment Phase**

Procedures to be completed during the treatment phase include the following:

##### **SRD Cohorts**

- Vital signs.
- Telemetry (36 hours postdose).
- Concomitant medications.
- Clinical laboratory tests (Days 1, 2, 5).
- ECG procedures (Days 1, 2, 5).
- CCI
- C-SSRS (Day 5) (Since Last Visit version).

- DNA (Day 1) and RNA (Days 1, 2) sample collections.
- PK blood collections.
- CCI blood collections (Days 1-5; SRD Cohort 6 onward only).
- Dispense study medication (Day 1).
- PTE assessments (Day 1 predose).
- AE assessments.

#### SRD/MRD Cohorts

- Vital signs.
- Concomitant medications.
- Clinical laboratory tests (Days 1, 6, 9, 12, 15, 18).
- ECG procedures (Days 1, 6, 9, 12, 15, 18).
- CCI
- C-SSRS (Day 11) (Since Last Visit version).
- DNA (Day 1) and RNA (Days 1 and 18) sample collections.
- PK blood collections (Days 1-7, 12, 14, 16, 18-19).
- CCI collections (Day 12, SRD/MRD Cohort 3 only).
- CCI blood collections (Days 1-5, 18, 19; SRD/MRD Cohort 3 onward only).
- PK urine collections (Days 1-4, 18-19).
- Dispense study medication (Day 1, Days 6-18).
- PTE assessments (Day 1 predose).
- AE assessments.

#### 9.3.4 Study Exit

Procedures to be completed by all Cohorts at Study Exit (SRD Cohorts 1-5 on Day 7, SRD Cohort 6 onward on Day 8, SRD/MRD on Day 21) include the following:

- Physical examination, including complete neurological examination (described in [Appendix G](#)).
- Vital signs.
- Weight.
- Concomitant medications.

- Clinical laboratory tests.
- Serum pregnancy test (hCG).
- Pregnancy avoidance counseling.
- ECG.
- EEG assessments.
- C-SSRS (Since Last Visit version).
- PK blood collections (SRD only).
- AE assessments.

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

### 9.3.5 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. All of the procedures listed in Section 9.3.4, Study Exit, should be performed with the following differences:

- EEG assessments should be performed at early termination.
- PK blood collection is not required at early termination in either SRD or SRD/MRD.

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

### 9.3.6 Follow-up Call/Visit

Follow-up assessments are scheduled to occur on Day 14 ( $\pm 2$  days) for SRD subjects and Day 31 ( $\pm 2$  days) for SRD/MRD subjects to inquire for any ongoing AEs or SAEs, worsening of AEs or SAEs, or development of new AEs or SAEs, and for concomitant medications taken since final dose.

Subjects with unresolved SAEs, CS laboratory abnormalities, ECG or physical examination findings or at the investigator's discretion should return to the clinic for appropriate repeat procedure(s). A follow-up phone call will be made to all other subjects on Day 14 ( $\pm 2$ ) for an assessment of AEs and concomitant medications.

### 9.3.7 End-of-Trial Date

The End-of-Trial date will be based on the final data collection date for the entire study, which is the date of the last Follow-up call/visit.

## 9.4 Blood Volume

Total blood sampling volume for an individual subject in the SRD Cohorts is shown in [Table 9.f](#).

**Table 9.f Approximate Blood Volume: SRD Cohorts 1 to 5**

Sample Type	Sample Volume (mL)	Number of Samples per Subject									Total Volume (mL)
		Screening	Study Day								
			-1	1	2	3	4	5	6	7	
Safety Laboratory (a)	10	1(b)	1	1	1	--	--	1	--	1	60 (110 for food-effect cohort)
PK	4	--	--	13	2	1	1	1	1	1	80 (160 for food-effect cohort)
CCI	6	--	--	1	--	--	--	--	--	--	6
CCI	2.5	--	--	6	2	--	--	--	--	--	20
Total Blood Sampling Volume (mL)											166 (296 for food-effect cohort)

-- = no samples collected.

(a) No blood is collected on Days 3, 4, and 6 for safety laboratory assessments.

(b) For the food effect cohort, blood will be collected for safety laboratory collections only once at Screening.

**Table 9.g Approximate Blood Volume: SRD Cohort 6 Onward**

Sample Type	Sample Volume (mL)	Number of Samples per Subject										Total Volume (mL)	
		Screening	Study Day										
			-1	1	2	3	4	5	6	7	8		
Safety Laboratory (a)	10	1	1	1	--	--	1	--	--	1	60		
PK	4	--	--	13	2	1	1	1	1	1	84		
CCI	4	--	--	4	1	1	1	1	--	--	32		
CCI	6	--	--	1	--	--	--	--	--	--	6		
CCI	2.5	--	--	6	2	--	--	--	--	--	20		
Total Blood Sampling Volume (mL)												202	

-- = no samples collected.

(a) No blood is collected on Days 3, 4, 6, and 7 for safety laboratory assessments.

The maximum volume of blood collected per subject on any single day is approximately 99 mL, and the approximate total volume of blood per subject in SRD Cohorts 1 to 5 is 166 mL and in SRD Cohort 6 onward is 202 mL. Subjects in the food effect cohort will have participated twice, once under fasted conditions and again under fed conditions. Therefore, the total volume of blood per subject in the food effect cohort will be approximately 296 mL. These totals do not include overage (eg, repeat samples, discard blood volume).

Total blood sampling volume for an individual subject in the SRD/MRD Cohorts is shown in [Table 9.h](#).



**Table 9.h Approximate Blood Volume: SRD/MRD Cohorts**

Sample Type	Sample Volume (mL)	Screening	Number of Samples per Subject															Total Volume (mL)
			Study Day															
			-1	1	2	3-5	6	7	9	12	14	15	16	18	19	21		
Safety Laboratory	10	1	1	1	-	-	1	-	1	1	--	1	--	1	--	1	90	
PK	4	--	--	13	2	3	9	1	--	2 (a)	1	-	1	13	1	--	184	
CCI (b)	4	--	--	4	1	3	--	--	--	--	--	--	--	4	1	--	52	
CCI	6	--	--	1	-	-	-	-	--	--	--	--	--	--	--	--	6	
CCI	2.5	--	--	2	-	-	-	-	--	--	--	--	--	2	--	--	10	
Total Blood Sampling Volume (mL)																	342	

-- = no samples collected.

(a) An additional PK sample will be taken following the CCI collection procedure in SRD/MRD Cohort 3 only.

(b) Collected only for SRD/MRD Cohort 3 onward.

The maximum volume of blood collected per subject on any single day in the SRD/MRD is approximately 89 mL and the approximate total volume of blood collected per subject is 342 mL. These totals do not include overage (eg, repeat samples, discard blood volume).

Direct venipuncture is the preferred method of blood collection. Any other method will need to be approved by Takeda. If an intravenous cannula with a normal saline flush is used, the total blood volume does not include discarded blood from predraws (assuming approximately 3 mL of blood is discarded each time a sample is collected from an intravenous cannula).

## **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 drug; it does not necessarily have to have a causal relationship with study participation.

#### **10.1.2 AEs**

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

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

#### **10.1.3 Additional Points to Consider for PTEs and AEs**

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug 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 PTE(s) or as 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 drug) or an AE (worsening or complication occurs after start of study drug). 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 drug, 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 drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).

Changes in severity of AEs/Serious PTEs:

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

Preplanned surgeries or procedures:

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

worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Overdose:

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

#### 10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
3. 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.
4. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
5. Results in persistent or significant DISABILITY/INCAPACITY.
6. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
7. 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**

Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes /ventricular fibrillation /ventricular tachycardia	Acute liver failure
Malignant hypertension	Anaphylaxis
Convulsive seizure	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected endotoxin shock
Neuroleptic malignant syndrome / malignant hyperthermia	Confirmed or suspected transmission of infectious agent by a medicinal product
	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 Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

Based on nonclinical data to date and AMPA receptor potentiator class effects, the AESIs for this study are:

- Tremors.
- Convulsions.

#### 10.1.6 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.

### 10.1.7 Causality of AEs

The relationship of each AE to study drug(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.  |

### 10.1.8 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.

### 10.1.9 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.

### 10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

### 10.1.11 Frequency

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

### 10.1.12 Action Concerning Study Drug

Drug withdrawn – a study drug is stopped due to the particular AE.

Dose not changed – the particular AE did not require stopping a study drug.

Unknown – only to be used if it has not been possible to determine what action has been taken.

Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.

- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

### 10.1.13 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 are considered 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 will continue until the subject is first administered study drug or until screen failure. For subjects who discontinue prior to study drug 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 drug. Routine collection of AEs will continue for 30 days after the last dose of study drug.

#### 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 drug 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:

- Event term.
- Start and stop date and time.
- Frequency.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study drug (not applicable for PTEs).
- Outcome of event.
- Seriousness.

#### *10.2.1.3 AESI Reporting*

If an AESI that occurs during the treatment period or the follow-up period is considered clinically significant based on the criteria below, it should be recorded in an AESI Form or an SAE Form. The Form should be completed and reported to the clinical contract research organization (CRO)/Pharmacovigilance (PV) department within 24 hours.

AESI / abnormality criteria include:

- Laboratory value threshold, if applicable.
- Premature termination for the AESI, if applicable.
- Tremors.
- Convulsion.

The standard query form in the eCRF is to be completed for tremors and convulsions. All other AESIs must be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.



### 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 drug(s).
- Causality assessment.

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

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

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

### 10.2.3 Reporting of Abnormal Liver Function Tests

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

If a subject is noted to have ALT or AST  $>3 \times \text{ULN}$  and total bilirubin  $>2 \times \text{ULN}$  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 9.1.8 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, IEC, and Regulatory Authorities**

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and the IEC, in accordance with national regulations in the country 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 within 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 the IEC in accordance with national regulations.

## **11.0 STUDY-SPECIFIC COMMITTEES**

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

Takeda (at a minimum, the clinical science representative, clinical pharmacologist, and pharmacovigilance physician) and the Principal Investigator will review the safety and tolerability data and available PK data for each Cohort prior to dosing an additional Cohort. The decision for the subsequent dose must be agreed upon by all representatives of Takeda and the Principal Investigator. If any one person has concerns regarding subsequent dosing then this acts as veto and the decision not to proceed with an additional Cohort will be escalated to management.

## **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. Data are transcribed directly onto the eCRFs.

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

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

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), 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 Council for 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 database lock. 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

##### 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.

##### PD Set

The PD set will consist of all subjects who receive study drug and have at least 1 postdose PD measurement.

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.

#### 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-653 dose level, TAK-653 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-653 dose level, TAK-653 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

##### 13.1.3.1 Concentrations in Plasma, Urine, and CCI

The concentration of TAK-653, CCI ) in plasma and urine (urine collected in SRD/MRD Cohorts only) will be summarized by Day, period (fasted vs fed) and dose level over

each scheduled sampling time using descriptive statistics. Individual plasma concentration data vs time will be presented in a data listing.

The concentrations of TAK-653 and CCI in CCI if available, will be presented in a listing for SRD/MRD Cohort 3 only. The ratio of TAK-653 concentration in plasma to the concentration in CCI on Day 12 will be presented.

#### 13.1.3.2 PK Parameters

Descriptive statistics (N, arithmetic mean, SD, median, minimum, maximum and percent coefficient of variation [%CV]) will be used to summarize the plasma and urine PK parameters for TAK-653, CCI by Day, period (fasted vs fed) and dose level. In addition, geometric mean and CV will be computed for  $C_{max}$  and AUCs.

Dose proportionality will be tested for TAK-653  $C_{max}$  and AUCs using a power model. For the SRD part, data from the SRD fed Cohort will not be included in the power model. For the SRD/MRD cohorts, the power model will be run after multiple dosing only. The power fit will be assumed as described by the following equation:

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

where  $\beta_0$  is the intercept and  $\beta_1$  is the slope. The dose proportionality would be declared when the

90% CI for  $\beta_1$  lies entirely within the critical region  $\left(1 + \frac{\ln(0.80)}{\ln(r)}, 1 + \frac{\ln(1.25)}{\ln(r)}\right)$ , where r is the ratio of the highest and the lowest dose in this study. This criterion implies that the 90% CI for the ratio of the central values of PK parameter of interest from the highest dose to the lowest dose is contained completely within the bioequivalence range of (0.80, 1.25). Plots of  $\ln(AUC)$  or  $\ln(C_{max})$  vs  $\ln(Dose)$  may also be used to illustrate dose proportionality or lack of it.

A more detailed analysis will be presented in the SAP.

#### 13.1.4 Pharmacodynamic Analysis

CCI

### 13.1.5 Safety Analysis

All safety data will be presented in listings. Where applicable, within each part, safety data will be summarized by placebo, each TAK-653 dose level, TAK-653 overall, and overall total. Placebo data will be pooled across cohorts within each part. These summaries will not contain data from the fed portion. Data from the food effect cohort will be summarized separately by placebo fed, placebo fasted, TAK-653 fed, and TAK-653 fasted.

### 13.1.6 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. TEAEs with onset occurring within 30 days (onset date – last date of dose +1≤30) after study drug administration will be listed, and included in the summary tables. TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs not-related), severity of AEs and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

#### 13.1.6.1 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal value (MAV) criteria to be defined in the SAP will be listed and summarized. Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized. All clinical laboratory data will be listed.

#### 13.1.6.2 Vital Signs

Individual results of vital signs that meet Takeda's MAV criteria to be defined in the SAP will be listed and summarized. Observed values and changes from Baseline in vital sign measurements (systolic and diastolic blood pressure, heart and respiratory rate, and oral temperature) will be summarized. All vital signs data will be provided in the data listings.

#### 13.1.6.3 ECGs

Individual results of ECG parameters that meet Takeda's MAV criteria to be defined in the SAP will be listed and summarized. Observed values and changes from Baseline in ECG parameters will be summarized. All vital signs data will be provided in the data listings.

Shift tables will be generated for the investigator's ECG interpretations by above group. All ECG data will be provided in the data listings.

#### 13.1.6.4 Safety EEGs

All screening and postdose safety EEG assessments will be listed. A shift table will summarize the number of subjects who changed status from Baseline.



### **13.2 Interim Analysis and Criteria for Early Termination**

No interim analysis is planned.

### **13.3 Determination of Sample Size**

The sample size chosen of 8 subjects in each Cohort (6 active: 2 placebo) is considered to be sufficient for evaluation of safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

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

Every attempt will be made to collect each PK and/or PD blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. [Table 14.a](#) defines the windows allowed for sample collections.

However, blood samples not collected within the interval specified for the scheduled sample time should be reported to Takeda using the Protocol Deviation Form.

Protocol Deviation Forms are to be completed for PK/PD samples collected outside of the following intervals:

**Table 14.a Windows for PK/PD Blood Sample Collection**

Minutes	Nominal Sampling Time
no more than 30 minutes predose	0 hour
±5	immediately postdose to ≤6 hours
±10	>6 hours to ≤12 hours postdose
±15	>12 hours to ≤24 hours
±30	>24 hours

### 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 [MHRA], 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 D](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

### 15.1 IEC Approval

The IEC must be constituted according to the applicable requirements of the participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the IEC. If any member of the IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the IEC for review and approval of the protocol. This protocol, the Investigator’s Brochure, a copy of the informed consent form (ICF), and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to the IEC for approval. The 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 IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify the site and ship drug 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. Until the site receives drug, no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by the IEC. This may include notification to the IEC regarding protocol amendments, updates to the ICF, 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 IEC, and submission of the investigator’s final status report to the IEC. All 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 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 describes the planned and permitted uses, transfers, and disclosures of the subject’s personal and personal health information for purposes of conducting the study. The ICF further explains the nature of the study, its objectives,

and potential risks and benefits, as well as the date informed consent is given. The ICF 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 IEC approval of the ICF. The informed consent form, must be approved by the IEC and the sponsor prior to use.

The ICF 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 ICF to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the 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 ICF 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 name, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form 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 ICF 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 ICF shall be given to the subject.

All revised ICFs 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 PGx samples 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 IEC 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).

## **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 Americas 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.

## 16.0 REFERENCES

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**Appendix A SRD Part 1 Schedule of Study Procedures: Cohorts 1 to 5**

	Screening	Check-in	Treatment Period						Study Exit	Early Termination (ET) (a)	Follow-up (b)
			Confinement								
Study Day:	-28 to -2	-1	1	2	3	4	5	6	7		14 (±2)
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographics and medical history	X										
Medication history	X										
Physical examination, including neurological examination (c)	X	X							X	X	
Vital signs (d)	X	X	X	X	X	X	X	X	X	X	
Telemetry (e)			X	X							
Weight, height, and BMI (f)	X	X							X	X	
Concomitant medications (g)		X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X									
Clinical laboratory tests (h)	X	X	X	X			X		X	X	
Hepatitis panel	X										
FSH (i)	X										
Serum pregnancy test (hCG) (j)	X								X	X	
Urine pregnancy test (hCG) (j)		X									
Pregnancy avoidance counseling	X								X	X	
Urine drug screen	X	X									
Alcohol breathalyzer	X	X									
ECG (k)	X	X	X	X			X		X	X	
EEG Assessment (l)	CCI										
C-SSRS (m)	X	X					X		X	X	
CCI											
CCI											
PK blood collection (p)			X	X	X	X	X	X	X		
Dispense study medication			X								
PTE assessment (q)	X	X	X								
AE assessment (r)			X	X	X	X	X	X	X	X	X

Footnotes are on the last table page.

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Note: Subjects from a selected cohort will come back to the clinical site and receive the study drug in fed state (Period 2). During Period 2, the procedures to be performed for Day -1 to Follow-up as in the table above will be: physical examination, including neurological examination, vital signs, telemetry, weight, clinical laboratory tests, serum pregnancy test (hCG), urine pregnancy test (hCG), pregnancy avoidance counseling, urine drug screen, alcohol breathalyzer, ECG, EEG, C-SSRS and PK blood collection. There is no screening period for this part of the study.

(a) Procedures for subjects discontinued early per Section 7.6.

(b) Subjects with unresolved SAEs, CS laboratory abnormalities, ECG or physical examination findings or at the investigator's discretion should be seen for a Follow-up visit on Day 14 ( $\pm 2$ ) for appropriate repeat procedure(s). A follow-up phone call will be made to all other subjects on Day 14 ( $\pm 2$ ) for an assessment of AEs and concomitant medications.

(c) The physical examination will include a complete neurological examination. Details are provided in [Appendix G](#).

(d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (predose [within 50 minutes prior to dosing], and at 1, 2, 4, 6, 8, 10, 12, and 16 hours postdose), Days 2 through 5 (upon rising), Days 6 and 7 or ET, and as appropriate at the Follow-up Visit Day 14 ( $\pm 2$ ). Heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing. In addition, pulse will be obtained on Day 1 at 0.5 and 1.5 hours postdose. If a vital sign is found to be abnormal, it will be collected every 30 minutes till it returns to the baseline/normal range.

(e) Continuous 12-lead cardiac telemetry will be performed from dosing until approximately 36 hours postdose.

(f) Height and BMI will only be collected at Screening.

(g) Record all ongoing medications from Screening and throughout the study.

(h) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be collected at Screening, Day -1, Days 1, 2, and 5 (upon rising), Day 7 or ET, and as appropriate at the Follow-up Visit Day 14 ( $\pm 2$ ). Fasting is required on dosing day (Day 1).

(i) An FSH level will be obtained on postmenopausal women (defined as no menses for 12 months without an alternative medical cause).

(j) For all female subjects.

(k) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Day 1 (predose [within 50 minutes prior to dosing], and at 1, 4, 8, and 12 hours postdose), Days 2 and 5 (upon rising/waking up), Day 7, or ET, and as appropriate at Follow-up Day 14 ( $\pm 2$ ).

(l) For subjects who meet all other eligibility criteria (eg, clinical laboratory assessments), EEGs will be performed during Screening, Check-in (Day -1), on Day 1 approximately 1.5 hours postdose, Day 2 at least 23 hours but not more than 25 hours postdose, Days 5 and 7, at ET, or if a subject develops a tremor (resting or otherwise). The investigator must review the Screening EEG results and verify that there are no CS abnormalities for the subject to be eligible for randomization.

(m) C-SSRS: Columbia-Suicide Severity Rating Scale. The C-SSRS (Baseline/Screening version) will be administered at Screening and Day -1 (Check-in). The 'Since Last Visit' version of the C-SSRS will be administered on Discharge Day 5 and Study Exit Day 7, ET.

(n) CCI

(p) For SRD Cohorts 1 to 5, blood samples (4 mL) for PK analyses will be collected at predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours postdose.

(q) PTEs will be collected from signing of informed consent up until dosing on Day 1.

(r) Any event after dosing on Day 1 will be captured as an AE.

## Appendix B SRD Part 1 Schedule of Study Procedures: Cohort 6 Onward

	Screening -28 to -2	Check-in -1	Treatment Period							Study Exit 8	Early Termination (ET) (a)	Follow-up (b) 14 (±2)
			Confinement					6	7			
Study Day:	-28 to -2	-1	1	2	3	4	5	6	7	8		
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Demographics and medical history	X											
Medication history	X											
Physical examination, including neurological examination (c)	X	X								X	X	
Vital signs (d)	X	X	X	X	X	X	X	X	X	X	X	
Telemetry (e)			X	X								
Weight, height, and BMI (f)	X	X								X	X	
Concomitant medications (g)		X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X										
Clinical laboratory tests (h)	X	X	X	X			X			X	X	
Hepatitis panel	X											
FSH (i)	X											
Serum pregnancy test (hCG) (j)	X									X	X	
Urine pregnancy test (hCG) (j)		X										
Pregnancy avoidance counseling	X									X	X	
Urine drug screen	X	X										
Alcohol breathalyzer	X	X										
ECG (k)	X	X	X	X			X			X	X	
EEG Assessment (l)	X	X	X	X			X			X	X	
CCI												
C-SSRS (n)	X	X					X			X	X	
CCI												
CCI												
PK blood collection (q)			X	X	X	X	X	X	X	X		
Dispense study medication			X									
PTE assessment (r)	X	X	X									
AE assessment (s)			X	X	X	X	X	X	X	X	X	X

Footnotes are on the last table page.

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- (a) Procedures for subjects discontinued early per Section 7.6.
- (b) Subjects with unresolved SAEs, CS laboratory abnormalities, ECG or physical examination findings or at the investigator's discretion should be seen for a Follow-up visit on Day 14 ( $\pm 2$ ) for appropriate repeat procedure(s). A follow-up phone call will be made to all other subjects on Day 14 ( $\pm 2$ ) for an assessment of AEs and concomitant medications.
- (c) The physical examination will include a complete neurological examination. Details are provided in [Appendix G](#).
- (d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1), Day 1 (predose [within 50 minutes prior to dosing], and at 1, 2, 4, 6, 8, 10, 12, and 16 hours postdose), Days 2 through 5 (upon rising), Days 6, 7, and 8 or ET, and as appropriate at the Follow-up Visit Day 14 ( $\pm 2$ ). Heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing. In addition, pulse will be obtained on Day 1 at 0.5 and 1.5 hours postdose. If a vital sign is found to be abnormal, it will be collected every 30 minutes till it returns to the baseline/normal range.
- (e) Continuous 12-lead cardiac telemetry will be performed from dosing until approximately 36 hours postdose.
- (f) Height and BMI will only be collected at Screening.
- (g) Record all ongoing medications from Screening and throughout the study.
- (h) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be collected at Screening, Day -1, Days 1, 2, and 5 (upon rising), Day 8 or ET, and as appropriate at the Follow-up Visit Day 14 ( $\pm 2$ ). Fasting is required on dosing day (Day 1).
- (i) An FSH level will be obtained on postmenopausal women (defined as no menses for 12 months without an alternative medical cause).
- (j) For all female subjects.
- (k) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Day 1 (predose [within 50 minutes prior to dosing], and at 1, 4, 8, and 12 hours postdose), Days 2 and 5 (upon rising/waking up), Day 8, or ET, and as appropriate at Follow-up Day 14 ( $\pm 2$ ).
- (l) For subjects who meet all other eligibility criteria (eg, clinical laboratory assessments), EEGs will be performed during Screening, Check-in (Day -1), on Day 1 approximately 1.5 hours postdose, CCI at ET, or if a subject develops a tremor (resting or otherwise). The investigator must review the Screening EEG results and verify that there are no CS abnormalities for the subject to be eligible for randomization.
- (m) CCI).
- (n) C-SSRS: Columbia-Suicide Severity Rating Scale. The C-SSRS (Baseline/Screening version) will be administered at Screening and Day -1 (Check-in). The 'Since Last Visit' version of the C-SSRS will be administered on Discharge Day 5 and Study Exit Day 8 or ET.
- (o) CCI
- (p) CCI
- (q) For SRD Cohort 6 onward, blood samples (4 mL) for PK analyses will be collected at predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose.
- (r) PTEs will be collected from signing of informed consent up until dosing on Day 1.
- (s) Any event after dosing on Day 1 will be captured as an AE.

## Appendix C SRD/MRD Part 2 Schedule of Study Procedures

	Screening	Check-in	Treatment Period													Study Exit	ET (a)	Follow-up (b)
			SRD		MRD													
Study Day:	-28 to -2	-1	1	2-5	6	7-8	9	10	11	12	13-14	15	16-17	18	19-20	21		31 (±2)
Informed consent	X																	
Inclusion/exclusion criteria	X	X																
Demographics and medical history	X																	
Medication history	X																	
Physical examination, including neurological examination (c)	X	X														X	X	
Vital signs (d)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight, height, and BMI (e)	X	X														X	X	
Concomitant medications (f)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X																
Clinical laboratory tests (g)	X	X	X		X		X			X		X		X		X	X	
Hepatitis panel	X																	
FSH (h)	X																	
Serum pregnancy test (hCG) (i)	X															X	X	
Urine pregnancy test (hCG) (i)		X																
Pregnancy avoidance counseling	X															X	X	
Urine drug screen	X	X																
Alcohol breathalyzer	X	X																
ECG (j)	X	X	X		X		X			X		X		X		X	X	
CCI																		
CCI																		
CCI																		
C-SSRS (n)	X	X							X							X	X	
CCI																		
CCI																		
PK blood collection (q)			X	X	X	X				X	X		X	X	X			

Footnotes are on the last table page.

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## Appendix C SRD/MRD Part 2 Schedule of Study Procedures (continued)

	Screening	Check-in	Treatment Period													Study Exit	ET (a)	Follow-up (b)
			SRD		MRD													
Study Day:	-28 to -2	-1	1	2-5	6	7-8	9	10	11	12	13-14	15	16-17	18	19-20	21		31 (±2)
PK urine collection (r)		X	X	X										X	X			
Dispense study medication (s)			X		X	X	X	X	X	X	X	X	X	X				
PTE assessment (t)	X	X	X															
AE assessment (u)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(a) Procedures for subjects discontinued early per Section 7.6.

(b) Subjects with unresolved SAEs, CS laboratory abnormalities, ECG, or physical examination findings or at the investigator's discretion should be seen for a Follow-up visit on Day 31 (±2) for appropriate repeat procedure(s). A follow-up phone call will be made to all other subjects on Day 31 (±2) for an assessment of AEs and concomitant medications.

(c) The physical examination will occur at Screening, Day -1, Day 21 (study exit) or ET and will include a complete neurological examination. Details are provided in [Appendix G](#).

(d) Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Check-in (Day -1); on days of dosing (Day 1 and Days 6 through 18) (predose [within 30 minutes prior to dosing], and at 1, 6, and 12 hours postdose); on days with no dosing (Days 2-5 and 19-20), and Study Exit (Day 21) or ET, and as appropriate at the Follow-up assessment on Day 31 (±2). In addition, heart rate will be obtained on the days of dosing (Day 1 and Days 6-18) at 0.5, 1.5, and 2 hours postdose. If a vital sign is found to be abnormal, it will be collected every 30 minutes till it returns to the baseline/normal range. Heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after standing for all scheduled time points *except* for the CCI collection in SRD/MRD Cohort 3 (Day 12). On Day 12, the vitals at 15 minutes, 30 minutes, and 1 hour post-lumbar puncture will be collected supine only. After the procedure, the subject will be observed by staff and will preferably lie in the supine position for 1 hour—at the investigator's discretion for up to 4 hours if necessary. Subjects may also rest comfortably in a seated or semirecumbent position at the investigator's discretion.

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

(f) Record all ongoing medications from Screening and throughout the study.

(g) Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be collected at Screening, Day -1, predose on Days 1, 6, 9, 12, 15, and 18 (upon rising), and prior to check-out on Study Exit (Day 21) or ET, and as appropriate at the Follow-up assessment Day 31 (±2). Fasting is required on dosing days (Day 1 and Days 6 to 18).

(h) An FSH level will be obtained on postmenopausal women (defined as no menses for 12 months without an alternative medical cause).

(i) For all female subjects.

(j) A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1), Days 1, 6, 9, 12, 15, and 18 at predose (within 50 minutes prior to dosing), and Study Exit (Day 21) or ET, and as appropriate at Follow-up Day 31 (±2).

(k) For subjects who meet all other eligibility criteria (eg, clinical laboratory assessments), EEGs will be performed during Screening and on Days 1, CCI, hours postdose, or ET. The investigator must review the Screening EEG results and verify that there are no CS abnormalities for the subject to be eligible for randomization.

(l) Part 2 SRD/MRD Cohort 3 onward only: Blood samples (serum and plasma, 2 mL each for Cohort 3; serum only, 4 mL each for Cohort 4 onward CCI).

(m) Part 2 SRD/MRD Cohort 3 only: CCI samples (1 mL per subject) for PK (CCI) will be collected on Day 12. All attempts will be made to have a distribution of CCI collection times within the prescribed window of 2 to 6 hours postdose on Day 12; for example, the CCI sample may be collected at 2 hours postdose from the first subject, 3 hours postdose from the second subject, 4 hours postdose from the third subject, and 6 hours postdose from the fourth subject with a collection window of +1 hour for each subject.

(n) C-SSRS: Columbia-Suicide Severity Rating Scale. The C-SSRS Baseline/Screening version will be administered at Screening and Check-in (Day -1); the C-SSRS Since last visit version will be administered on Day 11 and Day 21 or ET.

(o) CCI

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- (p) CCI [REDACTED]
- (q) Blood samples (4 mL) for PK analyses will be collected on Day 1 at predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 hours postdose (the 120-hour collection should occur predose on Day 6). Blood samples for PK analyses will be collected on Day 6 at 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 hours postdose (the 24-hour collection should occur predose on Day 7). Blood samples will be collected predose (within 15 minutes prior to dosing) on Days 12, 14, and 16. Blood samples will be collected on Day 18 predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose. For Part 2 SRD/MRD Cohort 3 only, an additional PK blood sample will be collected following the CCI collection procedure.
- (r) Urine samples for PK analyses will be collected on Day 1 predose at (-12 to 0 hours) and at (0 to 6), (6 to 12), (12 to 24), (24 to 48), and (48 to 72) hour intervals postdose. Urine samples for PK analyses will be collected on Day 18 at (0 to 6), (6 to 12), and (12 to 24) hour intervals postdose.
- (s) Study medication is dispensed QD on Day 1 and Days 6-18.
- (t) PTEs will be collected from signing of informed consent up until dosing on Day 1.
- (u) Any event after dosing on Day 1 will be captured as an AE.



## **Appendix D Responsibilities of the Investigator**

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

The investigator agrees to assume the following responsibilities:


1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. 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.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by the IEC that conform to ICH and local regulatory requirements.
7. Ensure that the IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the 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 IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
9. 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 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.
10. 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.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

## **Appendix E Elements of the Subject Informed Consent**

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

- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the subject's participation.
- A description of the procedures to be followed, including invasive procedures.
- The identification of any procedures that are experimental.
- The estimated number of subjects involved in the study.
- A description of the subject's responsibilities.
- A description of the conduct of the study.
- A statement describing the treatment(s) and the probability for random assignment to each treatment.
- A description of the possible side effects of the treatment that the subject may receive.
- A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- 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.
- 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.
- 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), 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.
- 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.
- The anticipated prorated payment(s), if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IEC and whom to contact in the event of a research-related injury to the subject.

- 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.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- 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.
- CCI 
- The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
- 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) IEC.
  - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law.
  - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies.
  - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research.

- e) that the subject's identity will remain confidential in the event that study results are published.
- Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study, and for 30 days after 5 half-lives have elapsed since the last dose of study drug (ie, 30 days from the Follow-up Call/Visit unless data indicates otherwise). Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
- Male subjects must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study and for 90 days after 5 half-lives have elapsed since the last dose of study drug (ie, 90 days from the Follow-up Call/Visit unless data indicates otherwise). 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.
- A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

## **Appendix F 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 drug.
- 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 G Neurological Examination**

- I. Basic mental status
  - Level of consciousness
  - Orientation
  - Memory
  - Language / speech
- II. Cranial nerves II –XII
  - CN II: visual acuity, visual fields, papillary reaction and fundi
  - CN III, IV and VI: papillary reaction and extra-ocular movements
  - CN V: facial sensation, corneal response and muscles of mastication
  - CN VII: muscles of facial expression
  - CN VIII: hearing, nystagmus and balance
  - CN IX and X: palatal rise to phonation and coordinated swallowing
  - CN XI: sternocleidomastoid and upper trapezius strength
  - CN XII: tongue size and movement
- III. Motor function
  - Muscle bulk
  - Muscle tone
  - Strength of upper major and lower extremity muscle groups
- IV. Reflexes
  - Upper extremity DTRs (deep tendon reflexes = biceps, brachioradialis and triceps)
  - Lower extremity DTRs (patellar and Achilles)
  - Plantar (Babinski) response
- V. Sensation
  - Pinprick (anterolateral spinothalamic tract) and/ or light touch (combined spinothalamic and posterior [dorsal] column tracts)
  - Joint position and / or vibration sense (posterior column tracts)
  - Romberg's test
- VI. Cerebellar function
  - Finger-to-nose and heel-to-shin tests
  - Rapid alternating movements
  - Gait (including heel-to-toe walking)

## Appendix H Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 06 are indicated. The corresponding text has been revised throughout the protocol.

**Change 1:** The approximate total number of subjects to be enrolled in the study has been increased.

The primary change occurs in Section 6.1 Study Design:

Initial wording:	This FIH, double-blind, placebo-controlled, combined SRD/MRD phase 1 study in healthy subjects is designed to assess the safety and tolerability of TAK-653. Approximately 72 healthy male and female volunteers will be enrolled.
------------------	--

This study consists of 2 parts: (1) single ascending doses in 5 cohorts (SRD) and (2) single and multiple ascending doses in 4 cohorts (SRD/MRD). SRD/MRD Cohort 4 is optional; the decision to dose will be based on emerging safety, PK, and PD data. Each cohort will consist of 8 subjects (6 active:2 placebo). Subjects will be fasted for 10 hours before dosing. Cohorts may be added or removed.

Amended or new wording:	This FIH, double-blind, placebo-controlled, combined SRD/MRD phase 1 study in healthy subjects is designed to assess the safety and tolerability of TAK-653. Approximately <del>72</del> <b>112</b> healthy male and female volunteers will be enrolled.
-------------------------	--

This study consists of 2 parts: (1) single ascending doses in 5 cohorts (SRD) and (2) single and multiple ascending doses in 4 cohorts (SRD/MRD). ~~SRD/MRD Cohort 4 is optional; the decision to dose will be based on emerging safety, PK, and PD data.~~ Subjects will ~~fast~~ be fasted for **at least** 10 hours before dosing. Cohorts may be added or removed.

### Rationale for Change:

Given the favorable preliminary safety/tolerability data, including lack of CNS AEs, the linear PK profile for cohorts that have completed dosing to date, the determination from the 13-week monkey toxicity study that seizures are related to  $C_{max}$  (thus allowing revision of the AUC NOAEL margin from AUC<sub>24</sub> on the first day of dosing to AUC<sub>24</sub> at the end of the dosing period), and a consequent improvement in the safety margin, further dose escalation in additional SRD and SRD/MRD cohorts is planned.

Section 2.0 STUDY SUMMARY also contains this change.



---

**Change 2:** The nonclinical basis used to support dose escalation decisions has been revised.

---

The primary change occurs in Section 6.1.3 Dose Escalation:

Initial wording:	<ul style="list-style-type: none"><li>In any case, the predicted exposure of the highest dose administered should not exceed the NOAEL mean exposure achieved in females on Day 1/2 in the 13-week GLP safety monkey study (CCI [REDACTED]). If PK collected during a cohort shows that exposure to TAK-653 has surpassed the exposures at the NOAEL, lower doses will be used in subsequent cohort(s).</li></ul>
Amended or new wording:	<ul style="list-style-type: none"><li><del>In any case, the predicted exposure of the highest dose administered should not exceed the NOAEL mean exposure achieved in females on Day 1/2 in the 13-week GLP safety monkey study (CCI [REDACTED]).</del> <b>In a 13-week repeat-dose toxicity study conducted with TAK-653 in cynomolgus monkeys, test article-related toxicities occurred around <math>t_{max}</math>, typically within the first few days of dosing, and were considered to be related to the <math>C_{max}</math> rather than to the <math>AUC_{24}</math>. Therefore, the predicted exposure for the TAK-653 dose selected for any cohort should not exceed the mean <math>C_{max}</math> value (CCI [REDACTED]) achieved in female monkeys on the first day of dosing or the mean <math>AUC_{24}</math> value (CCI [REDACTED]) achieved in female monkeys at the end of the dosing period at the NOAEL of 3 mg/kg/mL in the 13-week repeat-dose toxicity study.</b> If PK data collected during a cohort shows <b>indicate</b> that exposure to TAK-653 has surpassed the exposures <del>mean</del> (CCI [REDACTED]) at the NOAEL, lower doses will be used in subsequent cohort(s).</li></ul>

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**Rationale for Change:**

In the 13-week repeat-dose monkey toxicity study conducted with TAK-653, test article-related toxicities occurred around  $t_{max}$ , typically within the first few days of dosing, and were considered to be related to the  $C_{max}$  rather than to the  $AUC_{24}$ . Therefore, the mean  $C_{max}$  value (362 ng/mL) achieved on the first day of dosing and mean  $AUC_{24}$  value (14,000 h\*ng/mL) achieved at the end of the dosing period in female monkeys at the NOAEL of 3 mg/kg/mL in the toxicity study are more appropriate exposure caps to support dose escalation decisions.

---

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
  - Section 6.2.1 Study Design.
  - Section 6.2.2 Dose.
-

---

**Change 3:** The summary of the 13-week repeat-dose monkey toxicity data has been revised.

---

The primary change occurs in Section 4.1 Background:

---

Initial wording: A draft report is available of the results of a 13-week repeat-dose toxicity study in cynomolgus monkeys, dosed at 0, 0.3, 3, and 10 mg/kg/day; except for some exceptions, the study was Good Laboratory Practice (GLP)-compliant. In this study, monkeys were monitored continuously for EEG and EMG activity and behavior the first 28 days of dosing and toxicokinetics were evaluated after the first, 29th, and 90th dose administrations and after a convulsion was observed.

...

Given the apparent intolerability of 10 mg/kg/day in female monkeys, the high dose in this group was reduced to 6 mg/kg/day. At 6 mg/kg/day on Day 7, 1 female showed clinical signs of a convulsion but examination of the EEG, EMG, and video-recorded behavior of the animal indicated that it was likely to be an episode of ataxia rather than a generalized seizure as it was not accompanied by EEG signs of seizure activity (although a partial seizure could not be ruled out). On Day 79 of dosing the same monkey showed clinical signs of a convulsion; as videographic and EEG activity were not being recorded at that time, confirmation of seizure activity was not possible. Therefore, the event was considered to be a seizure.

...

Overall, the draft results of the 13-week toxicity study in monkeys indicate no adverse effects of treatment except on clinical signs. There was no adverse effect of treatment on mortality, body weights, or food consumption, electrocardiography, ophthalmology, urinalysis, hematology, clinical chemistry, organ weights, or macroscopic or microscopic observations. Evaluation of videographic recordings of clinical signs throughout the study indicate that tremors occurred in all dose groups, including vehicle controls, although the incidence was increased in females at 10/6 mg/kg/day. Tremors were not associated with EEG changes indicative of seizure activity (ie, no synchrony, paroxysmal activity), were not predictive of a seizure, and likely represent an extension of the pharmacology of the compound. The NOAEL in this study was 10 mg/kg/day in males and 3 mg/kg/day in females based on the observation of seizure (unconfirmed by EEG) in 1 female at 6 mg/kg/day (draft report). At the NOAEL, mean exposures in females on the first and last days of dosing were 362 and 825 ng/mL ( $C_{max}$ ) and 5940 and CCI (AUC<sub>24</sub>), respectively.

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Amended or new wording: A draft report is available of the results of a 13-week repeat-dose toxicity study **was conducted** in cynomolgus monkeys, dosed at 0, 0.3, 3, and 10 mg/kg/day; **except for with** some exceptions, the study was ~~Good Laboratory Practice~~ (GLP)-compliant. In this study, monkeys were monitored continuously for EEG and EMG activity and behavior the first 28 days of dosing and **for 24-hour periods**

---

**midstudy and at the end of the study;** toxicokinetics were evaluated after the first, 29th, and 90th dose administrations and after a convulsion was observed.

...

Given the apparent intolerability of 10 mg/kg/day in female monkeys, the high dose in this group was reduced to 6 mg/kg/day **after a dosing holiday.** ~~At~~ **After the second dosing of** 6 mg/kg/day ~~on Day 7,~~ 1 female showed clinical signs of a convulsion but examination of the EEG, EMG, and video-recorded behavior of the animal indicated that it was likely to be an episode of ataxia rather than a generalized seizure as it was not accompanied by EEG signs of seizure activity (although a partial seizure could not be ruled out). On Day 79 of dosing the same monkey showed clinical signs of a convulsion; as videographic and EEG activity were not being recorded at that time, **as per protocol, EEG** confirmation of seizure activity was not possible. **However, to err on the side of safety** ~~Therefore,~~ the event was considered to be a seizure.

...

Overall, the ~~draft~~ results of the 13-week toxicity study in monkeys indicate no adverse effects of treatment except on clinical signs. There was no adverse effect of treatment on mortality, body weights, or food consumption, electrocardiography, ophthalmology, urinalysis, hematology, clinical chemistry, organ weights, or macroscopic or microscopic observations. Evaluation of videographic recordings of clinical signs throughout the study indicate that tremors occurred in all dose groups, including vehicle controls, although the incidence was increased in females at 10 **and** 6 mg/kg/day. Tremors were not associated with EEG changes indicative of seizure activity (ie, no synchrony, paroxysmal activity), were not predictive of a seizure, and likely represent an extension of the pharmacology of the compound. The NOAEL in this study was 10 mg/kg/day in males and 3 mg/kg/day in females based on ~~the~~ **a clinical** observation of seizure (unconfirmed by EEG) in 1 female at 6 mg/kg/day ~~(draft report)~~. At the NOAEL, mean exposures in females on the first and last days of dosing were 362 and 825 ng/mL ( $C_{max}$ ) and 5940 and **CC1** (AUC<sub>24</sub>), respectively.

---

#### Rationale for Change:

The report for the 13-week repeat-dose monkey toxicity study has been finalized.

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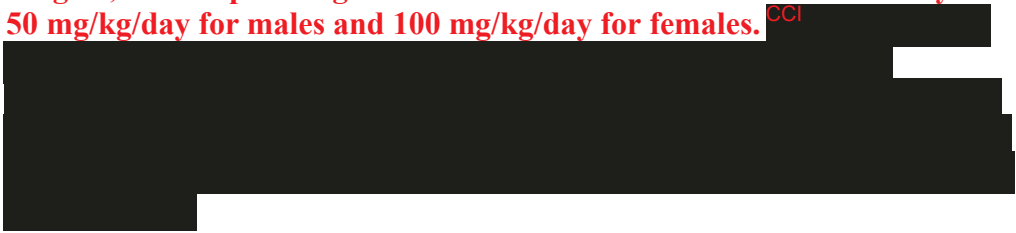
**Change 4:** A summary of the 13-week repeat-dose rat toxicity data has been added.

---

The primary change occurs in Section 4.1 Background:

---

Added text: **A 13-week GLP-compliant repeat-dose toxicity study was conducted in rats. Tonic convulsion was observed in 1 female at 200 mg/kg/day; therefore, the highest dose in females was reduced to 100 mg/kg/day beginning on Day 2 of the study. After lowering the dose to 100 mg/kg/day, no convulsions were observed in any group through the end of the dosing period. In addition, there were no test article-related abnormalities observed in clinical signs, body weights, food consumption, ophthalmologic examination, urine output, urinalysis, hematology, coagulation tests, clinical chemistry, necropsy, organ weights, or histopathological examination. The NOAELs in this study were 50 mg/kg/day for males and 100 mg/kg/day for females.** CCI



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**Rationale for Change:**

To report the data from the completed 13-week repeat-dose toxicity study in rats.

---

**Change 5:** A summary of preliminary blinded safety/tolerability and PK data has been added for completed single-rising dose (SRD) Cohorts 1 to 5 and SRD/multiple-rising dose (MRD) Cohorts 1 and 2.

---

The primary change occurs in Section 4.1 Background:

---

Initial wording:	This first-in-human (FIH) phase 1 study has been designed to mitigate the known risks associated with AMPA receptor potentiators as a class and the results of the nonclinical toxicity studies in TAK-653. Descriptions of the risk mitigation measures included in this study are detailed in Section 6.2 and summarized in Section 6.2.4.
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Amended or new wording: ~~This first-in-human (FIH) phase 1 study has been designed to mitigate the known risks associated with AMPA receptor potentiators as a class and the results of the nonclinical toxicity studies in TAK-653. Descriptions of the risk mitigation measures included in this study are detailed in Section 6.2 and summarized in Section 6.2.4.~~

...

#### 4.3 Risk-Benefit Profile

**This FIH phase 1 study has been designed to mitigate the known risks associated with AMPA receptor potentiators as a class and the potential risks based on the nonclinical toxicity data and preliminary clinical data for TAK-653. Descriptions of the risk mitigation measures included in this study are detailed in Section 6.2 and summarized in Section 6.2.4. As this is a study in healthy subjects, there is no expected clinical benefit to the study participants.**

**To date in this study, a total of 56 subjects have been enrolled and administered study drug (42 active, 14 placebo) in 5 single-rising dose (SRD) cohorts (0.3, 1, 3, 5, and 9 mg) in Part 1 and 2 SRD/multiple-rising dose (MRD) cohorts (0.3 and 1 mg) in Part 2. In addition, dosing in SRD/MRD Cohort 3 (3 mg) has started. A blinded review of the preliminary safety and tolerability data for these completed cohorts indicate that TAK-653 was generally well tolerated at single doses up to 9 mg in Part 1 and multiple doses up to 1 mg QD in Part 2. No serious treatment-emergent adverse events (TEAEs) or CNS-type adverse events (AEs) were reported. No clinically meaningful clinical laboratory, vital sign, electrocardiogram (ECG), or physical examination results were reported. Preliminary PK data from these cohorts indicate that TAK-653 exhibits linear PK across the dose range tested.**

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#### Rationale for Change:

To provide support for further dose escalation based on blinded review of the available preliminary data collected in the study to date.

---

The following sections also contain this change:

- Section 6.2.2 Dose.
  - Table 6.a Summary of SRD Dose Cohorts.
  - Table 6.b Summary of SRD/MRD Dose Cohorts.
-

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**Change 6:** The need for an independent medical reviewer from the sponsor to endorse dose escalation decisions has been removed.

---

The primary change occurs in Section 6.1.3 Dose Escalation:

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Initial wording:	All decisions concerning dose escalation will be made by Takeda (at a minimum, the clinical science representative and pharmacovigilance physician, or appropriate delegates) and the principal investigator. The investigator and subjects will remain blinded throughout the study, but at the completion of each cohort, Takeda personnel may be unblinded to analyze data considered necessary to determine subsequent doses. Such decisions will need to be endorsed by an independent medical reviewer (a Takeda physician who is not involved with the conduct of the study) after reviewing all available safety, tolerability, PK, and PD data from the previous cohort.
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Amended or new wording:	All decisions concerning dose escalation will be made by Takeda (at a minimum, the clinical science representative and pharmacovigilance physician, or appropriate delegates) and the principal investigator. The investigator and subjects will remain blinded throughout the study, but at the completion of each cohort, Takeda personnel may be unblinded to analyze data considered necessary to determine subsequent doses. <del>Such decisions will need to be endorsed by an independent medical reviewer (a Takeda physician who is not involved with the conduct of the study) after reviewing all available safety, tolerability, PK, and PD data from the previous cohort.</del>
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**Rationale for Change:**

Text has been amended to reflect the requirements in the most current sponsor Standard Operating Procedure on dose escalation.

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**Change 7:** Text has been added to clarify that study drug-related central nervous system disorders/adverse events may result in the stopping of dose escalation or study drug dosing.

---

The primary change occurs in Section 6.1.3 Dose Escalation:

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Initial wording:	Dose escalation will be stopped if an SAE or 2 severe or clinically significant AEs occur that can be considered related to study drug.
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Amended or new wording:	<del>Dose escalation will be stopped if an SAE or 2 severe or clinically significant AEs occur that can be considered related to study drug.</del>
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---

**Dose escalation and study drug administration will be stopped if an SAE or 2 severe or clinically significant AEs, including CNS disorders/AEs (Section 6.3.1), are observed in a particular cohort and are considered by the investigator to be related to TAK-653.**

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**Rationale for Change:**

To be more descriptive in the type of TEAEs that would result in stopping dose escalation or study drug administration.

---

Section 6.3.1 Criteria for Premature Termination or Suspension of the Study also contains this change.

---

**Change 8:** Change in peripheral levels of the CCI

SRD/MRD Cohort 3).

---

The primary change occurs in Section 5.4.3 Exploratory/Additional Endpoints:

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Initial wording:	Additional endpoint for all cohorts:
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CCI

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Amended or new wording:	Additional endpoint for all cohorts:
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CCI

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**Rationale for Change:**

CCI levels in plasma and/or serum will be measured for subjects in all cohorts to explore the potential effect of TAK-653 on this biomarker.

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The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1.1 Part 1: SRD.
- Figure 6.a SRD Study Schematic.
- Section 6.1.2 Part 2: SRD/MRD.
- Figure 6.b SRD/MRD Study Schematic, Footnote (d).
- Section 6.2.1 Study Design.
- Section 9.1.17.2 CCI
- Table 9.e Collection of Blood Samples for Analysis of CCI
- Section 9.3.3 Treatment Phase.
- Section 9.4 Blood Volume.
- Table 9.g Approximate Blood Volume: SRD Cohort 6 Onward.
- Table 9.h, Approximate Blood Volume: SRD/MRD Cohorts, Footnote (b).
- Section 13.1.4 Pharmacodynamic Analysis.
- Appendix B SRD Part 1 Schedule of Study Procedures: Cohort 6 Onward.
- Appendix C SRD/MRD Part 2 Schedule of Study Procedures, Footnote (l).

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**Change 9:** An additional blood sample collection at 168 hours postdose has been included for SRD Cohort 6 onward in Part 1.

---

The primary change occurs in Table 9.c Collection of Blood and Urine Samples for Pharmacokinetic Analysis:

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Description of change:	• Row added with PK blood sampling times specifically for SRD Cohort 6 onward.
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**Rationale for Change:**

To more precisely characterize the  $t_{1/2,z}$  for the higher-dose SRD cohorts.

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The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1.1 Part 1: SRD.
- Figure 6.a SRD Study Schematic.
- Section 9.3.4 Study Exit.
- Section 9.4 Blood Volume.
- Table 9.f Approximate Blood Volume: SRD Cohorts 1 to 5.
- Table 9.g Approximate Blood Volume: SRD Cohort 6 Onward.
- Appendix B SRD Part 1 Schedule of Study Procedures: Cohort 6 Onward.

**Change 10:** Text was clarified to indicate that TAK-653 and the [REDACTED] only will be measured in [REDACTED] if feasible.

The primary change occurs in Section 9.1.15.3 Bioanalytical Methods:

Initial wording:	Plasma, urine, and [REDACTED] concentrations of TAK-653 and [REDACTED], if feasible, will be measured by high-performance liquid chromatography with tandem mass spectrometry.
Amended or new wording:	Plasma <b>and</b> urine, <del>and</del> [REDACTED] concentrations of TAK-653 and <i>cis/trans</i> [REDACTED], <del>if feasible,</del> <b>and [REDACTED] concentrations of TAK-653 and [REDACTED]</b> , <b>if feasible,</b> will be measured by high-performance liquid chromatography with tandem mass spectrometry.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 9.1.15.2 Collection of [REDACTED]
- Section 13.1.3.1 Concentrations in Plasma, Urine, and [REDACTED]

**Rationale for Change:**

Only TAK-653 and the [REDACTED] will be measured in [REDACTED] if feasible.

**Change 11:** Text has been added to indicate that screening data for subjects who have undergone general screening procedures (ie, panel screening) before the effective date of this protocol amendment may be used to assess subject eligibility for enrollment in this study.

---

The primary change occurs in Section 9.3.1 Screening:

---

Added text: **In the event that subjects have undergone general screening assessments (ie, panel screening) before the effective date of this protocol amendment, the data from this general screening may be used to assess subject eligibility for enrollment in this study, provided that the procedures were performed within the protocol-defined Screening Period window.**

---

#### Rationale for Change:

To allow enrollment into this study of subjects who have been screened by the clinical site in accordance with their internal approved panel screening protocol and ICF.

---

**Change 12:** The responsibilities of the investigator have been revised to reflect the updated International Council for Harmonisation E6(R2) Good Clinical Practice Consolidated Guideline.

---

The primary change occurs in Appendix D Responsibilities of the Investigator:

---

Added text: **3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.**

---

#### Rationale for Change:

The responsibilities of the investigator have been revised in the ICH E6(R2) GCP Consolidated Guideline.

---

**Change 13:** Procedures for bioanalytical and pharmacogenomic sample collecting, processing, and shipping have been removed and referenced to the laboratory manual instead.

---

The primary change occurs in Appendix F (Collection, Storage, and Shipment of Bioanalytical Samples) and Appendix G (Collection, Shipment, and Storage of Pharmacogenomic Samples):

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Deleted text: **Appendix F Collection, Storage, and Shipment of Bioanalytical Samples**  
**Instructions for Processing of Plasma Samples for Pharmacokinetic Analysis of TAK-653 and Metabolites**  
Collect 4 mL of venous blood for the plasma into a chilled Becton-Dickinson Vacutainer. All TAK-653 and <sup>CCI</sup> -blood samples should be collected into Vacutainers containing K<sub>2</sub>EDTA.  
Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.  
Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at 4°C. Note: if using a collection device other than Becton-Dickinson, refer to

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~~manufacturer's instruction for proper centrifugation force and time.~~

~~Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.2 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-653-1001), sample matrix (ie, plasma), 4-digit randomization number, Part 1 or 2, profile day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).~~

~~Cap the labeled storage tubes and freeze the plasma samples immediately at approximately 20°C or lower until shipment to PPD, Richmond, Virginia, USA. No more than 45-60 minutes should elapse between blood collection and freezing the plasma sample.~~

#### **~~Instructions for Processing of Urine Samples for Pharmacokinetic Analysis of TAK-653 and Metabolites~~**

~~Collect urine into polypropylene containers. During the collection interval, the urine will be stored at approximately 4°C. The urine collection will require the use 10% (w/v) Tween80 to prevent compound absorption to collection/storage containers.~~

~~At the end of each void, mix the urine, transfer to a graduated cylinder, measure and record the volume. For the urine sample in the graduated cylinder intended for bioanalysis, measure "X" amount of 10% Tween80 solution (10% Tween80 by weight in water) into a separate graduated cylinder (where "X" equals 1 part in 10 of the urine volume in the cylinder).~~

~~Pour  $\frac{3}{4}$  of the "X" amount of the 10% Tween80 solution into the graduated cylinder containing the subject's urine. Mix and transfer to the bioanalysis sample jug for the time period.~~

~~With the remaining 10% Tween80 solution, rinse the original collection jug and combine with the sample in the bioanalysis sample jug for the time period.~~

~~Store the collection jug at approximately 4°C during the collection period. Record the final volume of the urine fortified with the 10% Tween80 solution.~~

~~Mix well and measure the urine volume within 2 hours of the end of the collection period.~~

~~Transfer approximately 10 mL aliquots of urine in duplicate into appropriate polypropylene containers. Container should be filled to within 60%-90% of the nominal volume. Labeling should include protocol number (TAK-653-1001), 4-digit randomization number, Part 1 or 2, profile day and time, and either "SET 1" (for original sample), or "SET 2" (for duplicate sample).~~

~~Freeze the urine samples immediately and store frozen at approximately -80°C or~~

lower. Keep samples frozen at approximately -80°C or lower until shipment to (PPD, Richmond, Virginia, USA).

**Instructions for processing ~~CCI~~ samples will be provided in a laboratory manual.**

### **Shipping of Plasma, Urine, and ~~CCI~~ Samples**

The following instructions are recommended unless they differ from the site's SOPs for labeling, packaging, or shipping of PK samples.

1. ~~Biological samples should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.~~
2. ~~Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:~~
3. ~~Separate the duplicate SET 2 samples from the SET 1 samples.~~
4. ~~Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.~~
5. ~~Using a permanent marker, write the 4-digit randomization number, sample matrix (ie, plasma, urine, or ~~CCI~~ number of samples, and "SET 1" on each self-sealing bag.~~
6. ~~Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 1 through 4 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."~~
7. ~~An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study drug (TAK-653), protocol number (TAK-653-1001), investigator's name, sample type (ie, plasma, urine, or ~~CCI~~ subject's 4-digit randomization number, Part 1 or 2, profile collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.~~
8. ~~For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from~~

~~direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.~~

- ~~9. Place the inventory paperwork (in a large self sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.~~
- ~~10. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).~~
- ~~11. Affix an address label to each shipping carton. Complete the address label with the following information:~~

~~Plasma, Urine, and CCI Samples for TAK-653~~

~~PPD~~  
PPD

~~Affix a carbon dioxide label on each carton, specifically:~~

~~Carbon Dioxide Solid UN-1845~~

~~Class 9 PKG GR III~~

~~Quantity \_\_\_\_\_~~

~~(fill in weight to nearest lb/kg and specify unit of measure used)~~

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

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

~~After shipping of the TAK-653 samples, please contact PPD~~  
PPD ~~to notify her of next day delivery. When contacting, provide the following information:~~

~~Name of courier or transport company~~

~~Time and date the shipment left the clinical site~~

~~Airway bill number~~

#### ~~CCI~~ **Processing and Shipping Samples**

~~Instructions for processing and shipping biomarker CCI serum and plasma samples will be provided in a laboratory manual.~~

~~CCI~~

---

**Samples**

CCI



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**Rationale for Change:**

Detailed procedures for PK, PD, and PGx sample collecting, processing, and shipping are provided in the laboratory manual.

---

The following sections also contain this change:

- Section 9.1.15.1 Collection of Plasma and Urine for Pharmacokinetic Sampling.
- Section 9.1.15.2 Collection of CCI

---

**Change 14:** The sponsor signatories for this protocol have been updated.

---

The primary change occurs in Section 1.2 [Approval](#):

---

Initial      The responsible Takeda medical officer and other signatories are shown below.  
wording:      Electronic signatures are located on the last page of the document.

PPD



---

Amended or      The responsible Takeda medical officer and other signatories are shown below.  
new wording:      Electronic signatures are located on the last page of the document.

PPD



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**Rationale for Change:**

Signatories were updated to reflect current signature requirements at the sponsor.

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Amendment 6-A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Escalating Single and Multiple Doses of TAK-653 in Healthy Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD 	Statistical Approval	24-Mar-2017 14:59 UTC
	Clinical Science Approval	24-Mar-2017 16:09 UTC
	Clinical Pharmacology Approval	24-Mar-2017 16:11 UTC
	Clinical VP Approval	24-Mar-2017 20:57 UTC