



Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Single-and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-020 in Healthy Volunteers

NCT Number: TAK-020-1001

Protocol Approve Date: 27-March-2017

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.



## PROTOCOL

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-020 in Healthy Volunteers

### Phase 1 TAK-020 SRD/MRD Study

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

**Study Number:** TAK-020-1001

**IND Number:** 123,875 **EudraCT Number:** Not Applicable

**Compound:** TAK-020

**Date:** 27 March 2017 **Amendment Number:** 4.0

#### Amendment History:

Date	Amendment Number	Amendment Type	Region
17 December 2014	Initial Protocol	Not applicable	US
14 August 2015	01	Substantial	US
07 September 2016	02	Substantial	US
31 October 2016	03	Substantial	US
27 March 2017	04	Substantial	US

#### CONFIDENTIAL PROPERTY OF TAKEDA

This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

## 1.0 ADMINISTRATIVE INFORMATION

### 1.1 Contacts

A separate contact information list will be provided to each site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	PPD [REDACTED]
Medical Monitor (medical advice on protocol and compound)	PPD [REDACTED]
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD [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 Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

### **SIGNATURES**

The electronic signature of the responsible Takeda medical officer (and other signatories listed below), and electronic signature date, can be found on the signature page (the last page of this 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 Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- [Appendix B](#) – Responsibilities of the Investigator.

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

---

Signature of Investigator

---

Date

---

Investigator Name (print or type)

---

Investigator's Title

---

Location of Facility (City, State/Province)

---

Location of Facility (Country)

### 1.3 Protocol Amendment 4 Summary of Changes

#### Rationale for Amendment 4.0

This document describes the changes in reference to the Protocol Incorporating Amendment No. 4.0. The primary purpose of this amendment is to add an additional time point for the collection of the pharmacodynamic (PD) markers [REDACTED]

[REDACTED] to Part 2 (multiple rising dose [MRD]) of this study in order to explore the extended duration of the PD effects.

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 F](#).

#### Changes in Amendment 4.0

1. Changed name of Responsible Medical Officer.
2. Specified doses administered for initial cohorts of Part 2.
3. Added PD biomarkers to Follow-up Visit (Day 17).
4. Clarified method used for PD analyses.

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## 2.0 STUDY SUMMARY

<b>Name of Sponsor(s):</b> Takeda Development Center Americas, Inc. (TDC Americas)		<b>Compound:</b> TAK-020															
<b>Title of Protocol:</b> A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK-020 in Healthy Volunteers		<b>IND No.:</b> 123,875	<b>EudraCT No.:</b> Not Applicable														
<b>Study Number:</b> TAK-020-1001		<b>Phase:</b> 1															
<b>Study Design:</b> <p>This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple-dose study in healthy volunteers. The study is comprised of 2 parts, each with multiple cohorts and is presented in the Study Schematic below. The study population for each part will be composed of healthy subjects aged 18 to 55 years, inclusive, who weigh at least 45 kg, and have a body mass index (BMI) between 18 and 32 kg/m<sup>2</sup>, inclusive, at Screening and Day -1.</p> <p><b>Study Design Schematic</b></p> <table border="1"> <tr> <td> <p align="center"><b>Part 1: SRD</b></p> <p>Maximum 9 Cohorts</p> <p>Starting dose 0.1 mg (Cohort 1)</p> <p>Cohorts 2-4: maximum exposure escalation x 5-fold</p> <p>Cohorts 5-9: maximum exposure escalation x 2-fold</p> <p>Maximum dose estimated 122 mg (with unbound AUC 19.8 ng*h/mL)</p> </td> <td align="center">→</td> <td> <p align="center"><b>Part 2: MRD</b></p> <p>Maximum 7 Cohorts</p> <p>Doses to be determined from Part 1</p> <p>Starting dose 3.75 mg</p> <p>Cohorts 2-7: 2-fold maximum exposure increase per dose increment</p> </td> </tr> </table> <p>SRD=single-rising dose, MRD=multiple-rising dose.</p> <p><b>Part 1: SRD</b></p> <p>This part will comprise a maximum of 9 cohorts. Each cohort will comprise 8 randomized subjects, with 6 receiving TAK-020 and 2 receiving placebo in the fasted state. Sentinel dosing will be used for Cohort 1 with only 2 subjects dosed on the morning of Day 1 (1 receiving TAK-020 and 1 receiving placebo). The remaining subjects will be dosed following agreement with the investigator and Takeda after reviewing 24-hour postdose safety (adverse events [AEs], vital signs, 12-lead electrocardiograms [ECGs]) and tolerability data. Sentinel dosing will not be necessary for other cohorts, provided that exposure is observed in ≥4 subjects receiving active treatment and in agreement with the investigator and Takeda, otherwise sentinel dosing in the subsequent cohort will be required.</p> <p>TAK-020 will be orally administered as a solution with a starting dose of 0.1 mg for Cohort 1. Dosing for the subsequent cohorts will only occur after review of the safety, tolerability, and minimum 24-hour pharmacokinetic (PK) data from the previous cohort. For each dose escalation, exposures may be increased by a maximum of 5-fold for Cohorts 2-4 and a maximum of 2-fold for Cohorts 5 to 9. Doses may also be decreased as appropriate.</p> <p><b>Study Schematic for Part 1 (SRD)</b></p> <table border="1"> <tr> <td>Screening</td> <td>Check-in</td> <td>Dose</td> <td>Check-out</td> <td>Follow-up (a)</td> </tr> <tr> <td>Day -28 to -2</td> <td>Day -1</td> <td>Day 1</td> <td>Day 5</td> <td>Day 14 (±2)</td> </tr> </table> <p>(a) A phone call is planned but individual subjects may be asked to return to the unit at this time if abnormal clinical safety laboratory values are obtained at Check-out or treatment emergent adverse events (TEAEs) have not resolved at Check-out.</p>					<p align="center"><b>Part 1: SRD</b></p> <p>Maximum 9 Cohorts</p> <p>Starting dose 0.1 mg (Cohort 1)</p> <p>Cohorts 2-4: maximum exposure escalation x 5-fold</p> <p>Cohorts 5-9: maximum exposure escalation x 2-fold</p> <p>Maximum dose estimated 122 mg (with unbound AUC 19.8 ng*h/mL)</p>	→	<p align="center"><b>Part 2: MRD</b></p> <p>Maximum 7 Cohorts</p> <p>Doses to be determined from Part 1</p> <p>Starting dose 3.75 mg</p> <p>Cohorts 2-7: 2-fold maximum exposure increase per dose increment</p>	Screening	Check-in	Dose	Check-out	Follow-up (a)	Day -28 to -2	Day -1	Day 1	Day 5	Day 14 (±2)
<p align="center"><b>Part 1: SRD</b></p> <p>Maximum 9 Cohorts</p> <p>Starting dose 0.1 mg (Cohort 1)</p> <p>Cohorts 2-4: maximum exposure escalation x 5-fold</p> <p>Cohorts 5-9: maximum exposure escalation x 2-fold</p> <p>Maximum dose estimated 122 mg (with unbound AUC 19.8 ng*h/mL)</p>	→	<p align="center"><b>Part 2: MRD</b></p> <p>Maximum 7 Cohorts</p> <p>Doses to be determined from Part 1</p> <p>Starting dose 3.75 mg</p> <p>Cohorts 2-7: 2-fold maximum exposure increase per dose increment</p>															
Screening	Check-in	Dose	Check-out	Follow-up (a)													
Day -28 to -2	Day -1	Day 1	Day 5	Day 14 (±2)													

Part 2: MRD

TAK-020 will be orally administered as a solution. The dose to be used in each cohort will be selected based on data from Part 1 of the study and from the previous cohort in Part 2.

MRD Evaluation

The first cohort for the MRD will receive a dose of 3.75 mg, with a predicted exposure at steady state estimated to be below the no-observed adverse-effect level (NOAEL) rat (63 ng\*h/mL). The cohort may be initiated when the acceptable safety and tolerability have been collected in the SRD. The predicted steady state exposure in the first MRD cohort will be approximately 10-fold lower than the highest predicted steady state exposure determined from the SRD data. The MRD will comprise a maximum of 7 cohorts, each cohort with 8 subjects randomized with 6 receiving TAK-020 and 2 receiving placebo. In each successive cohort after the first, the dose increments will increase the predicted exposures by no more than 2-fold. The predicted steady state exposure in the MRD will not exceed the maximum exposure observed in the SRD.

Study Schematic for Part 2 (MRD)

Screening	Check-in	Dose	Washout	Dose	Check-out	Follow-up (a)
Day -28 to -2	Day -1	Day 1	Day 2	Days 3-9	Day 10	Day 17 (±2)

(a) All subjects will return to the unit and complete hematology, serum chemistry, renal biomarkers and pharmacodynamic (PD) tests, vital signs, concomitant medications, and adverse event (AE) assessment.

Primary Objective:

To characterize the safety and tolerability of TAK-020 following single and multiple oral doses in healthy subjects.

Secondary Objectives:

To characterize the PK of TAK-020 following single and multiple oral doses.

To characterize the PD of TAK-020 following single and multiple oral doses.

Subject Population: Healthy subjects aged 18-55, inclusive.

<div>Number of Subjects:</div> <div>Part 1: Maximum 9 cohorts with 8 subjects per cohort TAK-020: 6, Placebo: 2</div> <div>Part 2: Maximum 7 cohorts with 8 subjects per cohort TAK-020: 6, Placebo: 2</div> <div>Estimated Total Part 1: 72 subjects randomized Estimated Total Part 2: 56 subjects randomized</div>	<div>Number of Sites:</div> <div>Estimated total: 1 site in United States</div>
<div>Dose Level(s):</div> <div>Starting dose 0.1 mg once daily (QD) to approximately 122 mg QD solution</div>	<div>Route of Administration:</div> <div>Oral</div>
<div>Duration of Treatment:</div> <div>Part 1: single dose, QD Part 2: single dose, QD for maximum 8 days</div>	<div>Period of Evaluation:</div> <div>Screening = up to 28 days Part 1 treatment = approximately 14 days (includes Follow-up phone call) Part 2 treatment = approximately 17 days (includes Follow-up return to unit) Total Part 1 = approximately 42 days Total Part 2 = approximately 45 days</div>

**Main Criteria for Inclusion:**

The subject is a healthy adult male or female aged 18 to 55 years, inclusive, and weighs at least 45 kg and has a BMI between 18 and 32 kg/m<sup>2</sup>.

All subjects must be able to comply with the protocol and willing to sign the informed consent prior to undergoing any study-related procedures to be eligible for this study.

**Main Criteria for Exclusion:**

Subject has a known hypersensitivity to any component of the formulation of TAK-020, Captisol or related compounds. Subject has evidence of current cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking TAK-020, or a similar drug in the same class, or that might interfere with the conduct of the study. Subject has abnormal Screening or Day -1 laboratory values that suggest a clinically significant underlying disease or subject with the following lab abnormalities or any of the following: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.2× the upper limit of normal (ULN), positive screen test for drugs of abuse, positive blood screen for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus-1 or -2 antibodies, or a positive test for tuberculosis (TB) (QuantIFERON). In addition, subjects may not use any excluded medications, supplement, or food product outlined in Table 7.a.

**Main Criteria for Evaluation and Analyses:**

**PK**

Plasma and urine samples will be taken at the following time points in the first cohort. Based on emerging data in each cohort, the time points may be modified but will not exceed the number of samples presented and will not be taken after 96 hours in the SRD and 48 hours in the MRD.

**Part 1 (SRD)**

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose
Urine	1	Predose (-12-0), and 0-6, 6-12, 12-24, 24-48, 48-72, and 72-96 hour postdose intervals

**Part 2 (MRD)**

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
Plasma	9	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose
Urine	1	Predose (-12-0), and 0-6, 6-12, 12-24 hour postdose intervals
Urine	9	Predose (-12-0), and 0-6, 6-12, 12-24 hour postdose intervals

The following plasma PK parameters will be determined: area under the plasma concentration-time curve from time 0 to 24 hours (AUC<sub>24</sub>); area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC<sub>τ</sub>); area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (AUC<sub>t</sub>); area under the plasma concentration-time curve from time 0 to infinity (AUC<sub>∞</sub>); accumulation ratio (R, calculated as AUC<sub>τ</sub> at steady state/AUC<sub>∞</sub> after a single dose); accumulation ratio based on AUC (R<sub>ac(AUC)</sub>), calculated as AUC<sub>τ</sub> at steady state or AUC<sub>τ</sub> after a single dose); maximum observed plasma concentration (C<sub>max</sub>); maximum observed steady-state plasma concentration during a dosing interval (C<sub>max,ss</sub>); apparent clearance after extravascular administration (CL/F); terminal elimination rate constant (λ<sub>z</sub>); terminal disposition phase half-life (t<sub>1/2z</sub>); lag time (T<sub>lag</sub>, time from TAK-020 administration to first quantifiable

concentration); time to first occurrence of  $C_{max}$  ( $t_{max}$ ); and apparent volume of distribution during the terminal disposition phase after extravascular administration ( $V_z/F$ ). CCI

CCI

The following urine PK parameters will be determined: amount of drug excreted in urine from time 1 to time 2 ( $Ae_{t1-2}$ , calculated as  $C_{ur} \times V_{ur}$ ),  $Ae_t$ , amount of drug excreted in urine during a dosing interval ( $\tau$ ) at steady state ( $Ae_\tau$ ),  $fe$ , and renal clearance ( $CL_R$ ).

**Pharmacodynamics:**

CCI

CCI

**Safety:**

Safety parameters will include TEAEs, clinical laboratory results, physical examination findings, ECG findings, and vital signs measurements. Standard safety assessments for phase 1 studies will be collected as provided in Section 9.0 Study Plan.

**Laboratory tests:**

Standard laboratory tests will be assessed as provided in Table 9.a Clinical Laboratory Tests.

**Pharmacogenomics:**

Deoxyribonucleic acid (DNA) samples will be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of TAK-020. The sampling of whole blood for pharmacogenomic (PGx) and genotyping analysis is mandatory; every subject must sign the informed consent in order to participate in this study. Also, since PGx is an evolving science, many genes and their functions are not yet fully understood. CCI

**Maximum total volume of blood drawn:**

Part 1 (SRD): 300 mL; Part 2 (MRD): 413 mL

**Statistical Considerations:**

***Safety Analysis***

AEs will be presented in listings, and TEAEs will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis) will be listed and Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized. Individual results of vital signs will be listed and observed values and changes from Baseline in vital signs will be summarized. Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed and observed values and changes from Baseline in quantitative ECG parameters will be summarized. The subjects who meet predefined markedly abnormal values (MAV) criteria for laboratory tests, vital signs and ECG parameters will be summarized and listed. All summaries will be performed by pooled placebo, each TAK-020 dose level, and TAK-020 overall across cohorts as appropriate for single and multiple doses of Parts 1 and 2. Physical examination findings will be presented in data listings.

***PK Analysis***

Concentrations of TAK-020 in plasma will be summarized by dose level over each scheduled sampling time using descriptive statistics. Individual plasma concentration data vs time will be presented in a data listing.

Amount of TAK-020 excreted in urine will be summarized by dose level over each scheduled sampling interval using descriptive statistics. Individual urine concentration data along with volume versus time intervals will be presented in a data listing.

PK parameters of TAK-020 will be summarized by dose level using descriptive statistics. All PK parameter data will be listed.

The above summaries will be performed separately for Part 1 (SRD) and Part 2 (MRD).

Power model will be used to assess dose proportionality of single and multiple dosing in healthy subjects for  $C_{max}$  and AUC.

Analysis of variance (ANOVA) will be used to assess time dependency for Part 2 multiple dosing. In the model, the natural log-transformed AUCs and  $C_{max}$  will be used as response variable and dose level, Day and the interaction of dose level by Day will be fixed factors.

***Pharmacodynamic Analysis***

CCI



summarized.

The above summaries will be performed separately for Part 1 (SRD) and Part 2 (MRD).

The relationship between dose, TAK-020 concentrations, PK parameters, and PD response will be explored and PK/PD models developed if deemed appropriate.

**Interim Analysis and Criteria for Early Termination**

No formal interim analyses will be performed.

**Sample Size Justification:** The sample sizes chosen of 8 subjects per cohort (6 active: 2 placebo) in Part 1 and 2 is considered to be sufficient for evaluation of safety, tolerability, PK and the PD of TAK-020 in 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 Clinical Study Supplier List template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

#### **3.2 Principal Investigator**

PPD



### 3.3 List of Abbreviations

$\lambda_z$	terminal elimination rate constant
AE	adverse event
$Ae_{t1-t2}$	amount of drug excreted in urine from time 1 to time 2
$Ae_t$	amount of drug excreted in urine from time 0 to time t
$Ae_\tau$	amount of drug excreted in urine during a dosing interval ( $\tau$ ) at steady state
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{24}$	area under the plasma concentration-time curve from the time 0 to time 24 hours
$AUC_\tau$	area under the plasma concentration-time curve during a dosing interval, where tau ( $\tau$ ) is the length of the dosing interval
$AUC_t$	area under the plasma concentration-time curve from time 0 to time t
$AUC_\infty$	area under the plasma concentration-time curve from time 0 to infinity
BA	bioavailability
CCI	CCI
BCR	B cell receptor
BMI	body mass index
bpm	beats per minute
BTK	Bruton's tyrosine kinase
CI	confidence interval
CIA	collagen-induced arthritis
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
CS	clinically significant
$C_{ur\ t1-t2}$	concentration of drug excreted in urine from time 1 to time 2
%CV	percentage coefficient of variation
CYP	cytochrome P-450
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
EC90	90% effective concentration
ECG	electrocardiogram
eCRF	case report form electronic
ED50	median effective dose
eGFR	estimated glomerular filtration rate
$E_{max}$	maximum drug-induced effect

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FDA	Food and Drug Administration
$f_e$	fraction of drug excreted in urine
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
hERG	human ether-à-go-go-related gene
IC <sub>50</sub>	50% inhibitory concentration
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITAM	immunoreceptor tyrosine-based activation motifs
IUD	intrauterine device
K <sub>2</sub> EDTA	potassium ethylenediamine-tetraacetic acid
LFT	liver function test
LOAEL	low-observed-adverse-effect-level
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple rising dose
MSS	most sensitive species
NCS	not clinically significant
NOAEL	no observed adverse effect level
OTC	over-the-counter
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PGx	pharmacogenomic(s)
PI	principal investigator
PK	pharmacokinetic
PT	preferred term
PTE	pretreatment event
QD	once daily
QTcF	QT interval with Fridericia correction method
R	accumulation ratio (index)
RA	rheumatoid arthritis
R <sub>ac(AUC)</sub>	accumulation ratio (based on AUC)
RNA	ribonucleic acid

SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SRD	single rising dose
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal disposition phase half-life
TB	tuberculosis
TEAE	treatment emergent adverse event
$t_{max}$	time of first occurrence of $C_{max}$ .
$t_{max}(E)$	time to $E_{max}$
$t_{lag}$	lag time
ULN	upper limit of normal
$V_{ur\ t1-t2}$	volume of urine excreted from time 1 to time 2
$V_z/F$	apparent volume of distribution during the terminal phase after extravascular administration
WHODRUG	World Health Organization Drug Dictionary

### **3.4 Corporate Identification**

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-020 is an orally available small molecule irreversible inhibitor of Bruton's tyrosine kinase (BTK) for the treatment of autoimmune diseases. BTK is expressed in multiple cell types (including B cells, neutrophils, basophils, monocytes, mast cells and osteoclasts) and the function of BTK in these cell types may be clinically relevant in a variety of autoimmune diseases [1-4]. BTK plays a critical role in B-cell receptor activation, which results in proliferation and phenotypic differentiation of immature B cells into antibody-secreting cells [2,3]. It also plays an essential role in Fcγ and Fcε receptor signaling by mediating activation of immunoreceptor tyrosine-based activation motifs (ITAM) in multiple cell types [1,2,5]. Inhibiting B cell activation and ITAM signaling are 2 of the main mechanisms through which TAK-020 is proposed to contribute to clinical efficacy in the treatment of autoimmune disease.

The initiation of rheumatoid arthritis (RA) involves the presentation of self-antigens, leading to the activation of T and B lymphocytes. Activation of the adaptive immune response results in cytokine secretion and autoantibody production, which promotes inflammation [6]. Therapies directly or indirectly targeting B cells have been developed in an attempt to attenuate disease progression. Whereas current therapies for RA primarily target a single factor contributing to RA pathogenesis, BTK is an appealing therapeutic target because of its function in multiple signaling pathways downstream of the B cell receptor (BCR) and FcεRs.

TAK-020 engages the target rapidly and remains covalently bound, even after plasma concentrations are undetectable, with proven efficacy in a rat collagen-induced arthritis (CIA) model with median effective dose (ED<sub>50</sub>) of 0.31 mg/kg/day. The high selectivity of TAK-020 reduces potential off-target effects and it is anticipated to improve the benefit risk profile of this compound compared with competitors (eg, ibrutinib).

TAK-020 is poorly soluble, but using a Captisol formulation, appears well-absorbed across nonclinical species, with the predicted fraction absorbed in humans estimated as 98% from oral dosing solution. In nonclinical studies, TAK-020 was absorbed rapidly and extensively after oral administration, with peak plasma concentrations generally occurring within 2 hours postdose. Terminal disposition phase half-life ( $t_{1/2z}$ ) of TAK-020 after oral administration was 4.4-7.3 hours in rats and 3.8-6.7 hours in dogs. The oral bioavailability (BA) of TAK-020 in animals was low (12.6%-21.8% in rats and 8.17% to 16.5% in dogs). Absorption could be modulated by P-glycoprotein (P-gp), since TAK-020 is likely to be a P-gp substrate based on results obtained from a study using LLC-PK1-MDR1 cells.

TAK-020 is mainly metabolized by CYP3A4, CYP2C19, and CYP1A2, and is also metabolized to a minor extent by CYP2D6, CYP2C8, and CYP2C9 (TAK-020-10222, TAK-020-10223). TAK-020 has inhibitory effects on CYP2C19 activity with 50% inhibitory concentration (IC<sub>50</sub>) of 10 μmol/L without preincubation and 6.3 μmol/L with pre-incubation (TAK-020-10133). TAK-020 has little or no time-dependent inhibitory effects on the other cytochrome P-450 (CYP) activities (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A4/5) up to 30 μmol/L

(TAK-020-10133). TAK-020 is a weak inducer for CYP1A2 and CYP3A4 (TAK-020-10134). TAK-020 was found to be an inducer for CYP2B6.

A comprehensive series of nonclinical safety studies (Good Laboratory Practice [GLP]) was conducted with TAK-020 to support early human studies. No safety concerns were identified in safety pharmacology assessments (human ether-à-go-go-related gene [hERG], electrocardiography, cardiovascular, respiratory, central nervous system [CNS]), genetic toxicology studies (Ames, in vitro micronucleus, in vivo micronucleus), or an in vivo phototoxicity study. In addition, daily repeated-dose toxicology studies of 28 days in duration have been conducted in rats and dogs. The oral dose levels were 5, 25, and 75 mg/kg in the rat study and 5, 20, and 75 mg/kg in the dog study. The no-observed-adverse-effect level (NOAEL) in the rat study was 5 mg/kg (AUC=63 ng\*h/mL, sexes combined). The NOAEL in the dog study was 20 mg/kg (AUC=518 ng\*h/mL, sexes combined). At the low-observed-adverse-effect-level (LOAEL) the combined sex AUC in rat and dog were 431 ng\*h/mL and 6418 ng\*h/mL, respectively.

For further information on TAK-020, please refer to the Investigator's Brochure for TAK-020.

#### **4.2 Rationale for the Proposed Study**

The nonclinical pharmacology, toxicology, and pharmacokinetic (PK) studies support the proposed escalating single and multiple dose study of TAK-020 in healthy subjects.

The study will characterize the safety, tolerability, PK, and pharmacodynamic (PD) of TAK-020 in healthy subjects.

## 5.0 STUDY OBJECTIVES AND ENDPOINTS

### 5.1 Objectives

#### 5.1.1 Primary Objective

To characterize the safety and tolerability of TAK-020 following single and multiple oral doses in healthy subjects.

#### 5.1.2 Secondary Objectives

- To characterize the PK of TAK-020 following single and multiple oral doses.
- To characterize the PD of TAK-020 following single and multiple oral doses.

### 5.2 Endpoints

#### 5.2.1 Primary Endpoints

The primary safety endpoints include the number and percentage of subjects who:

- Experience at least 1 treatment-emergent adverse event (TEAE).
- Meet the Takeda Development Center, Inc. (TDC) markedly abnormal values (MAV) criteria for safety laboratory tests at least once postdose.
- Meet the TDC MAV criteria for vital sign measurements at least once postdose.
- Meet the TDC MAV criteria for safety electrocardiogram (ECG) parameters at least once postdose.

#### 5.2.2 Secondary Endpoints

The secondary endpoints will be the following PK parameters of TAK-020:

- Maximum observed plasma concentration ( $C_{\max}$ ).
- Time of first occurrence of  $C_{\max}$  ( $t_{\max}$ ).
- Area under the plasma concentration-time curve from time 0 to the time  $t$  ( $AUC_t$ ).
- Area under the plasma concentration-time curve from time 0 to infinity ( $AUC_{\infty}$ ).
- Area under the plasma concentration-time curve during a dosing interval, where tau ( $\tau$ ) is the length of the dosing interval ( $AUC_{\tau}$ ).
- Terminal disposition phase half-life ( $t_{1/2z}$ ).
- Apparent clearance after extravascular administration ( $CL/F$ ).
- Apparent volume of distribution during the terminal phase after extravascular administration ( $V_z/F$ ).



- Total amount of drug excreted in urine from time 0 to time  $t$  ( $Ae_t$ ).
- Fraction of drug excreted in urine ( $f_e$ ).
- Renal clearance ( $CL_R$ ).

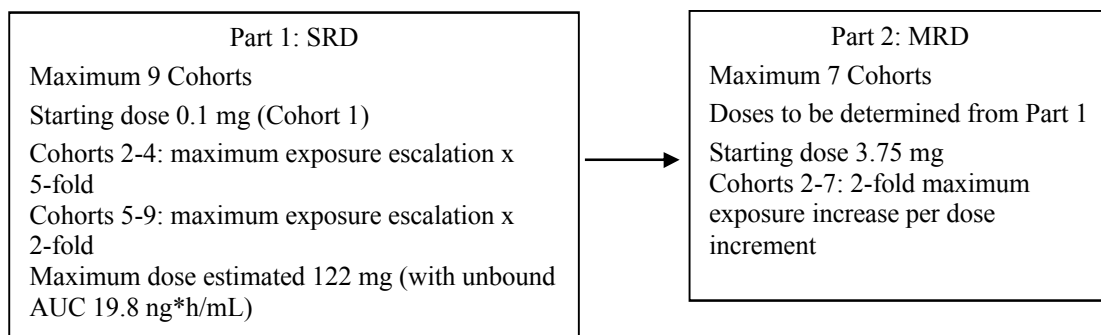
### 5.2.3 Exploratory Endpoints



## 6.0 STUDY DESIGN AND DESCRIPTION

### 6.1 Study Design

This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple-dose study in healthy volunteers. The study is comprised of 2 parts, each with multiple cohorts and is presented in the Study Schematic below. The study population for each part will be composed of healthy subjects aged 18 to 55 years, inclusive, who weigh at least 45 kg, and have a body mass index (BMI) between 18 and 32 kg/m<sup>2</sup>, inclusive, at Screening and Day -1.



SRD=single-rising dose, MRD=multiple-rising dose.

#### Part 1: SRD

This part will comprise a maximum of 9 cohorts. Each cohort will comprise of 8 randomized subjects, with 6 receiving TAK-020 and 2 receiving placebo in the fasted state. Sentinel dosing will be used for Cohort 1 with only 2 subjects dosed on the morning of Day 1 (1 receiving TAK-020 and 1 receiving placebo). The remaining subjects will be dosed following agreement with the investigator and Takeda after reviewing 24-hour postdose safety (adverse events [AEs], vital signs, 12-lead ECGs) and tolerability data. Sentinel dosing will not be necessary for other cohorts provided that exposure is observed in  $\geq 4$  subjects receiving active treatment and in agreement with the investigator and Takeda, otherwise sentinel dosing in the subsequent cohort will be required.

TAK-020 will be orally administered as a solution with a starting dose of 0.1 mg for Cohort 1. Dosing for the subsequent cohorts will only occur after review of the safety, tolerability, and minimum 24-hour PK data from the previous cohort. For each dose escalation, exposures may be increased by a maximum of 5-fold for Cohorts 2-4 and a maximum of 2-fold for Cohorts 5 to 9. Doses may also be decreased as appropriate.

#### Part 2: MRD

TAK-020 will be orally administered as a solution. The dose to be used in each cohort will be selected based on data from Part 1 of the study and from the previous cohort in Part 2.

#### 2) MRD Evaluation

The first cohort for the MRD will receive a dose of 3.75 mg, with a predicted exposure at steady state estimated to be below the NOAEL rat (63 ng\*h/mL). The cohort may be initiated when the

acceptable safety and tolerability have been collected in the SRD. The predicted steady state exposure in the first MRD cohort will be approximately 10-fold lower than the highest predicted steady state exposure determined from the SRD data. The MRD will comprise a maximum of 7 cohorts, each cohort with 8 subjects randomized with 6 receiving TAK-020 and 2 receiving placebo. In each successive cohort after the first, the dose increments will increase the predicted exposures by no more than 2-fold. The predicted steady state exposure in the MRD will not exceed the maximum exposure observed in the SRD.

A schematic of the study design is included as [Figure 6.a](#). A schedule of assessments is listed in [Appendix A](#).

### Figure 6.a Schematic of Study Design

#### Study Schematic for Part 1

Screening	Check-in	Dose	Check-out	Follow-up (a)
Day -28 to -2	Day -1	Day 1	Day 5	Day 14 ( $\pm 2$ )

(a) A phone call is planned but individual subjects may be asked to return to the unit at this time if abnormal clinical safety laboratory values are obtained at Check-out or TEAEs have not resolved at Check-out.

#### Study Schematic for Part 2

Screening	Check-in	Dose	Washout	Dose	Check-out	Follow-up (a)
Day -28 to -2	Day -1	Day 1	Day 2	Days 3-9	Day 10	Day 17 ( $\pm 2$ )

(a) All subjects will return to the unit and complete hematology, serum chemistry, renal biomarkers and pharmacodynamic tests, vital signs, concomitant medications, and AE assessment.

#### 6.1.1 Dose Escalation

The dose escalation scheme is shown in [Figure 6.b](#). All decisions concerning dose escalation will be made by Takeda (at a minimum, the clinical science representative(s) and pharmacovigilance physician) and the principal investigator (PI). Additionally, Takeda and the PI 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.

The AUC<sub>24</sub> will be calculated for each subject and subsequently the geometric mean of AUC<sub>24</sub> will be determined for each cohort (excluding placebo). Dose escalation will proceed to a dose level that is predicted to give a TAK-020 unbound AUC of (19.8 ng\*h/mL) approximately 2-fold higher than the unbound AUC of the rat LOAEL.

There will be a minimum period of 5 days between each dose escalation to allow for review of safety, tolerability and PK data. The blind of the PK data will remain intact during these reviews by using an alias number as the subject identifier instead of randomization sequence number for each subject.

For each dose level administered/completed cohort, the PI and Takeda will carefully review the available blinded safety, tolerability and blinded PK data (if data is available in time for the planned review). They will determine whether dosing should stop or continue (and, if continue, at what dose, including whether to repeat the previous dose), whether additional sequential dosing

should be implemented in future cohorts or whether the blind should be broken to identify whether the subjects received TAK-020 or placebo. In the next cohort (Part 1), exposures may be increased by a maximum of 5-fold as long as the predicted exposure will be below that at the NOAEL in the most sensitive nonclinical species, which is the rat (63 ng·hr/mL, sexes combined). For doses with exposure above the NOAEL doses may be increased to give a maximum of 2-fold increase in exposure. Doses may also be decreased as appropriate. In cohorts in the next part of the study (Part 2), the doses may be increased as long as the maximum exposure multiplier is below 2-fold. The predicted steady state exposure in the MRD will not exceed the maximum exposure observed in the SRD.

All AEs reported during the Treatment Period, both within and across cohorts, up to the time of discharge on Day 5 (Part 1) and Day 10 (Part 2) will be evaluated to assess the need for subject and/or study termination in accordance with the prespecified criteria for discontinuation/termination (Section 6.3.1).

Following assessment of the AE data and pre-defined 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 PI will decide if and how it is appropriate for the study to proceed.

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

## Figure 6.b Proposed Dose Escalation Scheme

### Part 1 SRD

Cohort 1→ (a)	Cohort 2→ (a)	Cohort 3→ (a)	Cohort 4→ (a)	Cohort 5→ (a)	Cohort 6→ (a)	Cohort 7→ (a)	Cohort 8→ (a)	Cohort 9 (a)
0.1 mg TAK-020 or placebo	0.5 mg TAK-020 or placebo	2.5 mg TAK-020 or placebo	4.4 mg TAK-020 or placebo	8.8 mg TAK-020 or placebo	17.5 mg TAK-020 or placebo	35 mg TAK-020 or placebo	70 mg TAK-020 or placebo	105 mg TBD TAK-020 or placebo
Completed	Completed	Completed	Completed	Completed	Completed	Completed	Completed	

(a) Dosing with TAK-020 will progress to the next cohort after review of the safety, tolerability and PK data from the previous cohort and the agreement of the PI and Takeda of the next proposed dose.

TBD = to be determined for actual dose level when PK data from the previous cohort is available.

### Part 2 MRD

Part 2 MRD Evaluation	Cohort 1→	Cohort 2→	Cohort 3→	Cohort 4→	Cohort 5→	Cohort 6→	Cohort 7
	3.75 mg TAK-020 or placebo	5.75 mg TAK-020 or placebo	13 mg TAK-020 or placebo	25 mg TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo

TBD = to be determined for actual dose level when PK data from the previous cohort is available.

### 6.1.2 Criteria for Stopping Dose Escalation

1. Two or more subjects in any single cohort or across more than 1 cohort experience any of the Takeda Medically Significant List events (as outlined in [Table 10.a](#)).\*
2. Two or more subjects in any single cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations  $> 3 \times$  upper limit of normal (ULN), irrespective of total bilirubin increase or other lab changes.
3. Two or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations  $> 5 \times$  ULN in the absence of a concomitant bilirubin increase.\*
4. One or more subjects in any single cohort or across more than 1 cohort experience 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”).
5. Two or more subjects in any single cohort or across more than 1 cohort experience 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. Within each dose level, if 2 subjects develop a dose limiting toxicity (DLT) listed in [Table 6.a](#) that is confirmed by repeat test if applicable, the subject(s) will be unblinded prior to any dose-escalation safety review meeting. If the unblinded subjects have received TAK-020, no further dosing will occur in that dose level and no further dose escalation beyond that dose level will be allowed.
7. Two or more subjects in the same cohort experience the same toxicity graded at least as moderate ( $\geq$  Grade 2) and requiring discontinuation of investigational drug.

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

- In addition to Takeda’s standard criteria for study termination, the following stopping criteria will also be implemented in this study for individual subjects:
  - Within each dose level, if at least 1 subject develops a DLT listed in [Table 6.a](#), and confirmed by repeat test, if applicable, the subject will be unblinded prior to any dose-escalation safety review meeting. If the unblinded subject has received TAK-020, no further dosing will occur in that subject.

**Table 6.a TAK-020 DLTs**

<b>Toxicity</b>	<b>Definition</b>
Leukopenia	Total leukocyte count $<2500 \text{ cells/mm}^3$ ( $2.5 \times 10^9/\text{L}$ )
Neutropenia	Absolute neutrophil count $<1500/\text{mm}^3$ ( $1.5 \times 10^9/\text{L}$ )
Thrombocytopenia	Platelet count $<75 \times 10^9/\text{L}$
Lymphopenia	Lymphocyte count $<1000 \text{ cells/mm}^3$ ( $1.0 \times 10^9/\text{L}$ )
Liver enzymes	ALT or AST $>3 \times \text{ULN}$
Renal changes	Serum Creatinine $>1.3 \times \text{ULN}$ Or eGFR decrease by 30% from Baseline
Abnormal coagulation	INR $>2 \times \text{ULN}$ aPTT $>2 \times \text{ULN}$ prothrombin time $>2 \times \text{ULN}$
QT interval with Fridericia correction method (QTcF)	QTcF $>500 \text{ msec}$ or a change from Baseline in QT/QTcF of $>60 \text{ ms}$ .
Severe infection	Serious infection requiring hospitalization, intravenous (IV) antibiotics (more than 1 dose), systemic antifungal or antiviral intervention

aPTT=activated partial thromboplastin time, eGFR= estimated glomerular filtration rate.

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

### Study Design

#### Parts 1 and 2

This study will be performed in healthy subjects rather than the target subject population (ie, diseased patients) in order to collect safety and tolerability information that will not be biased by common comorbidities. The study is double-blind in order to avoid subjective bias in the assessment of safety, tolerability, and pharmacological effects of the study medication. Placebo will be administered as a control in order to establish the frequency or magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Sentinel dosing is intended to be used in the first cohort in Part 1, but it may also be used in other cohorts if exposure is observed in fewer than 3 subjects or by agreement with Takeda and the investigator.

### Dose and Dose Regimen

The starting dose of 0.1 mg was based on both the Food and Drug Administration (FDA) guidance [7] and PK/PD modeling which predicted 20% BTK occupancy, which is considered to represent a minimum anticipated biological effect level.

Currently doses of 0.1, 0.5, 2.5, 4.4, 8.8, 17.5, 35, 70, and 105 mg have been tested in the SRD and 3.75, 5.75, 13 and 25 mg in the MRD and were shown to be safe and well tolerated. Draft PK data are summarized in Table 6.b and Table 6.c for the SRD and MRD, respectively.

**Table 6.b Summary of TAK-020 PK Parameters Cohorts 1 to 9 in SRD**

Cohort (Dose)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> <sup>*</sup> (hr)	AUC <sub>24</sub> (ng*h/mL)	AUC <sub>t</sub> (ng*h/mL)	AUC <sub>∞</sub> (ng*h/mL)	Half-life (hr)

\*Median value.

**Table 6.c Summary of TAK-020 PK Parameters Cohorts 1 to 7 in MRD**

Cohort (Dose)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> <sup>*</sup> (hr)	AUC <sub>24</sub> (ng*h/mL)	AUC <sub>t</sub> (ng*h/mL)	AUC <sub>∞</sub> (ng*h/mL)	Half-life (hr)	Accumulation Index

\*Median value.

Accumulation index=D9AUC<sub>24</sub>/D1AUC<sub>∞</sub>.

TBD=to be determined.

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Furthermore, plasma protein binding of TAK-020 in humans is higher than in the rat, (98.9% and 98.0% respectively) resulting in lower exposures to unbound (free) TAK-020 in humans at a given total exposure. Therefore unbound exposure estimates have been used to refine the dose escalation.

The exposure at the maximum proposed dose would not exceed 1808 ng\*h/mL (total) and 19.9 ng\*h/mL (unbound) which is 2.19-fold unbound exposure at the LOAEL, and corresponds to a safety factor of 0.43.

As the PK  $t_{1/2z}$  for this compound remains short, PK washout would be expected within 24-hours and time dependency of PK could be evaluated without the need for any additional washout period following Day 1 in the MRD study Part 2. Further, due to the short  $t_{1/2z}$ , no accumulation in plasma PK is expected during the MRD. PD washout following Day 1 in MRD was not considered necessary for evaluation.

The following safety variables will be used to describe the safety and tolerability of TAK-020:

- Physical examination findings.
- TEAEs.
- Clinical laboratory test results.
- Vital sign measurements and weight.
- 12-lead ECGs.

#### **Background safety information – anticipated risks**

##### **Risk factors relating to mode of action and nature of target**

Based on information from patients with inherited BTK deficiency, immunosuppression with low serum immunoglobulins, low circulating B-cells and opportunistic infections could be observed with >99% BTK inhibition by TAK-020.

##### **TAK-020 nonclinical studies**

Nonclinical toxicology studies were conducted with TAK-020 in rats and dogs. The rat was identified as the most sensitive toxicology species. Target organ toxicity in a GLP 4-week rat toxicology study administered doses in excess of the NOAEL ( $AUC > 63$  ng·hr/mL, sexes combined) was seen in the liver and kidney. Liver toxicity was seen in rats at an AUC of greater or equal to 431 ng·hr/mL (sexes combined), and kidney toxicity seen at an AUC of 2030 ng·hr/mL. Reversibility was not tested in the 4-week GLP rat study, however in a 2-week rat study, liver changes were fully reversible after a 2-week recovery period. In the absence of nonclinical information on reversibility, the kidney changes will be considered not reversible. Markers of kidney injury will be monitored in this study.

##### **Safety profile of other BTK inhibitors**

Based on first-in-human (FIH) safety data from BTK inhibitor CC-292 in healthy volunteers, grade 1 liver function test increase, hemoglobin decrease, blood glucose increase and diarrhea may be observed with TAK-020. CC-292 was well tolerated in the study with healthy volunteers, (assumed body weight 60 kg), who received 0.5 mg/kg (30 mg) to 7.0 mg/kg (420 mg) CC-292.

Based on the US prescribing information of BTK inhibitor ibrutinib, cytopenias, hemorrhage, renal toxicity, atrial fibrillation and serious infections were seen in patients with hematological



malignancies. No information is available about ibrutinib use in healthy volunteers for comparison.

These potential risks can be monitored clinically or with serial laboratory tests and were taken into consideration when setting the stopping rules and dose limiting toxicities in the proposed TAK-020 FIH study.

### **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 medication that indicates a change in the known risk/benefit profile for TAK-020, 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 meets predefined dose escalation stopping rules within or between cohorts and the sponsor and PI jointly decide not to study additional cohort(s) at a lower dose per Section 6.1.2.

#### **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(s)**

In the event that the sponsor, an institutional review board (IRB)/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 prior to randomization or first dose or other.

### 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 or, when applicable, the subject's legally acceptable representative 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 informed consent and first study medication dose.
5. [Previous criterion deleted.]
6. The subject weighs at least 45 kg and has a BMI between 18.0 and 32.0 kg/m<sup>2</sup>, inclusive at Screening and Day -1.
7. [Previous criterion deleted.]
8. 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 12 weeks after last dose.
9. A female subject of childbearing potential\* who is sexually active with a nonsterilized\* male partner agrees to use adequate contraception\* from signing of informed consent throughout the duration of the study and until the next menstrual period or 30 days after last dose, whichever is first. If the next menstrual period is delayed, a pregnancy test will be required for exclusion of pregnancy. See section 8.1.10 for Pregnancy Follow-up.

*\*Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.*

### 7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 30 days prior to Screening.
2. The subject is an immediate family member, study site employee, or 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 a known hypersensitivity to any component of the formulation of TAK-020, Captisol or related compounds.
4. The subject has a positive urine drug result for drugs of abuse at Screening or Check-in (Day -1).
5. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as 4 or more alcoholic beverages per day) within 1 year prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study. One unit is equivalent to a half-pint of beer or 1 measure of spirits or 1 glass of wine.
6. Subject has taken any excluded medication, supplements, or food products listed in [Table 7.a](#) Prohibited Medications and Dietary Products.
7. If female, the subject is pregnant or lactating or intending to become pregnant before, during or within 1 month after exit from this study (30 days post last dose); or intending to donate ova during such time period.
8. If male, the subject intends to donate sperm during the course of this study or for 12 weeks thereafter.
9. Subject has evidence of current cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking TAK-020, or a similar drug in the same class, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
10. Subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis frequent [more than once per week] occurrence of heartburn, or any surgical intervention [eg, cholecystectomy]).
11. Subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1.
12. 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).
13. The subject has poor peripheral venous access.
14. 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 30 days prior to Day 1.
15. Vaccination with any live vaccine within 4 weeks of study drug administration.

16. Subject has a Screening or Check-in (Day -1) abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by the PI medically qualified subinvestigator.
17. Subject has QTcF >450 msec for men and women or PR outside the range of 120 to 220 msec confirmed upon repeat testing within a maximum of 30 minutes, at the Screening Visit or Check-in (Day -1).
18. Subject has abnormal Screening or Day -1 laboratory values that suggest a clinically significant underlying disease or subject with the following lab abnormalities:
  - a) ALT or AST >1.2× the ULN.
  - b) Positive screen test for drugs of abuse.
  - c) Positive blood screen for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus-1 or -2 antibodies.
  - d) A positive test for tuberculosis (TB) (QuantiFERON).

### **7.3 Excluded Medications and Dietary Products**

Use of the agents in [Table 7.a](#) (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

**Table 7.a Prohibited Medications**

<b>28 days prior to Check-in (Day -1)</b>	<b>7 days prior to Check-in (Day -1)</b>	<b>72 hours prior to Check-in (Day -1)</b>
Prescription medications	OTC medications (a)	Products containing caffeine or xanthine
Hormonal Contraceptives		
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 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		
P-gp substrates or inhibitors		

OTC=over-the-counter.

(a) Occasional use of acetaminophen ( $\leq 2$  g/day) is allowed or other OTC medication as approved by Takeda's Medical Monitor or designee on a case-by-case basis during the 7 days prior to Day -1. Acetaminophen may be allowed from Day 1 in exceptional circumstances but its use should be carefully monitored.

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

Subjects must be instructed not to take any medications including OTC products, without first consulting with the investigator.

Use of concomitant medications will not be allowed during the study except for those approved by Takeda on a case-by-case basis, unless deemed necessary in a medical emergency or treatment of adverse events. Concomitant medications will include all medications the subject has taken from Screening to Follow-up.

If the subject reports taking any medication or if administration of any medication becomes necessary during the course of this study, the Takeda Medical Monitor or designee must be notified. All medications must be recorded in the source documents as well as on the appropriate electronic case report form (eCRF) along with dosage information, dates of administration, and reasons for use.

#### **7.4 Diet, Fluid, and Activity Control**

Subjects will be confined to the clinic for the duration of each treatment period: Part 1, Day -1 through Day 5, Part 2, Day -1 through Day 10.

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). On dosing days, breakfast will not be served. For Part 1 of the study, the meals served on the day of dosing should be identical for each cohort in the study. For Part 2 of the study, meals served on the PK assessment days (Days 1 and 9) should be identical for each cohort. Meals on other days should be standardized to ensure comparability if options are provided (consistent protein, carbohydrates, and fat content).

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. The meal start and stop times and percentage of the meal consumed will be recorded in the source and appropriate eCRF for all meals served on PK assessment days, Day 1 for Part 1 of the study (SRD), and Days 1 and 9 for Part 2 of the study (MRD).

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 arm of the study, Part 1, TAK-020 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.

During the MRD arm of the study, Part 2, TAK-020 and placebo will be administered on Days 1 and 3 through 9 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. The dosing regimen and diet should be consistent on each day of the study.

Subjects will remain upright (seated, standing, or ambulatory) for 1 hour following the dose administration, except as necessitated by the occurrence of an adverse event or study procedures (eg, obtaining 12-lead ECG). Subjects will refrain from strenuous 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 medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
    - Liver Function Test (LFT) Abnormalities
- Study medication should be discontinued immediately with appropriate clinical Follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to

normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

- ALT or AST  $>8 \times$  ULN, or
  - ALT or AST  $>5 \times$  ULN and persists for more than 2 weeks, or
  - ALT or AST  $>3 \times$  ULN in conjunction with elevated total bilirubin  $>2 \times$  ULN or INR  $>1.5$ , or
  - ALT or AST  $>3 \times$  ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ( $>5\%$ ).
2. Significant protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
  3. Lost to Follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
  4. 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 (ie, withdrawal due to an AE).

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. 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 9.1.10.

7. Other.

Note: The specific reasons 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. Subjects that are discontinued from the study due to non-safety reasons may be replaced at the discretion of the sponsor.

## 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 medication refers to all or any of the drugs defined below.

##### 8.1.1.1 Study Drug

#### **TAK-020 Drug Substance**

TAK-020 drug substance is manufactured by Albany Molecular Research, Inc., 21 Corporate Circle, Albany, NY 12203. The drug substance is packaged in an appropriate container with a single panel label that contains, but will not be limited to the following information: protocol number, lot number, US caution statement, and name and address of the sponsor.

A pharmacy manual will be provided to the unblinded pharmacist at site.

#### **TAK-020 Oral Solution**

The TAK-020 drug substance will be compounded at the clinical site pharmacy into TAK-020 oral solution. Compounding instructions will be provided to the pharmacy. The composition of the oral solution can be found below ([Table 8.b](#)). The oral solution will be filled into amber glass bottles and labeled at the pharmacy. The bottle size will be based upon the volume of dose required. The planned dose for Cohort 1 is 0.1 mg, but dose for subsequent doses have not been defined. They will be determined following review of the safety, tolerability and PK data from the previous cohort. The current estimates for the doses to be used in subsequent cohorts are provided in [Table 8.a](#). The dose may be adjusted by volume for subsequent cohorts based upon the previous cohort PK results.

The actual volume of solution given to a subject will be recorded on the eCRF.



**Table 8.a Proposed Dosing Levels and Volume of Each Cohort (SRD)**

Cohort	TAK-020 Dose Level	Volume of TAK-020 Solution (0.1 mg/mL)	Volume of TAK-020 Solution (1 mg/mL)	Volume of TAK-020 Solution (5 mg/mL)	Volume of TAK-020 Solution (7 mg/mL)
1	0.1 mg	1 mL			
2	0.5 mg	5 mL			
3	2.5 mg		2.5 mL		
4	4.4 mg		4.4 mL		
5	8.8 mg		8.8 mL		
6	17.5 mg			3.5 mL	
7	35 mg			7 mL	
8	70 mg				10 mL
9	105 mg (TBD)				15 mL

TBD=to be determined following review of safety, tolerability and PK data from the previous cohort.

**Table 8.b Composition of TAK-020 Oral Solution, 0.1, 1, 5, 7, and 7.5 mg/mL**

Component	Amount per mL*				
	0.1 mg/mL solution	1 mg/mL solution	5 mg/mL solution	7 mg/mL solution	7.5 mg/mL solution
TAK-020 (free base)	0.1 mg	1.0 mg	5.0 mg	7.0 mg	7.5 mg
Sodium hydroxide, NF grade	1.2 mg	1.2 mg	1.2 mg	1.2 mg	1.2 mg
Captisol, NF grade	200 mg	200 mg	200 mg	200 mg	200 mg
Phosphoric acid, NF grade	1.64 mg	1.64 mg	1.64 mg	1.64 mg	1.64 mg
Sterile water for irrigation, USP	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL

NF= National Formulary, q.s.= quantity sufficient, USP= United States Pharmacopeia.

\*The concentration may be prepared within the range of 0.1 mg/mL TAK-020 and 7.5 mg/mL TAK-020 to accommodate the dosing needs.

### Placebo for TAK-020 Oral Solution

The placebo for TAK-020 Oral Solution will be compounded at the clinical site pharmacy. The placebo solution will contain the same concentration of excipients as the active solution without the active drug substance. Compounding instructions will be provided to the pharmacy. The composition of the oral solution can be found below ([Table 8.c](#)). The oral solution will be filled into amber glass bottles and labeled by the pharmacy. The bottle and filled volumes of the placebo oral solution will be identical to the corresponding dose level volumes of the TAK-020 Solution, as listed in [Table 8.a](#).

**Table 8.c      Composition of Placebo for TAK-020 Oral Solution**

Component	Amount per mL
TAK-020 (free base)	0 mg
Sodium hydroxide, NF grade	1.2 mg
Captisol, NF grade	200 mg
Phosphoric acid, NF grade	1.64 mg
Sterile water for irrigation, USP	q.s. to 1 mL

NF= National Formulary, q.s.= quantity sufficient, USP= United States Pharmacopeia.

#### *8.1.1.2 Ancillary Materials*

Amber glass bottles will be used for dosing medication. The packaging for TAK-020 oral solution may use 5, 20, or 50 mL bottles. These will be provided by either the clinical site or Takeda based upon availability. If provided by Takeda, unused bottles will be accounted for and disposed of as directed by Takeda or a Takeda designee.

#### **8.1.2 Storage**

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

TAK-020 drug substance must be stored per the label at controlled room temperature 25°C (77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F). All TAK-020 compounded solution must be stored under the condition specified in the compounding worksheet at 2°C to 8°C (36°F to 46°F). A do not use beyond date of 14 days after compounding will be assigned. Bottles containing TAK-020 compounded solution may be stored at controlled room temperature for up to 24 hours prior to dosing. A daily temperature log of the drug storage area must be maintained every working day.

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

In Cohorts 1 to 9, doses of 0.1, 0.5, 2.5, 4.4, 8.8, 17.5, 35, 70, and 105 mg have been evaluated. The investigator or investigator's designee will instruct the subject on dosing procedures. All dosing will occur while subjects are in the clinic under the supervision of the PI or designee. On dosing days, subjects will be given TAK-020 or placebo oral solution. A separate pharmacy manual will describe how each dose regimen will be formulated.

Study drug will be administered at the same time on each dosing day (approximately 0800 hours). After initial administration, the dosing bottle shall be rinsed twice with about half the volume of the bottle with water. The rinse will be administered to the subject. The exact time of dose will be recorded in the source documents and on the appropriate eCRF.

#### **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 AEs.

Serious 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**

For each dosing cohort, subjects will be assigned to receive a 4-digit randomization sequence number. The number will be assigned by the clinic site personnel in sequential order. A separate randomization schedule will be provided for Part 1, and Part 2.

Part 1 (SRD), the randomization sequence number will be from X001 to X008 for Cohort X, for example: 1001 to 1008 for Cohort 1, and 2001 to 2008 for Cohort 2, etc.

Part 2 (MRD), randomization sequence number will be from X101 to X108 for Cohort X, for example: 1101 to 1108 for Cohort 1, and 2101 to 2108 for Cohort 2, etc.

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 PK and PD 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 which is assigned at the time the informed consent is obtained and which is used for all other procedures to identify the subjects throughout the study.

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

The randomization schedule will be generated by TDC Americas' Quantitative 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 Study Drug Blind Maintenance**

The investigational drug blind is maintained through a randomization schedule held by the site-designated unblinded pharmacist or designee.

The investigator will receive the subject's investigational drug blind information in the form of a sealed envelope, which will reveal the subject's study treatments if opened. During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform an inventory of blinded sealed envelopes.

### **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 or by opening the sealed envelope for that subject.

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 (TAK-020), 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 date/retest date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative or unblinded pharmacy monitor, otherwise uninvolved with study conduct, will review the randomization schedule and subject dosing log prior to Day 1 dosing and following dosing to ensure all subjects received the correct dose of study medication.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (TAK-020) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry and/or retest date, date and amount dispensed, including signature of the person dispensing the drug, including the 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.

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.

## 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 is located in [Appendix A](#).

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

##### 9.1.1.1 Pharmacogenomic Informed Consent Procedure

Pharmacogenomics informed consent is a component of the overall study informed consent. The requirements are described in Section [15.2](#).

The pharmacogenomic (PGx) sample collection is mandatory.

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

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, alcohol use, reproductive status 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 stopped at or within 28 days prior to signing of informed consent.

#### 9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the pretreatment assessment immediately prior to the start of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal change from the initial Screening physical examination must be assessed as not clinically significant (NCS) or clinically significant (CS) by the investigator and recorded in the source document and eCRF.

Any clinically significant change, as determined by the investigator, from the baseline physical examination will be recorded as an AE or pretreatment event in source documentation and on the Pretreatment Event/AE eCRF.

#### **9.1.4 Weight, Height and BMI**

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

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

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

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>.

#### **9.1.5 Vital Sign Procedure**

Vital signs will include body temperature oral measurement, respiratory rate, sitting blood pressure (after 5 minutes resting) and pulse (beats per minute [bpm]).

Vital signs should be measured at the same time of the day across visits if possible. 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.

#### **9.1.6 Documentation of Concomitant Medications**

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

#### **9.1.7 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 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. The maximum volume of blood at any single visit is approximately 140 mL, and the approximate total volume of blood for the study is 300 mL for Part 1 and 413 mL for Part 2. Laboratory samples will be taken following a minimum 10-hour overnight fast on the days stipulated in the Schedule of Study Procedures [Appendix A](#).

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



**Table 9.a Clinical Laboratory Tests**

Hematology	Serum Chemistry	Urinalysis
RBC	Alanine aminotransferase	pH
WBC with differential	Albumin	Specific gravity
[both % and absolute	Albumin: Globulin ratio	Protein
count]	Alkaline phosphatase	Glucose
Hemoglobin	Amylase	Blood
Hematocrit	Aspartate aminotransferase	Nitrite
Platelets	Total bilirubin	
prothrombin time /INR	Total protein	<u>Renal Biomarkers:</u>
aPTT	C-reactive protein	Kidney Injury Molecule-1
Fibrinogen	Cholesterol	(KIM-1)/ TIM-1 (T Cell
	Creatinine (eGFR) [8]	Immunoglobulin Mucin 1)
	Cystatin -C	Cystatin C
	Blood urea nitrogen	Neutrophil
	Creatine kinase	Gelatinase-Associated
	$\gamma$ -Glutamyl transferase	Lipocalin (NGAL)
	Glutamate dehydrogenase	Urine Albumin
	Lactate dehydrogenase	Urine Protein
	Potassium	
	Sodium	Microscopic Analysis
	Glucose	(performed only if urine
	Chloride	evaluations are abnormal):
	Quantitative IgA, IgG and IgM	RBC/high power field
	Triglycerides	WBC/high power field
	Bicarbonate	Epithelial cells, casts etc
	Calcium	
	Lipase	
<b>Diagnostic Screening:</b>		
<b>Serum</b>		<b>Urine</b>
Hepatitis panel, including HBsAg and anti-HCV, (and/or HCV RNA), HIV-1 and HIV-2 screening, TB screening (QuantiFERON)		Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine.
<u>Female subjects only:</u>		
hCG (for pregnancy)		
FSH if menopause is suspected		

aPTT= activated partial thromboplastin time, eGFR= estimated glomerular filtration rate, FSH= follicle-stimulating hormone, hCG=human chorionic gonadotropin, HIV= human immunodeficiency virus, Ig= immunoglobulin, RBC= red blood cells, RNA=ribonucleic acid, WBC= White blood cells.

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 the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing 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 PI or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

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 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 12 weeks after last dose of study medication, nonsterilized\*\* male subjects who are sexually active with a female partner of childbearing potential\* must use double 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 last dose of study medication, or until after the next menstrual period, female subjects of childbearing potential\* who are sexually active with a nonsterilized male partner\*\* must use adequate contraception. 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 medication is implemented).

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

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

<b>Barrier methods (each time the subject has intercourse):</b>	<b>Intrauterine devices (IUDs):</b>
---	-------------------------------------

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>• Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.</li><li>• Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.</li></ul> | <ul style="list-style-type: none"><li>• Copper T PLUS condom or spermicide.</li></ul> |
|---|---|

Contraception allowed in female partners of male subjects (hormonal contraception is allowed in female partners):

<b>Barrier methods (each time the subject has intercourse):</b>	<b>Intrauterine devices (IUDs):</b>	<b>Hormonal contraceptives:</b>
<ul style="list-style-type: none"><li>• Male condom PLUS spermicide.</li><li>• Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.</li><li>• Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.</li></ul>	<ul style="list-style-type: none"><li>• Copper T PLUS condom or spermicide.</li><li>• Progesterone T PLUS condom or spermicide.</li></ul>	<ul style="list-style-type: none"><li>• Implants.</li><li>• Hormone shot/injection.</li><li>• Combined pill.</li><li>• Minipill.</li><li>• Patch.</li><li>• Vaginal ring PLUS male condom and spermicide.</li></ul>

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.

During the course of the study, regular serum hCG pregnancy tests will be performed for all female subjects and also both male and female subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures ([Appendix A](#)). In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative serum hCG pregnancy test on Day -1 and at Check-out (Day 5 for Part 1 or Day 10 for Part 2) or Early Termination. If after Study Exit the expected menstruation is delayed, female subjects and female partners of male subjects must do a pregnancy test and inform the investigator immediately, if the pregnancy test is positive. See [Section 9.1.10](#) for Pregnancy reporting and Follow-up until outcome.

#### **9.1.10 Pregnancy**

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (TAK-020) should be immediately discontinued. In addition, any pregnancies in the female 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 medication, eg, after Day 1 or within 12 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in [Section 1.0](#).

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

If the female subject and/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/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

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

### 9.1.11 ECG Procedure

#### 9.1.11.1 Screening and Safety ECGs

A triplicate 12-lead ECG printed in standard format, will be collected at Screening, Check-in (Day -1), Day 1 predose (0 hours) and at 1, 4, 12, 24, 48, 72, and 96 hours postdose or at Early Termination in Part 1 (SRD) and at Screening, Check-in (Day -1), Day 1 predose (0 hours) and at 1, 4, 12, 24 hours postdose, and also on Dosing Days 3, 5, 9, and 10 at predose (0 hours), or at Early Termination for Part 2 (MRD).

The investigator will interpret the Safety ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded.

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, QRS interval, PR interval, QT interval, and QT (corrected) (Fridericia's and Bazett's corrections).

The investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the investigator for subject safety and will be provided in an appropriate format with the clinical study report.

Ad hoc 12-lead ECGs will also be required, if a subject complains of palpitations, dizziness, sudden onset of breathlessness, chest tightness or any other symptoms of arrhythmia, between Day 1 (postdose) and Study Exit/Early Termination. Pulse checked immediately, and if it is greater than 80 bpm, a 12-lead ECG, blood pressure and pulse will be measured and recorded. The ECG, blood pressure and pulse measurements shall be reviewed by the Investigator, who will use clinical judgment regarding further monitoring and management.

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 signed by the physician or archival quality paper can be utilized for ECG printouts, with a 25 year (or more) guarantee from the manufacturer (assuming appropriate storage conditions are satisfied). If a photocopy is made, it will be filed with the original ECG in the source.

When an ECG is scheduled at the same time as blood draws or vital signs, then the blood draws and vital signs will take priority and the ECG will be obtained within 0.5 hour before or after the

scheduled blood draw/vital sign assessment. If an ECG coincides with a meal, ECG will take precedence followed by the meal.

#### *9.1.11.2 Telemetry*

On Day 1 of Part 1 (SRD) and Days 1 and 9 of Part 2 (MRD), cardiac monitoring (telemetry) will be performed for approximately 2 hours prior to dosing through to approximately 12 hours postdose.

The site will use their standard telemetry system for monitoring rhythm and other ECG characteristics from approximately 2 hours prior to dosing through to approximately 12 hours postdose in each period. Subjects should remain sitting or supine for at least 5 minutes before each reading at each PK time point.

The data will be sent to Takeda who will engage a cardiac expert for reading the data, if required. Reporting of this data and any subsequent analysis will be reported separately.

Of interest are the ten (10) second triplicate ECGs that will be extracted at PK time-points for manual reading and precise ECG reading including QT interval measurement. The following parameters will be measured from the subject's ECG trace: heart rate, QT interval, PR interval, QRS interval, RR interval and QTcF and QTcB corrections. The effect of increasing concentrations of TAK-020 on these parameters will be explored.

#### **9.1.12 PGx Sample Collection**

When sampling of whole blood for PGx analysis occurs, every subject must sign informed consent/be consented in order to participate in the study.

Deoxyribonucleic acid (DNA) and RNA form the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "PGx research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to TAK-020.
- Finding out more information about how TAK-020 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to TAK-020.
- Identifying variations in genes related to the biological target of TAK-020.

This information may be used, for example, to develop a better understanding of the safety and efficacy of TAK-020 and other study medications, and for improving the efficiency, design and study methods of future research studies.

DNA samples will be used to evaluate drug metabolizing enzymes and transporter polymorphisms that may contribute to the variability in PK of TAK-020. Since PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these

genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

### **Part 1- PGx Sample Collection**

One whole blood sample (6 mL) for DNA isolation will be collected from each subject in the study before dosing on Day 1, into a plastic potassium ethylenediamine-tetraacetic acid (K<sub>2</sub>EDTA) spray-coated tube.

Two whole blood samples (2.5 mL per sample) will be collected for RNA analysis from each subject in the study predose on Day 1 and at 24 hours postdose, in a PAXgene tube.

### **Part 2 - PGx Sample Collection**

One 6-mL whole blood sample for DNA isolation will be collected before dosing on Day 1 from each subject in the study, into plastic K<sub>2</sub>EDTA spray-coated tubes.

Two whole blood samples (2.5 mL per sample) will be collected before dosing on Days 1, 3, and 9 for RNA isolation from each subject in the study, into a PAXgene tubes.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

The DNA samples will be used to evaluate common variations in genes which encode drug metabolizing enzymes and transporters. This could be helpful in understanding why there are differences in TAK-020 kinetics between subjects.

Each PGx sample for a study subject should be identifiable on the requisition form with a 7-digit subject ID (the 4-digit site number plus the 3-digit subject number).

The PGx samples will be shipped to Covance at the address listed in [Appendix E](#) of this protocol.

The samples will be stored for no longer than 15 years after completion of the TAK-020 study and/or until the drug development of TAK-020 is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. "Stored samples" are defined as samples that are key-coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drugs.

Detailed instructions for the handling and shipping of samples will be compiled in a laboratory manual and provided to the site.

### **9.1.13 PK Sample Collection**

#### *9.1.13.1 Collection of Plasma for PK Sampling*

Blood samples (one 6-mL sample per scheduled time) for pharmacokinetic analysis of TAK-020 will be collected into chilled Vacutainers containing K<sub>2</sub>EDTA according to the schedule in [Appendix A](#). Instructions for sample processing and shipment are provided in [Appendix E](#).

Serial blood samples for determination of TAK-020 will be collected according to [Table 9.b](#). Plasma samples will be taken at the following time points in the first cohort. Based on emerging data in each cohort, the time points may be modified but will not exceed the number of samples presented and will not be taken after 96 hours in the SRD and 48 hours in the MRD.

**Table 9.b Collection of Blood Samples for PK Analysis**

Part 1 (SRD)

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose

Part 2 (MRD)

Sample Type	Dosing Day	Time Postdose (hours)
Plasma	1	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
Plasma	9	Predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose

The actual time of sample collection will be recorded on the source document and eCRF.

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

Placebo samples will not be analyzed by the bioanalytical laboratory except 2 samples per subject receiving placebo, 1 predose and the other around the expected time at which  $C_{max}$  occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure protocol compliance that no additional subjects could have been on active treatment.

*9.1.13.2 Collection of Urine for PK Sampling*

Serial urine samples for determination of TAK-020 will be collected according to [Table 9.c](#). Urine samples will be taken at the following time points in the first cohort. Based on emerging data in each cohort, the time points may be modified but will not exceed the number of samples presented and will not be taken after 96 hours in the SRD and 48 hours in the MRD.

**Table 9.c Collection of Urine Samples for PK Analysis**

Part 1 (SRD)

Sample Type	Dosing Day	Time Postdose (hours)
Urine	1	Predose (-12-0), and 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 hour postdose intervals

Part 2 (MRD)

Sample Type	Dosing Day	Time Postdose (hours)
Urine	1	Predose (-12-0), and 0-6, 6-12, 12-24 hour postdose intervals
Urine	9	Predose (-12-0), and 0-6, 6-12, 12-24 hour postdose intervals

Instructions for sample processing and shipment are provided in [Appendix E](#).

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

*9.1.13.3 Bioanalytical Methods*

Plasma and urine concentrations of TAK-020 will be measured by high-performance liquid chromatography with tandem mass spectrometry.

Part of the archival plasma and urine samples will be sent to TDC Japan/Development Research Center for potential analysis of unknown metabolite characterization, if appropriate.

**9.1.14 PK Parameters**

The pharmacokinetic parameters of TAK-020 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.

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The following plasma PK parameters will be determined:

Symbol/Term	Definition
<b>Plasma/Blood/Serum</b>	
$AUC_{24}$	Area under the plasma/blood/serum concentration-time curve from the time 0 to time 24 hours.
$AUC_{\tau}$	Area under the plasma/blood/serum concentration-time curve during a dosing interval, where tau ( $\tau$ ) is the length of the dosing interval.
$AUC_t$	Area under the plasma/blood/serum concentration-time curve from time 0 to time of the last quantifiable concentration
$AUC_{\infty}$	Area under the plasma/blood/serum concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty} = AUC_t + C_{last}/\lambda_z$
R	Accumulation ratio (index) calculated as $AUC_{\tau}$ at steady state/ $AUC_{\infty}$ after a single dose.
$R_{ac(AUC)}$	Accumulation ratio (based on AUC), calculated as $AUC_{\tau}$ at steady state/ $AUC_{\tau}$ after a single dose.
$C_{max}$	Maximum observed plasma/blood/serum concentration.
$C_{max,ss}$	Maximum observed steady-state plasma/blood/serum concentration during a dosing interval.
CL/F	Apparent clearance after extravascular administration, calculated as $\text{Dose}/AUC_{\infty}$ after a single dose and as $\text{Dose}/AUC_{\tau}$ after multiple dosing (at steady state).
$\lambda_z$	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$t_{1/2z}$	Terminal disposition phase half-life, calculated as $\ln(2)/\lambda_z$ .
$t_{lag}$	Lag time.
$t_{max}$	Time of first occurrence of $C_{max}$ .
$V_z/F$	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$ .

The following urine PK parameters of TAK-020 will be determined:

<b>Urine</b>	
$Ae_{t1-t2}$	Amount of drug excreted in urine from time 1 to time 2, calculated as $C_{ur} \times V_{ur}$ , where $C_{ur}$ is the concentration of drug excreted in urine and $V_{ur}$ is the volume of urine excreted.
$Ae_t$	Total amount of drug excreted in urine from time 0 to time t.
$Ae_{\tau}$	Amount of drug excreted in urine during a dosing interval ( $\tau$ ) at steady state.
$f_e$	Fraction of drug excreted in urine, calculated as $(Ae_t/\text{dose}) \times 100$ . Molecular weight adjustment needed for metabolites.
$CL_R$	Renal clearance, calculated as $Ae_{0-24}/AUC_{24}$ .

### 9.1.15 PD Sample Collection

Sampling times for sampling collection are shown in the tables below.

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Instructions for sample processing and shipment are provided in [Appendix E](#).

9.1.15.1

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9.1.15.2 *BTK Occupancy Assay*

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9.1.16 PD Parameters

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### 9.1.17 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.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

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

### 9.1.18 Documentation of Randomization

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

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

## 9.2 Monitoring Subject Treatment Compliance

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

## 9.3 Schedule of Observations and Procedures

The 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).

### 9.3.1 Final Visit/Check-out

Final Visit for Part 1 will be on Day 5 and Part 2 will be on Day 10. The following procedures will be performed and documented:

- Physical exam.
- Vital signs.
- Weight.
- Concomitant medications.
- Clinical lab tests.
- Serum pregnancy test (female subjects only).
- CCI [REDACTED]
- 12-lead ECG.
- PK blood collection.
- PK urine collection.
- PD blood collection.
- AE assessment.

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

### 9.3.2 Early Termination

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

- Physical exam.
- Vital signs.
- Weight.
- Concomitant medications.
- Clinical lab tests.
- Serum pregnancy test (female subjects only).
- CCI [REDACTED]
- 12-lead ECG.
- PK blood collection.
- PK urine collection.

- PD blood collection.
- AE assessment.

The PK/PD sample collection should be collected at the Early Termination Visit, if possible and relatively close to a protocol-specified time point. For example, collect samples if early withdrawal is due to an AE, and/or if several hours elapsed since last blood draw.

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

### **9.3.3 Follow-up Visit/Telephone Call**

Subjects with unresolved SAEs, CS laboratory abnormalities, ECG or physical exam findings or at the PI's discretion should be seen for a Follow-up visit on Day 14 ( $\pm 2$  days) in Part 1 for appropriate repeat procedure(s). A Follow-up phone call will be made to all other subjects on Day 14 ( $\pm 2$  days) in Part 1 for an assessment of AEs and concomitant medications. In Part 2, all subjects will return the clinical site on Day 17 ( $\pm 2$  days) for laboratory tests (Hematology, Serum Chemistry, Urinary renal biomarkers, and PD tests), assessment of vital signs, AEs and concomitant medications.

## **9.4 Biological Sample Retention and Destruction**

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. The genetic material will be preserved and retained at Covance for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

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

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

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

## 9.5 Blood Volume

Total blood sampling volume for an individual subject is shown in [Table 9.d](#).

**Table 9.d Approximate Blood Volume**

Part 1									
Sample Type	Sample Volume (mL)	Number of Samples							Total Volume (mL)
		Day -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5 (a)	
Safety laboratory samples	29 (b) 19 (c)	1	1	1	1	1		1	124
PK samples	6	--	--	13	2	1	1	1	108
PD samples	4	--	--	8	2	1	1	1	52
PGx - DNA	6	--	--	1		--	--	--	6
PGx - RNA	2.5	--	--	2	2	--	--	--	10
Blood volume (mL)		29	19	140	44	29	10	29	300

(a) If abnormal labs at Check Out are outside markedly abnormal values (to be provided by Takeda in the final study protocol), repeat labs on Day 14 ( $\pm 2$ ) until resolution and report as a TEAE.

(b) Screening Visit only.

(c) Days -1 to 5.

Part 2													
Sample Type	Sample Volume (mL)	Number of Samples										Total Volume (mL)	
		Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Days 6 to 8	Day 9	Day 10 (a)		Follow-up
		8 to -2											
Safety laboratory samples	29 (b) 19 (c)	1	1	1	1	1	--	1	--	--	1	1	162
PK samples	6	--	--	13	2	--	--	--	--	13	1		174
CCI													
CCI													
PGx - DNA	6	--	--	1	--	--	--	--	--	--	--		6
PGx - RNA	2.5	--	--	2	--	2	--	--	--	2	--		15
Blood volume (mL)		29	19	130	37	26	0	19	0	105	29	23	417

(a) If abnormal labs at Check Out are outside markedly abnormal values (to be provided by Takeda in the final study protocol), repeat labs on Day 17 ( $\pm 2$ ) until resolution and report as a TEAE.

(b) Screening Visit only.

(c) Days -1 to 10.

The maximum volume of blood at any single day is approximately 140 mL, and the approximate total volume of blood for the study is 300 mL for Part 1 and 417 mL for Part 2.

Direct venipuncture is the preferred method of blood collection. Any other method of blood collection will need to be approved by the sponsor before use.

If a catheter with a normal saline flush is used, the total blood volume does not include discarded blood from predraws (assuming approximately 1 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study must not exceed 500 mL.

## **10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS**

### **10.1 Definitions**

#### **10.1.1 PTEs**

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

#### **10.1.2 AEs**

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; 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 medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

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



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

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

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

#### 10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
  - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
  - May require intervention to prevent items 1 through 5 above.
  - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
  - Includes any event or synonym described in the Takeda Medically Significant AE List ([Table 10.a](#)).

**Table 10.a Takeda Medically Significant AE List**

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

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

#### 10.1.5 Severity of PTEs and AEs

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

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

#### 10.1.6 Causality of AEs

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

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

#### 10.1.7 Relationship to Study Procedures

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

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

### **10.1.8 Start Date**

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

### **10.1.9 Stop Date**

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

### **10.1.10 Frequency**

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

### **10.1.11 Action Concerning Study Medication**

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

### **10.1.12 Outcome**

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

## 10.2 Procedures

### 10.2.1 Collection and Reporting of AEs

#### 10.2.1.1 PTE and AE Collection Period

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

Collection of AEs will commence from the time that the subject is first administered study medication on Day 1. Routine collection of AEs will continue until the Follow-up telephone call at 14 ( $\pm 2$ ) days for Part 1 and the Follow-up visit at 17 ( $\pm 2$ ) days for Part 2 after last dose of study medication.

#### 10.2.1.2 PTE and AE Reporting

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

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

1. Event term.
2. Start and stop date {and time}.
3. Frequency.
4. Severity.
5. Investigator’s opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator’s opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.

9. Seriousness.

### 10.2.2 Collection and Reporting of SAEs

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

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

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

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

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

### 10.2.3 Reporting of Abnormal LFTs

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. Concerning ALT/AST increases, please also see Section 6.1.2 Criteria for Stopping Dose Escalation.

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, IRBs or IECs, and Regulatory Authorities**

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or 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(s) and pharmacovigilance physician) and the PI will review the safety and tolerability data, pharmacokinetic data for each cohort prior to dosing any additional cohort. The decision for the next subsequent dose must be agreed by all representatives of Takeda and the PI. If any one person has concerns regarding subsequent dosing, 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 Drug Dictionary (WHODRUG).

### **12.1 Electronic CRFs**

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

The PI 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 PI must review the data change for completeness and accuracy, and must sign and date.

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

### **12.2 Record Retention**

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

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

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

## 13.0 STATISTICAL METHODS

### 13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment and 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

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (eg. age, height, weight, and BMI) for pooled placebo, each TAK-020 dose level, TAK-020 overall, and total overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (eg. gender, ethnicity, and race) will be tabulated for pooled placebo group, each TAK-020 dose level, TAK-020 overall, and total overall. Individual subject demographic and baseline characteristics data will be listed. Placebo data will be pooled across the cohorts. Part 1 and Part 2 data will be summarized separately.

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 PK Analysis

#### 13.1.3.1 Concentrations in Plasma and Urine

Concentrations of TAK-020 in plasma will be summarized by dose level over each scheduled sampling time using descriptive statistics. Individual plasma concentration data vs time will be presented in a data listing.

Amount of TAK-020 excreted in urine will be summarized by dose level over each scheduled sampling interval using descriptive statistics. Individual urine concentration data along with volume vs time intervals will be presented in a data listing.

PK concentration data in Part 1 and Part 2 will be summarized separately.

#### 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 PK parameters for TAK-020 by dose level and population. In addition, geometric mean and coefficient of variation will be computed for  $C_{\max}$  and AUCs. All PK parameter data will be listed.

Power model will be used to assess dose proportionality for  $C_{\max}$  and AUC in each part.

The power model will be assumed as described by the following equation:

$$\log(PKParameter) = \beta_0 + \beta_1 \log(Dose) + \varepsilon$$

Where  $\beta_0$  is the intercept,  $\beta_1$  is the slope and  $\varepsilon$  is the random error.

The 90% confidence interval (CI) of the slope estimate will be presented. 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).

Analysis of variance (ANOVA) will be performed for  $T_{\max}$  and  $\lambda_z$  after a single or multiple dose administration to evaluate the effect of dose on  $T_{\max}$  for SRD and MRD parts and  $\lambda_z$  for SRD part.

ANOVA will be used to assess time dependency for Part 2 (MRD). The natural log-transformed AUCs and  $C_{\max}$  will be used as response variable and dose level, Day and the interaction of dose level and Day will be fixed factors. Within the frame work of ANOVA, 90% CIs for the ratio of AUCs and  $C_{\max}$  central values between Days 9 and 1 will be presented.

Detailed analysis methodologies will be presented in SAP as necessary.

#### 13.1.4 PD Analysis

CCI

Descriptive statistics will be used to summarize PD parameters.

The relationship between dose, TAK-020 concentrations, PK parameters, and PD response will be explored and PKPD models developed if deemed appropriate.

CCI

Detailed analysis methodologies will be presented in SAP as necessary.

#### 13.1.5 Safety Analysis

The safety summary tables presented under this section will be summarized by placebo group, each TAK-020 dose level and TAK-020 overall for single and multiple doses of Part 1 and Part 2 if not specified otherwise. Placebo data will be pooled across the cohort of each Part. The subjects who meet pre-defined MAV criteria for laboratory tests, vital signs and ECG parameters will be summarized and listed.

##### 13.1.5.1 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 included in the summary tables. All AEs will be in the listings. 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.

##### 13.1.5.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet TDC's markedly abnormal criteria will be summarized and listed. Baseline, postdose, and change from Baseline to postdose laboratory data will be summarized by placebo and TAK-020 dose level. All clinical laboratory data will be listed.

##### 13.1.5.3 Vital Signs

Individual results of vital signs that meet TDC's markedly abnormal criteria will be summarized and listed. Baseline, postdose, and changes from Baseline in vital sign measurements will be

summarized by placebo and TAK-020 dose level. All vital sign data will be provided in the data listings.

#### *13.1.5.4 ECGs*

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that meet TDC's markedly abnormal criteria will be summarized and listed. Baseline, postdose, and changes from Baseline in quantitative ECG parameters will be summarized by placebo and TAK-020 dose level. Shift tables will be generated for the investigator's ECG interpretations that changed from Baseline to the postdose assessments. All ECG data will be provided in the data listings.

The relationship between telemetry ECG parameters (change from Baseline) and TAK-020 concentration will be assessed.

The analysis end points and baseline choice of the triplicate ECG will be defined in detail in SAP.

#### *13.1.5.5 Safety Biomarkers*

Renal biomarkers will be summarized, and the relationship between serum eGFR or serum creatinine and renal biomarkers will be explored.

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

No interim analysis is planned. Section 6.1.1 describes the blinded safety and PK review which will take place after completion of each cohort and prior to the next dose escalation stage in the study.

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

The sample sizes chosen of 8 subjects per cohort (6 active: 2 placebo) in Part 1 and 2 is considered to be sufficient for evaluation of safety, tolerability, PK and the PD of TAK-020 in 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 (contract research organization) and by the IRB or IEC.

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

### **14.2 Protocol Deviations**

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

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, 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.

The investigator should document all protocol deviations.

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 by entering it into the significant deviation eCRF.

Protocol Deviation Forms are to be entered for pharmacokinetic/pharmacodynamic 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 postdose

### 14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.



## 15.0 ETHICAL ASPECTS OF THE STUDY

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

### 15.1 IRB and/or IEC Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol’s review and approval. This protocol, the Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

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

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

## 15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

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

### **15.3 Subject Confidentiality**

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

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

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

### **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 [www.ClinicalTrials.gov](http://www.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 Schedule of Study Procedures

### Part 1 (SRD)

Study Day:	Screening	Check-in	Treatment				Check-out	Early Termination	Follow-up
	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	(a)	Day 14 (±2) (b)
Confinement		X	X	X	X	X	X		
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics and medical history	X	X							
Medication history	X								
Physical examination	X		X(c)	X	X	X	X	X	
Vital signs (d)	X	X	X	X	X	X	X	X	
Weight, height, and BMI (e)	X	X					X	X	
Concurrent medical conditions	X	X							
Concomitant medications (f)	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (g)	X	X		X	X		X	X	
Hepatitis panel	X								
HIV screening	X								
TB screening	X								
Pregnancy test (hCG) (h)	X	X					X	X	
Urine drug/alcohol/cotinine screen	X	X							
CCI									
ECG (j)	X	X	X	X	X	X	X	X	
Telemetry (k)			X						
PGx DNA sample collection (l)			X						
PGx RNA sample collection (m)			X	X					
PK blood collection (n)			X	X	X	X	X	X	
PK urine collection (o)			X	X	X	X	X	X	
CCI									
CCI									
Dispense study medication			X						
PTE assessment (q)	X	X	X						
AE assessment			X	X	X	X	X	X	X

Footnotes are on the next page.

- (a) Conduct procedures for subjects discontinued early. The PK sample collection should be collected at the Early Termination Visit, if possible. For example, collect samples if early withdrawal is due to an AE, and/or if several hours elapsed since last blood draw.
- (b) The Follow-up Visit will occur by telephone on Day 14 ( $\pm 2$ ) unless abnormal, clinically significant findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per investigator's discretion.
- (c) The physical examination can be conducted within 24 hours prior to study drug administration.
- (d) Vital signs (oral temperature, sitting pulse, and blood pressure) will be collected at Screening and Check-in (Day -1), Day 1 predose (0 hours) and at 1, 4, 12, 24, 48, 72, 96 hours postdose or Early Termination.
- (e) Height will only be collected at Screening.
- (f) Record all medications (other than study drug) from Screening and throughout the study.
- (g) Clinical laboratory tests (hematology, serum chemistries, and urinalysis) will be collected at Screening, Day -1, Days 2 and 3, and prior to check-out (Day 5) or Early Termination. Laboratory samples will be taken following a minimum 10-hour overnight fast.
- (h) Pregnancy test (hCG) will be performed for all female subjects.
- (i) CCI
- (j) Triplicate 12-lead ECGs printed in standard format, will be collected at Screening, Check-in (Day -1), Day 1 predose (0 hours) and at 1, 4, 12, 24, 48, 72 and 96 hours postdose or Early Termination. For ad hoc ECGs, as required, see Section 9.1.11.
- (k) Telemetry will be performed approximately 2 hours predose until 12 hours postdose on Day 1. Ten (10) sec triplicate ECGs will be extracted at PK time-points for manual reading and precise ECG reading including QT interval measurement.
- (l) One blood sample (6 mL) will be collected prior to dosing on Day 1.
- (m) Two whole blood samples (2.5 mL per sample) will be collected on Days 1 (predose) and 24 hours postdose.
- (n) Blood samples for PK analysis will be collected on Day 1 at predose (within 30 minutes prior to dosing), and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose.
- (o) Urine samples for PK analysis will be collected on Day 1 at predose (-12-0) and 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 hour postdose intervals.
- (p) Blood samples for PD analysis will be collected on Day 1 at predose (within 30 minutes prior to dosing) and at 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, 72 and 96 hours postdose.
- (q) PTEs will be collected from signing of informed consent up until dosing on Day 1.

**Part 2 (MRD)**

Study Day:	Screening	Check-in	Treatment	Washout	Treatment	Check-out	Early Termination	Follow-up Visit
	Days -28 to -2	Day -1	Day 1	Day 2	Day 3-9	Day 10	(a)	Day 17 (±2) (b)
Confinement		X	X	X	X	X		
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics and medical history	X	X						
Medication history	X							
Physical examination	X		X (c)	X	X	X	X	
Vital signs (d)	X	X	X	X	X	X	X	X
Weight, height, and BMI (e)	X	X				X	X	
Concurrent medical conditions	X	X						
Concomitant medications (f)	X	X	X	X	X	X	X	X
Clinical laboratory tests (g)	X	X		X	X	X	X	X (s)
Hepatitis panel	X							
HIV screening	X							
TB screening	X							
Pregnancy test (hCG) (h)	X	X				X	X	
Urine drug/alcohol/cotinine screen	X	X						
ECG (i)	X	X	X	X	X	X	X	
Telemetry (j)			X		X			
PGx DNA sample collection (k)			X					
PGx RNA sample collection (l)			X		X			
PK blood collection (m)			X	X	X	X	X	
PK urine collection (n)			X	X	X	X	X	
CCI								
CCI								
CCI								
Dispense study medication			X		X			
PTE assessment (r)	X	X	X					
AE assessment			X	X	X	X	X	X

Footnotes are on the next page.

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- (a) Conduct procedures for subjects discontinued early. The PK sample collection should be collected at the Early Termination Visit, if possible. For example, collect samples if early withdrawal is due to an AE, and/or if several hours elapsed since last blood draw].
- (b) All subjects will return to the unit and complete Hematology and Serum Chemistry tests, vital signs, concomitant medications, and AE assessment.
- (c) The physical examination can be conducted within 24 hours prior to study drug administration.
- (d) Vital signs (oral temperature, sitting pulse, and blood pressure) will be collected at Screening and Check-in (Day -1) and on Day 1 at predose (0 hours) and 1, 4, 12, 24 hours postdose, then twice daily until Study Exit (Day 10) or Early Termination and once during the Follow-up visit.
- (e) Height will only be collected at Screening.
- (f) Record all medications (other than study drug) from Screening and throughout the study.
- (g) Clinical laboratory tests (hematology, serum chemistries, and urinalysis) will be collected at Screening, Day -1, Days 2, 3, 5, 8 and prior to check-out (Day 10) or Early Termination. Laboratory samples will be taken following a minimum 10-hour overnight fast
- (h) Pregnancy test (hCG) will be performed for all female subjects.
- (i) Triplicate 12-lead ECGs printed in standard format, will be collected at Screening, Check-in (Day -1), Day 1 predose (0 hours) and at 1, 4, 12, and 24 hours postdose, Days 3, 5, 9, 10 at predose (0 hours) or Early Termination. For ad hoc ECGs, as required, see Section 9.1.11.
- (j) Telemetry will be performed approximately 2 hours predose until 12 hours postdose on Days 1 and 9 only. Ten (10) sec triplicate ECGs will be extracted at PK time-points for manual reading and precise ECG reading including QT interval measurement.
- (k) One blood sample (6 mL) will be collected prior to dosing on Day 1.
- (l) Two whole blood samples (2.5 mL per sample) will be collected at predose on Days 1, 3 and 9.
- (m) Blood samples for PK analysis will be collected at predose on Day 1 (within 30 minutes prior to dosing) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose and at predose on Day 9 (within 30 minutes prior to dosing) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose.
- (n) Urine samples for PK analysis will be collected on Day 1 and Day 9 at predose (-12-0), and 0-6, 6-12, 12-24 hour postdose intervals
- (o) CCI [REDACTED]
- (p) CCI [REDACTED]
- (q) CCI [REDACTED]
- (r) PTEs will be collected from signing of informed consent up until dosing on Day 1
- (s) Hematology and Serum Chemistry only.

## **Appendix B Responsibilities of the Investigator**

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

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

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

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

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

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

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

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

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

25. Female subjects of childbearing potential (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 until the next menstrual period or 30 days after last dose, whichever is first. Regular pregnancy tests will be performed throughout the study for all female subjects. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening, throughout the duration of the study and for 12 weeks after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

## **Appendix D Investigator Consent to Use of Personal Information**

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

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

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

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

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

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

## **Appendix E Collection, Storage, and Shipment of Bioanalytical/Genotyping/RNA Samples**

### **Instructions for Processing of Plasma Samples for Pharmacokinetic Analysis of TAK-020**

1. Collect 6 mL of venous blood into a chilled Becton-Dickinson Vacutainer. All TAK-020 blood samples should be collected into vacutainers containing K<sub>2</sub>EDTA.
2. Gently invert the vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. 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 manufacturer's instruction for proper centrifugation force and time.
4. 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 should include protocol number (TAK-020-1001), sample matrix (ie, plasma) randomization sequence number, Part (ie. 1 or 2), profile day and nominal time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower until shipment to PPD, Whitesboro, NY, USA. No more than 45 to 60 minutes will elapse between blood collection and freezing the plasma sample.

### **Instructions for Processing of Urine Samples for PK Analysis of TAK-020**

1. 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 of 2% Tween 80 to prevent absorption to containers.
2. At the end of each void, mix the urine, transfer to a graduated cylinder and measure and record the volume. For the urine sample in the graduated cylinder, measure "X" amount of 2% Tween 80 solution (2% Tween 80 by volume in water) into a separate graduated cylinder (where "X" equals 1 part in 10 of the urine volume in the cylinder).
3. Pour 3/4 of the "X" amount of Tween 80 solution into the graduated cylinder containing the subject's urine collection. Mix and transfer to the collection jug for the time period.
4. With the remaining Tween 80 solution, rinse the collection container and combine with the sample in the collection jug for the time period.
5. Store the collection jug refrigerated during the collection period. Record the total volume of urine sample collected.
6. Mix well and measure the urine volume within 2 hours of the end of the collection period.
7. Transfer approximately 10 mL aliquots of urine in duplicate into appropriate polypropylene containers. Containers should be filled to between 60% and 90% of nominal volume. Labeling should include protocol number (TAK-020-1001), Part (ie, 1 or 2), sample matrix (ie, urine),



randomization number, nominal day, nominal collection time interval, and either “SET 1” (for original sample), or “SET 2” (for duplicate sample).

8. Cap the labeled storage tubes and immediately freeze the urine samples and store at approximately -70°C or lower in an upright position until shipment to PPD [REDACTED], Whitesboro, NY, USA.

### Shipping of Plasma and Urine Samples

The following instructions are recommended unless they differ from the site’s standard operating procedures for labeling, packaging, or shipping of PK samples.

1. Biological samples (ie, plasma or urine) 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 sequence number, sample matrix (ie, plasma or urine), 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 3 through 6 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 medication (TAK-020), protocol number (TAK-020-1001), investigator’s name, sample type (ie, plasma or urine), subject randomization sequence number, Part (ie. 1 or 2), nominal 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 and Urine Samples for TAK-020

PPD

Project Leader 1

PPD

12. 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)

13. 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.
14. Obtain the airway bill number and a receipt of shipment from the carrier.
15. After shipping of the TAK-020 samples, please notify PPD at PPD by email PPD ) and copy PPD ( PPD to notify them of next day delivery. When emailing, provide the following information:

Name of courier or transport company

Time and date the shipment left the clinical site

Airway bill number

#### Instructions for Processing and shipping of Blood Samples for PD Analysis (CCI Occupancy Assay)

Sample tube requirements and processing instructions for the PD assays will be compiled in a laboratory manual and provided to the site.

**Instructions for processing and shipping of plasma samples for DNA and RNA PGx**

Sample tube requirements and processing instructions for the PGx samples will be compiled in a laboratory manual and provided to the site.

The storage provider has validated procedures in place for transport, delivery, retention, retrieval, and destruction of the specimens, and will appropriately retain the specimens for up to but not longer than 15 years as required by applicable law.

## Appendix F Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 04 are indicated. The corresponding text has been revised throughout the protocol.

### Change 1: Changed name of Responsible Medical Officer.

The primary change occurs in Section 1.1, [Contacts](#)

Initial wording: PPD [REDACTED]

New wording: PPD [REDACTED]

#### Rationale for Change:

This change reflects a staffing change at Takeda PPD [REDACTED] has replaced PPD [REDACTED] as Responsible Medical Officer for the study and as a Protocol Signatory.

Section 1.2, [Approval](#) also contains this change.

### Change 2: Specified doses administered for initial cohorts of Part 2.

The primary change occurs in Section 6.1.1 [Dose Escalation](#)

Initial wording:	<b>Part 2 MRD Evaluation</b>	<b>Cohort 1→</b>	<b>Cohort 2→</b>	<b>Cohort 3→</b>	<b>Cohort 4→</b>	<b>Cohort 5→</b>	<b>Cohort 6→</b>	<b>Cohort 7</b>
		3.75 mg TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo
New wording:	<b>Part 2 MRD Evaluation</b>	<b>Cohort 1→</b>	<b>Cohort 2→</b>	<b>Cohort 3→</b>	<b>Cohort 4→</b>	<b>Cohort 5→</b>	<b>Cohort 6→</b>	<b>Cohort 7</b>
		3.75 mg TAK-020 or placebo	X <b>5.75</b> mg <del>TBD</del> TAK-020 or placebo	X <b>13</b> mg <del>TBD</del> TAK-020 or placebo	X <b>25</b> mg <del>TBD</del> TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo	X mg TBD TAK-020 or placebo

#### Rationale for Change:

The actual doses were based on PK data that is now available.

Section 6.2, [Justification for Study Design, Dose, and Endpoints](#) also contains this change.

**Change 3:** Added PD biomarkers to Follow-up Visit (Day 17).

The primary change occurs in Section 9.1.15, PD Sample Collection.

Initial wording:

CCI



New wording:

CCI



**Rationale for Change:**

CCI



CCI



Sections that also contain this change are:

- Section 2.0, STUDY SUMMARY.
- Section 9.3.3, Follow-up Visit/Telephone Call.
- Section 9.5, Blood Volume.
- Appendix A, Schedule of Study Procedures, Part 2 MRD.

**Change 4:** Clarified method used for PD analyses.

This change occurs in Section 13.1.4 PD Analysis

Initial wording: PD data in Part 1 and Part 2 will be summarized separately. All PD results will be included in the listing.

New wording: CCI [REDACTED]  
CCI [REDACTED] PD data in Part 1 and Part 2 will be summarized separately. All PD results will be included in the listing.

**Rationale for Change:**

The change was made to clarify the methods used to analyze the data.

Amendment 04 to A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of TAK 020 in Healthy Volunteers

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	23-Mar-2017 12:21 UTC
	Biostatistics Approval	23-Mar-2017 14:49 UTC
	Clinical Approval	24-Mar-2017 08:19 UTC
	Clinical VP Approval	27-Mar-2017 15:03 UTC