Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects Following Intravenous Administration

NCT Number: NCT04486950

Protocol Approve Date: 8 January 2021

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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.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects Following Intravenous Administration

Study Identifier: TAK-951-1004

Compound: TAK-951

Date: 08 January 2021 **Version/Amendment No.** 2

Amendment History:

Date	Amendment Number	Type	Region
08 January 2021	1		

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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Takeda Development Center Americas, Inc, (TDC Americas) 95 Hayden Avenue Lexington, Massachusetts USA 02421 Telephone: +PPD	TAK-951
Study Identifier: TAK-951-1004	**Phase:** 1
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-951 in Healthy Subjects Following Intravenous Administration	

Study Design:

This is a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics (PK) of TAK-951 administered intravenously in healthy adult subjects.

At least 3 cohorts of 8 subjects each will be dosed sequentially. Subjects from each cohort will be admitted into the clinical research unit (CRU) on Day -2. On Day -1 baseline heart rate and blood pressure assessments will be taken, time-matched to the Day 1 assessments. Subjects will receive a single dose with TAK-951 or matching placebo on Day 1, according to the randomization scheme, after a minimum of 8 hours of fasting. Subjects will be randomized to receive TAK-951 or matching placebo in a 6:2 ratio in a double-blind manner. Pharmacokinetic samples will be taken up to 30 hours after the start of infusion. Subjects will be discharged after the completion of the study assessments on Day 2.

All subjects who received any amount of study drug (including subjects who terminate the study early) will return to the CRU 14 (±2) and 28 (±3) days after dosing for follow-up procedures, and to determine if any adverse event (AE) has occurred since the last study visit.

Subjects may be admitted earlier than Day -2 for COVID-19 testing not related to study protocol as per clinical study unit requirements.

Dosing regimen for each cohort:

Cohort 1: a low dose (20 µg) TAK-951 or placebo administered as a 60-minute intravenous (IV) infusion on Day 1,

Cohort 2: a high dose (1.0 mg) TAK-951 or placebo administered as a 60-minute IV infusion on Day 1,

Cohort 3: 1.0 mg TAK-951 or placebo administered as a 120-minutes IV infusion on Day 1.

Two (2) dose levels will allow assessment of the PK/pharmacodynamic (PD) relationship between exposure and heart rate and blood pressure (ie, semi-recumbent heart rate increase, blood pressure decrease, and orthostatic vital sign changes [orthostatic heart rate increase and orthostatic blood pressure decrease]) and will support development of an IV dosage form in the future if deemed necessary.

Two (2) additional cohorts may be enrolled (for a total of 5 cohorts), each cohort with 8 subjects, to explore additional IV dosing regimens. In total the enrollment will be up to approximately 40 subjects. Dosing regimen of the subsequent cohort will be based on the analysis of the previous cohort's data.

For Cohort 4 and 5, as applicable, PK sampling and time-matched vital sign assessments scheduled relative to infusion timing will be based on emerging clinical data analysis. As such, this timing will be provided in a separate document and will not exceed 30 hours post start of infusion. The number of planned PK and vital sign assessments may be less than or equal to those in the protocol.

A staggered dosing approach will be used. The sentinel subjects will be dosed at least 24-hours before the remaining 6 subjects in each cohort. In each cohort, after dosing the first 2 subjects (the sentinel group – 1 receiving TAK-951 and 1 receiving placebo) the Investigator will review all available blinded safety and tolerability data up to 8 hour post-dose. If after dosing the sentinel group, the Investigator and the Sponsor agree that there are no significant safety/tolerability concerns, then the rest of the cohort will be dosed. There will be at least 1 hour between dosing of each subject in each cohort, except for the sentinel subjects. A dose-escalation/blinded safety review meeting will be

held between the Investigator and Sponsor after each cohort is completed to review the safety and available PK data from samples taken up to 1-day post-dose, in order to confirm the dose level and/or infusion rate for the subsequent cohort. PK data from the first low dose cohort is required to allow dosing of the high dose for the second and third cohorts and the determination of the rate of infusion for the third cohort. The dose and the infusion rate for Cohorts 4 and 5 will be selected based on emerging clinical data analysis and is not expected to exceed the highest exposures seen in the first in human (FIH) TAK-951-1001 study.

Sponsor is to remain blinded during the review of available safety and PK data. Once a decision is made to proceed to the next cohort, the Sponsor may be unblinded following dose escalation/safety meetings to allow additional analysis.

Cohort 4 and 5 may run concurrently, sequentially or be omitted and will not exceed the highest exposure observed in the FIH study.

Safety will be assessed by monitoring for AEs, vital signs, safety 12-lead electrocardiograms (ECG)s/telemetry, safety laboratory assessments, and physical examinations throughout the study.

Immunogenicity will be assessed prior to dosing and approximately 14 and 28 days after dosing.

Study Primary Objective:

To evaluate the overall safety and tolerability of a single IV infusion of TAK-951 administered with at least 2 different infusion rates (rapid and slow) at the same dose level in healthy subjects.

Secondary Objectives:

To assess the PK of TAK-951 following a single IV infusion of TAK-951 in healthy subjects.

To assess for anti-drug antibodies following a single IV infusion of TAK-951 in healthy subjects.

CCI

Study Subject Population: Healthy male and female (non-childbearing potential only) subjects aged 19 to 55 years inclusive, at screening. Body Mass Index (BMI) 18.0-32.0 kg/m^2, inclusive, at screening.

Planned Number of Subjects:	**Planned Number of Sites:**
Up to 40 subjects and up to 5 cohorts Eight (8) subjects per cohort At least 3 cohorts are planned for this study. Cohorts 4 and 5 may be added based on emerging clinical data analysis from this study.	1
Dose Levels: Cohort 1: 20 µg infusion of TAK-951 or matching placebo, 60-minute IV on Day 1 Cohort 2: 1.0 mg infusion of TAK-951 or matching placebo, 60-minute IV on Day 1 Cohort 3: 1.0 mg infusion of TAK-951 or matching placebo, 120-minute IV on Day 1 If dosed, Cohorts 4 and 5 dose(s) of TAK-951 and infusion rate(s) of TAK-951 and placebo will be decided based on the emerging clinical data analysis of the previous cohorts.	**Route of Administration:** IV

Duration of Treatment:	**Planned Study Duration:**
Cohort 1: a single IV infusion over a 60-minute infusion Cohort 2: a single IV infusion over a 60-minute infusion Cohort 3: a single IV infusion over a 120-minute. If dosed, the treatment duration(s) for Cohorts 4 and 5 will be decided based on the emerging clinical data analysis from the previous cohorts.	Approximately 57 days from screening until last follow-up visit.

Criteria for Inclusion:

In order to be eligible for study participation, subjects must:

1. Healthy, adult, male or female (of non-childbearing potential only), 19-55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine- and tobacco-containing products and/or cannabis products for at least 3 months prior to dosing and throughout the study.
3. Body mass index (BMI) ≥18.0 and ≤32.0 kg/m2 at screening.
4. Medically healthy based on no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.
5. Female must be of non-childbearing potential as described in Appendix D.
6. A non-vasectomized, male subject must agree to use a barrier contraception (eg, condom with spermicide) or abstain from sexual intercourse from dosing and until 90 days after dosing. No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to dosing of study drug. A male who has been vasectomized less than 4 months prior to dosing must follow the same restrictions as a non-vasectomized male (see Appendix D).
7. If male, must agree not to donate sperm from dosing until 90 days after dosing.
8. Understands the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol.

Criteria for Exclusion:

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. Has a documented history of any clinically significant disorders, including psychiatric, cardiovascular, nephrological, neurological, metabolic, or gastrointestinal disease.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
5. Drink alcohol in excess of 21 glasses/units per week for males or 14 glasses/units per week for females, with one unit = 150 mL of wine or 360 mL of beer or 45 mL of 45% alcohol.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
7. Have any tattoos, scars or skin issue at planned IV infusion site which could interfere with dosing.
8. History or presence of:
   - Three (3) or more incidences of vasovagal syncope within the last 5 years prior to screening.
   - Family history of unexplained sudden death or channelopathy.
   - Brugada syndrome (ie, right bundle branch block [RBBB] pattern with ST-elevation in leads V1-V3).
   - Cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, stroke, sick sinus syndrome, pulmonary congestion, symptomatic or significant cardiac arrhythmia, second-degree atrioventricular (AV) block type 2, third-degree AV block, prolonged QTcF interval, hypokalemia, hypomagnesemia, or conduction abnormalities;
   - Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT

Syndrome);
- Any clinically significant ECG findings or medical history including: long or short QT interval with Fridericia correction method (QTcF) (over 450 milliseconds [msec] or less than 360 msec), bifascicular block or QRS ≥120 msec or PR interval >200 msec at screening or Day -1 pre-Hour 0.
- Documented history of sinoatrial block or sinus pause ≥3 seconds.

9. Semi-recumbent blood pressure (average of duplicate) is less than 90/60 mmHg or greater than 140/90 mmHg at screening.
10. Has an average semi-recumbent heart rate <60 or >100 bpm (at screening, at Day -1 pre-Hour 0, or at pre-dose Day 1); athletic subjects with an average semi-recumbent heart rate <60 bpm can be enrolled only with medical monitor approval. If subject has heart rate <60 bpm Investigator should obtain medical approval from Sponsor.
11. Has orthostatic hypotension defined as a decrease in systolic blood pressure ≥20 mmHg or a decrease in diastolic blood pressure ≥10 mmHg after 2 minutes of standing when compared with blood pressure from the semi-recumbent position at screening and at Day -1 pre-Hour 0. The semi-recumbent blood pressure will be an average of duplicate measurements.
12. Has postural orthostatic tachycardia, defined as an increase of 30 bpm or heart rate >120 bpm after standing for 2 minutes.
13. Female subjects of childbearing potential.
14. Female subjects with a positive pregnancy test or who is lactating.
15. Positive urine drug or alcohol results at screening or check-in.
16. Positive urine cotinine at screening or check-in.
17. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
18. Unable to refrain from or anticipates the use of any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to dosing and throughout the study. Thyroid hormone replacement medication may be permitted if the subject has been on same stable dose for the last 3 months prior to study drug administration. After dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Hormone replacement therapy will also be allowed.
19. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to dosing and throughout the study.
20. Donation of blood or significant blood loss within 56 days prior to dosing.
21. Plasma donation within 7 days prior to dosing.
22. Participation in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.
23. Positive results for Coronavirus disease 2019 (COVID-19) testing at screening or check-in.

Criteria for Evaluation and Analyses:

Primary Endpoint:

The primary endpoint of the study is safety and tolerability as assessed through AEs,vital signs, safety ECGs/telemetry, safety laboratory assessments, and physical examinations.

Secondary Endpoints:

The secondary endpoints will be assessed through evaluation of the following parameters:

Pharmacokinetic parameters:

- Area under the TAK-951 plasma concentration time curve from time 0 to infinity (AUC_{∞}).
- TAK-951 plasma concentration at end of infusion (Ceoi).
- Area under the TAK-951 plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUClast).
- Terminal disposition phase half-life ($t_{½z}$).
- Terminal disposition phase rate constant (λz).

Immunogenicity:

- Anti-drug antibodies titer.

CCI [redacted]

Statistical Considerations:

The safety analysis set will consist of all subjects who are enrolled and receive full or partial dose of study drug or placebo. The PK analysis set will consist of all subjects who received the active study drug and have at least one measurable plasma concentration of TAK-951.

Safety summaries will be based on the safety analysis set. All safety data including AEs, clinical laboratory tests, vital signs, and ECG will be summarized using descriptive statistics. No formal statistical tests or inference will be performed for safety analyses. All summaries will be performed by treatment (cohort) and pooled placebo (placebos pooled from all cohorts).

The plasma concentrations of TAK-951 will be summarized by TAK-951 dose and infusion rate over each scheduled sampling time, using descriptive statistics. The PK parameters of TAK-951 will be determined from the concentration-time profiles for all evaluable subjects using noncompartmental analysis approach. Actual sampling times, rather than scheduled sampling times, will be involved in the derivation of PK parameters. Additional PK parameters may be calculated as appropriate. Further details will be specified in the statistical analysis plan (SAP).

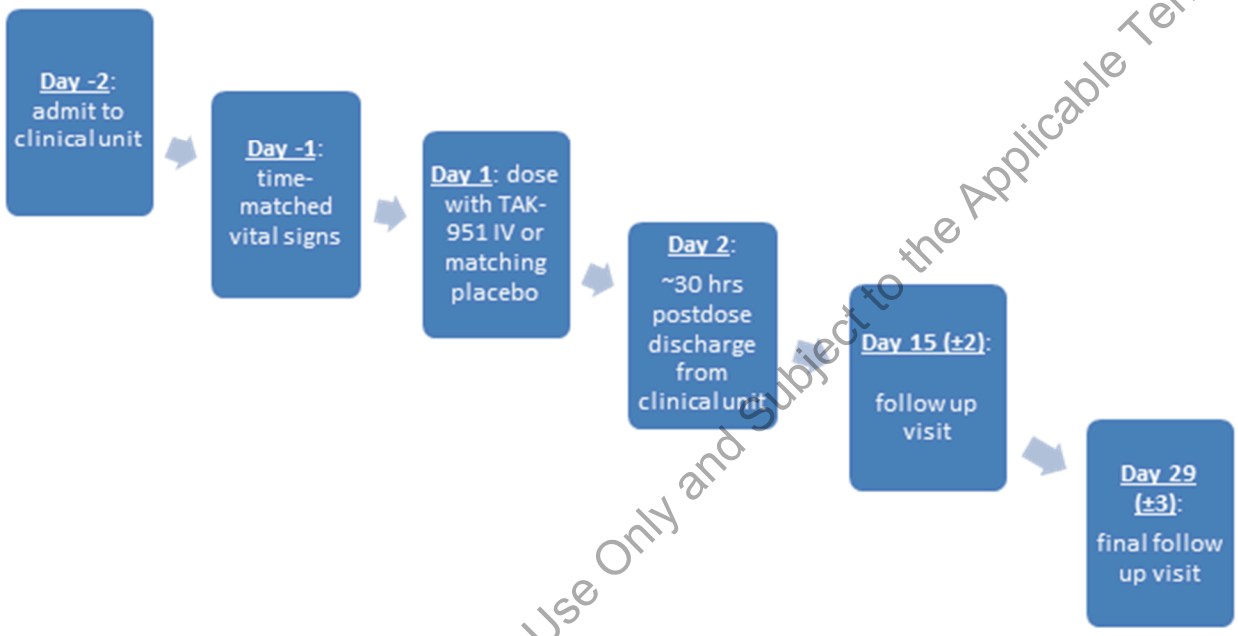
Plasma PK parameters of TAK-951 will be calculated and summarized as detailed in the Clinical Pharmacology Analysis Plan (CPAP).

The relationship of time-matched TAK-951 exposure and PD effects (ie, semi-recumbent heart rate and blood pressure changes and orthostatic vital sign changes) will be assessed.

Sample Size Justification:

Up to approximately 40 adult subjects (8 per cohort) are planned to be randomized. A formal sample size calculation was not performed for this study. The current sample size is deemed appropriate to evaluate the safety, tolerability, PK, and PD of TAK-951 following IV administration. A minimum of 3 cohorts will be evaluated.

2.0 STUDY SCHEMATIC



Study schematic per cohort. Dosing of subsequent cohorts is based on dose escalation criteria as listed in Section 6.2. Within a cohort, sentinel subjects will be dosed at least 24 hours before the remaining subjects. There will be at least 1 hour between dosing of each subject in each cohort, except for the sentinel.

3.0 SCHEDULE OF STUDY PROCEDURES

3.1 Cohorts 1 and 2 and any Cohort with an Infusion less than or Equal to 60 Minutes

Study Procedures [a]		**Study Days**														
Days →		**-2**	**-1**													
Hours →			Pre	0	0.083	0.17	0.25	0.5	1	(EOI) [f]	1.25	1.5	2	4	8	12
Hour:Minutes →	**Scr** [b]	**C-I** [e]		0	0:05	0:10	0:15	0:30	1:00		1:15	1:30	2:00	4:00	8:00	12:00
Administrative Procedures																
Informed Consent	X															
Inclusion/Exclusion Criteria	X	X														
Medical History	X															
Safety Evaluations																
Full Physical Examination [g]	X	X														
Height	X															
Weight and BMI	X	X														
12-Lead Safety ECG (triplicate)	X		X [h]													
Vital Signs (HR) [i]					X	X										
Vital Signs (HR and BP) [i]							X		X	X	X	X				X
Orthostatic Vital Signs (HR and BP) [j]	X		X [h]					X					X	X	X	
Vital Signs (RR and T)	X															
Hem and Serum Chem [l]	X	X														
Urinalysis	X	X														
Serum Pregnancy Test (females only)	X	X														
Serum FSH (PMP females only)	X															
Urine Drug and Alcohol Screen	X	X														
Urine Cotinine Screen	X	X														
HIV/Hepatitis Screen [m]	X															
AE Monitoring	X	X														

Study Procedures [a]		**Study Days**														
Days →		**-2**	**-1**													
Hours →	**Scr** [b]	**C-I** [e]	Pre	0	0.083	0.17	0.25	0.5	1	(EOI) [f]	1.25	1.5	2	4	8	12
ConMeds Monitoring	X	X														
Other Procedures																
Confinement in the CRU		X														
Visit	X															

Study Procedures [a]	**Study Days**																	**FU** [d]	
Days →	**1**													**2**			**ET** [c]	**Day 15 (±2)**	**Day 29 (±3)**
Hours →	Pre	0	0.083	0.17	0.25	0.5	1	(EOI) [l]	1.25	1.5	2	4	8	12	24	30			
Hour:Minutes →		0	0:05	0:10	0:15	0:30	1:00		1:15	1:30	2:00	4:00	8:00	12:00	24:00	30:00			
Safety Evaluations																			
Full Physical Examination [g]																	X		X
12-Lead Safety ECG (triplicate)	X [h]														X		X		
Vital Signs (HR) [i]			X	X															
Vital Signs (HR and BP) [i]					X		X	X	X	X				X		X	X		
Orthostatic Vital Signs (HR and BP) [j]	X [h]					X					X	X	X		X				
Telemetry [k]	X																		
Hem and Serum Chem [l]											X				X		X		
Urinalysis															X		X		
Serum Pregnancy Test (females only)															X		X		
AE Monitoring	X																	X	X
ConMeds Monitoring	X																	X	X
Study Drug Dosing / PK																			
TAK-951 IV or Matching Placebo Dosing [n]		X																	
Blood for TAK-951 PK [o]	X		X	X	X	X	X [p]	X [p]	X	X	X	X	X	X	X	X			
Other Procedures																			
Holter Monitoring [q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X				
ADA	X																X	X	X
Confinement in the CRU	X																		
Return Visits																		X	X

a) For details on Procedures, refer to Section 9.0.
b) Within 28 days prior to dosing.
c) To be performed prior to early termination from the study.

Study Procedures [a]	**Study Days**																	**FU** [d]	
Days →	**1**														**2**		**ET** [c]	**Day 15 (±2)**	**Day 29 (±3)**
Hours →	Pre	0	0.083	0.17	0.25	0.5	1	(EOI) [l]	1.25	1.5	2	4	8	12	24	30			

d) All subjects who received any amount of study drug (including subjects who terminate the study early) will return to the CRU 14 (±2) and 28 (±3) days after dosing for follow-up procedures, and to determine if any AE has occurred since the last study visit.
e) Subjects will be admitted to the CRU on Day -2, at the time indicated by the CRU. In accordance with local regulatory guidance for the COVID-19 pandemic, the clinical study unit will implement standard COVID-19 procedures as per their internal guidance documents. Subjects may be admitted earlier than Day -2 for COVID-19 testing not related to study protocol as per CRU requirements.
f) A sample will be obtained at the end of infusion for each cohort. For Cohorts 1 and 2, end of infusion time point will be 1 hour, events listed at the 1 hour timepoint and the EOI timepoint will only be performed once. The study events at the end of infusion will proceed in this order: blood samples, vital signs, safety ECGs, and Holter ECGs, meals and snacks.
g) Symptom-driven physical examination may be performed at other times, at the Investigator's or designee's discretion.
h) To be performed within 2 hour prior to Hour 0.
i) All blood pressure and heart assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The Investigator can take a third measurement if there is inconsistency between assessments. Day -1 time points will time-matched (± 5 minutes) to the Day 1 clock time (ie, time-matched baseline).
j) For orthostatic vital signs, a blood pressure and heart rate assessment will be performed after the duplicate semi-recumbent assessment has been completed. Standing assessments **must not** be performed if semi-recumbent systolic blood pressure is <85 mmHg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing. Day -1 time points will be time-matched (± 5 minutes) to the Day 1 clock time (ie, time-matched baseline).
k) To be monitored from 2 hours prior to the start of infusion until 24 hours following the start of infusion.
l) Samples for serum chemistry will be obtained after a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample is taken.
m) Hepatitis panel, including antibodies for HBsAg and HCV.
n) The sentinel subjects will be dosed at least 24-hour before the remaining 6 subjects in each cohort. Dosing in the remaing subjects of the cohort will be staggered by at least 1 hour.
o) PK blood sample collection should be collected as close to exact time points as possible. Please refer to section 9.2.
p) Performed immediately after the end of infusion.
q) Three pre-dose samples will be taken at -0.75, -0.5 and -0.25 hours before the start of infusion. Each time point will be extracted in triplicate. During the extractions that are less than 1 hour post start of infusion subjects may not have been resting for 10 minutes due to the proximity of sample collection.

Abbreviations: ADA = Anti-drug antibodies, AE = Adverse event(s), BMI = Body mass index, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, ConMeds = Concomitant medications, CRU = Clinical research unit, ECG = Electrocardiogram, EOI = End of infusion, ET = Early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, HBsAg = hepatitis B surface antigen, HCV = hepatatist C virus, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, IV = Intravenous, mmHg = millimeters of mercury, PK = Pharmacokinetics, PMP = Postmenopausal, Pre = Predose or prior to Hour 0, RR = Respiratory rate, Scr = Screening, T = Temperature.

3.2 Cohort 3 and any Cohort with an Infusion greater than 60 Minutes

Study Procedures [a]		**Study Days**																
Days →		**-2**	**-1**															
Hours →			Pre	0	0.25	0.5	1	1.5	2	(EOI) [f]	2.083	2.25	2.5	3	5	8	12
Hour:Minutes →	**Scr** [b]	**C-I** [e]		0	0:15	0:30	1:00	1:30	2:00		2:05	2:15	2:30	3:00	5:00	8:00	12:00
Administrative Procedures																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History	X																	
Safety Evaluations																		
Full Physical Examination [g]	X	X																
Height	X																	
Weight and BMI	X	X																
12-Lead Safety ECG (triplicate)	X		X [h]															
Vital Signs (HR) [i]											X							
Vital Signs (HR and BP) [i]					X	X		X	X	X		X						X
Orthostatic Vital Signs (HR and BP) [j]	X		X [h]				X						X	X	X	X		
Vital Signs (RR and T)	X																	
Hem and Serum Chem [l]	X	X																
Urinalysis	X	X																
Serum Pregnancy Test (females only)	X	X																
Serum FSH (PMP females only)	X																	
COVID-19 test	X	X																
Urine Drug and Alcohol Screen	X	X																

Study Procedures [a)]		**Study Days**																
Days →		**-2**	**-1**															
Hours →	**Scr** [b)]	**C-I** [e)]	Pre	0	0.25	0.5	1	1.5	2	(EOI) [f)]	2.083	2.25	2.5	3	5	8	12
Urine Cotinine Screen	X	X																
HIV/Hepatitis Screen [m)]	X																	
AE Monitoring	X	X																
ConMeds Monitoring	X	X																
Other Procedures																		
Confinement in the CRU		X																
Visit	X																	

Study Procedures [a]	**Study Days**																	**ET** [c]	**FU** [d]	
Days →	**1**															**2**			**Day 15 (±2)**	**Day 29 (±3)**
Hours →	Pre	0	0.25	0.5	1	1.5	2	(EOI) [f]	2.083	2.25	2.5	3	5	8	12	24	30			
Hour:Minutes →		0	0:15	0:30	1:00	1:30	2:00		2:05	2:15	2:30	3:00	5:00	8:00	12:00	24:00	30:00			
Safety Evaluations																				
Full Physical Examination [g]																		X		X
12-Lead Safety ECG (triplicate)	X [h]															X		X		
Vital Signs (HR) [i]									X											
Vital Signs (HR and BP) [i]			X	X		X	X	X		X					X		X	X		
Orthostatic Vital Signs (HR and BP) [j]	X [h]				X						X	X	X	X		X				
Telemetry [k]	X																			
Hem and Serum Chem [l]												X				X		X		
Urinalysis																X		X		
Serum Pregnancy Test (females only)																X		X		
AE Monitoring	X																		X	X
ConMeds Monitoring	X																		X	X
Study Drug Dosing / PK																				
TAK-951 IV or Matching Placebo Dosing [n]	x																			
Blood for TAK-951 PK [o]	X		X	X	X	X	X [p]	X [p]	X	X	X	X	X	X	X	X	X			
Other Procedures																				
Holter Monitoring [q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ADA	X																	X	X	X
Confinement in the CRU	X																			
Return Visits																			X	X

Study Procedures [a]	**Study Days**																	**ET** [c]	**FU** [d]	
Days →	**1**															**2**			**Day 15 (±2)**	**Day 29 (±3)**
Hours →	Pre	0	0.25	0.5	1	1.5	2	(EOI) [f]	2.083	2.25	2.5	3	5	8	12	24	30			

a) For details on Procedures, refer to Section 9.0.
b) Within 28 days prior to dosing.
c) To be performed prior to early termination from the study.
d) All subjects who received any amount of study drug (including subjects who terminate the study early) will return to the CRU 14 (±2) and 28 (±3) days after dosing for follow-up procedures, and to determine if any AE has occurred since the last study visit.
e) Subjects will be admitted to the CRU on Day -2, at the time indicated by the CRU. In accordance with the local regulatory guidance for COVID-19 pandemic, the clinical study unit will implement standard COVID-19 procedures as per their internal guidance documents. Subjects may be admitted earlier than Day -2 for COVID-19 testing not related to study protocol as per CRU requirements.
f) A sample will be obtained at the end of infusion for each cohort. For Cohorts 4 and 5, infusion rate will be determined from emerging clinical data analysis and end of infusion sample will occur at one of the existing sampling time points. The study events at the end of infusion will proceed in this order: blood samples, vital signs, safety ECGs and Holter ECGs, meals and snacks.
g) Symptom-driven physical examination may be performed at other times, at the Investigator's or designee's discretion.
h) To be performed within 2 hour prior to Hour 0.
i) All blood pressure and heart assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The Investigator can take a third measurement if there is inconsistency between assessments. Day -1 time points will time-matched (± 5 minutes) to the Day 1 clock time (ie, time-matched baseline).
j) For orthostatic vital signs, a blood pressure and heart rate assessment will be performed after the duplicate semi-recumbent assessment has been completed. Standing assessments **must not** be performed if semi-recumbent systolic blood pressure is <85 mmHg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing. Day -1 time points will be time-matched (± 5 minutes) to the Day 1 clock time (ie, time-matched baseline).
k) To be monitored from 2 hours prior to the start of infusion until 24 hours following the start of infusion.
l) Samples for serum chemistry will be obtained after a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample is taken.
m) Hepatitis panel, including antibodies for HBsAg and HCV.
n) The sentinel subjects will be dosed at least 24-hour before the remaining 6 subjects in each cohort. Dosing in the remaing subjects of the cohort will be staggered by at least 1 hour.
o) PK blood sample collection should be collected as close to exact time points as possible. Please refer to section 9.2.
p) Performed immediately after the end of infusion.
q) Three pre-dose samples will be taken at -0.75, -0.5 and -0.25 hours before the start of infusion. Each time point will be extracted in triplicate. During the extractions that are less than 1 hour post start of infusion subjects may not have been resting for 10 minutes due to the proximity of sample collection.

Abbreviations: ADA = Anti-drug antibodies, AE = Adverse event(s), BMI = Body mass index, BP = Blood pressure, C-I = Check-in, Chem = Chemistry,

Study Procedures [a]	**Study Days**																	**ET** [c]	**FU** [d]	
Days →	**1**															**2**			**Day 15 (±2)**	**Day 29 (±3)**
Hours →	Pre	0	0.25	0.5	1	1.5	2	(EOI) [f]	2.083	2.25	2.5	3	5	8	12	24	30			

ConMeds = Concomitant medications, CRU = Clinical research unit, ECG = Electrocardiogram, EOI = End of infusion, ET = Early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, HBsAg = hepatitis B surface antigen, HCV = hepatatist C virus, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, IV = Intravenous, mmHg = millimeters of mercury, PK = Pharmacokinetics, PMP = Postmenopausal, Pre = Predose or prior to Hour 0, RR = Respiratory rate, Scr = Screening, T = Temperature.

4.0 INTRODUCTION

4.1 Background

TAK-951 is a peptide agonist of the glucose insulinotropic peptide (GIP) receptor that is resistant to dipeptidyl peptidase-4 degradation. GIP is an incretin hormone that results in glucose dependent insulin secretion via its action on the GIP receptor on pancreatic beta cells. The glucose dependence of GIP's insulinotropic action suggests a low risk of hypoglycemia following administration of TAK-951 to humans when administered in normoglycemic conditions. In addition to pancreatic beta cells, nonclinical studies have revealed that the GIP receptor is also expressed on gamma aminobutyric acid (GABA)ergic neurons in the area postrema. The area postrema (the chemoreceptor trigger zone) not only has excitatory pathways to the brainstem to induce emesis, but also has GABAergic inhibitory inputs, directly activated by GIP receptor agonists. Studies conducted by Takeda have demonstrated expression of the GIP receptor in humans on these neurons. By specifically activating the inhibitory GABAergic neurons of the area postrema via GIP receptor agonism, TAK-951 has the potential to inhibit nausea and vomiting via neural pathways triggered by a variety of chemical agents and physiological signals, including the neurotransmitters dopamine, serotonin, and substance P.

TAK-951 is currently proposed for the treatment of nausea and vomiting. From the human GIP IV infusion studies under hyperglycemic clamp in healthy subjects and in diabetic and glucose intolerant patients, reversible heart rate increases of about 8 to 10 beats per minute were observed. Although these findings indicate that TAK-951 has the potential for cardiovascular effects in humans, the changes are anticipated to be transient, reversible, and monitorable through noninvasive approaches. Preliminary data from the TAK-951-1001 FIH study indicate that subcutaneous administration of TAK-951 can increase heart rate, decrease diastolic blood pressure and lead to orthostatic changes in vital signs including orthostatic tachycardia and hypotension.

In addition, refer to the IB for detailed background information on TAK-951.

4.2 Rationale for the Proposed Study

The ongoing FIH study (TAK-951-1001) is assessing the safety and tolerability of single and multiple ascending doses of TAK-951 administered subcutaneously to adult subjects. This IV infusion study will support development of an IV dosage form if deemed necessary.

To that end, this study is designed as a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of TAK-951 in at least 3 cohorts of healthy adult subjects following a single IV infusion administration with at least two dose levels. Infusion duration for the first two cohorts will be 60 minutes. Infusion duration for subsequent cohorts may be longer or shorter than 60 minutes and will be determined based upon emerging clinical data analysis from previous cohorts.

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4.3 Benefit/Risk Profile

The single dose of subcutaneous TAK-951 (Study TAK-951-1001) was safe and well tolerated up to 4000 µg (4000 µg preliminary geometric mean PK: C_{max} 54.3 ng/mL, AUC_{last} 339 h*ng/mL). Although the subcutaneous bioavailability of TAK-951 is assumed to be high (~90%) based on non-clinical data (minipig), starting with a low infusion dose of 20 µg (20 µg preliminary geometric mean PK following subcutaneous dose: C_{max} 0.201 ng/mL, AUC_{last} 0.562 h*ng/mL) allows for a potentially greater exposure following IV administration if the subcutaneous bioavailability is actually very low (~1%). In this hypothetical case, a potential 100-fold greater bioavailability would result in AUC and C_{max} exposures 100 fold greater than predicted at 20 µg. This would still be within the exposures seen at the 4000 µg subcutaneous dose level in TAK-951-1001. Thus, the exposure in this study is not anticipated to exceed the exposure observed following subcutaneous doses in study TAK-951-1001 and therefore should have a comparable AE profile.

Risk mitigation measures have been incorporated into this study by adding a sentinel dosing of 2 subjects in each cohort and dosing the sentinel group at least 24-hours prior to dosing of the remaining 6 subjects in each cohort.

Safety monitoring procedures, such as frequent heart rate and blood pressure assessments, orthostatic blood pressure and heart rate measurements, telemetry, and 12-lead ECGs are being implemented in this study to assess subject safety and tolerability of study drug. The potential risks related to heart rate increase, decreased blood pressure, and injection site reactions will be monitored clinically and/or with laboratory tests and have been considered when determining the stopping rules for this clinical study. Subjects will be evaluated for the development of anti-drug antibodies (ADA) as part of the study. The use of a clinical study facility monitored by the Investigator increases subject safety since subjects are closely monitored and rapid institution of appropriate care can be given when needed in a timely manner.

There will be no direct health benefit for study subjects from receipt of study drugs. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

Overall, the potential risks associated with the study are considered reasonable and well managed.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Study Primary Objective

To evaluate the overall safety and tolerability of a single IV infusion of TAK-951 administered with at least 2 different infusion rates (rapid and slow) at the same dose level in healthy subjects..

5.1.2 Study Secondary Objectives

To assess the PK of TAK-951 following a single IV infusion of TAK-951 in healthy subjects.

To assess for anti-drug antibodies following a single IV infusion of TAK-951 in healthy subjects.

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5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint of the study is safety and tolerability as assessed through AEs, vital signs, safety ECGs/telemetry, safety laboratory assessments, and physical examinations.

5.2.2 Secondary Endpoints

Secondary endpoints will be assessed through evaluation of the following:PK parameters:

- Area under the TAK-951 plasma concentration time curve from time 0 to infinity (AUC_{∞}).
- TAK-951 plasma concentration at end of infusion (C_{eoi}).
- Area under the TAK-951 plasma concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Terminal disposition phase half-life ($t_{½z}$).
- Terminal disposition phase rate constant (λ_z).

Immunogenicity:

- Anti-drug antibodies titer.

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6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of TAK-951 administered intravenously in healthy adult subjects.

At least 3 cohorts of 8 subjects each will be dosed sequentially. Subjects from each cohort will be admitted into the CRU on Day -2. On Day -1 baseline heart rate and blood pressure assessments will be taken, time-matched to the Day 1 assessments. Subjects will receive a single dose with TAK-951 or matching placebo on Day 1, according to the randomization scheme, after a minimum of 8 hours of fasting. Subjects will be randomized to receive TAK-951 or matching placebo in a 6:2 ratio in a double-blind manner. Pharmacokinetic samples will be taken up to 30 hours after the start of infusion. Subjects will be discharged after the completion of the study assessments on Day 2.

All subjects who received any amount of study drug (including subjects who terminate the study early) will return to the CRU 14 (±2) and 28 (±3) days after dosing for follow-up procedures, and to determine if any AE has occurred since the last study visit.

Dosing regimen for each cohort:

Cohort 1: a low dose (20 µg) TAK-951 or placebo administered as a 60-minute IV infusion on Day 1,

Cohort 2: a high dose (1.0 mg) TAK-951 or placebo administered as a 60-minute IV infusion on Day 1,

Cohort 3: 1.0 mg TAK-951 or placebo administered as a 120-minutes IV infusion on Day 1.

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Two (2) additional cohorts may be enrolled (for a total of 5 cohorts), each cohort with 8 subjects, to explore additional IV dosing regimens. In total the enrollment will be approximately 40 subjects. Dosing of the subsequent cohort will be based on the analysis of the previous cohort's data; however, the cohorts will not exceed the highest exposure observed in the FIH study.

For Cohort 4 and 5, PK sampling and time-matched vital sign assessments scheduled relative to infusion timing will be based on emerging clinical data analysis. As such, this timing will be provided in a separate document and will not exceed 30 hours post start of infusion. The number of planned samples may be less than or equal to those in the protocol.

A staggered dosing approach will be used. The sentinel subjects will be dosed at least 24-hours before the remaining 6 subjects in each cohort. In each cohort, after dosing the first 2 subjects (the sentinel group - 1 receiving TAK-951 and 1 receiving placebo) the Investigator will review all available blinded safety and tolerability data up to 8 hour post-dose. If after dosing the sentinel group, the Investigator and the Sponsor agree that there are no significant safety/tolerability concerns, then the rest of the cohort will be dosed. There will be at least 1 hour between dosing of each subject in each cohort, except for the sentinel subjects. A dose-escalation/blinded safety review meeting will be held between the Investigator and Sponsor after each cohort is completed to review the safety and available PK data from samples taken up to 1-day post-dose, in order to confirm the dose level and/or infusion rate for the subsequent cohort. PK data from the first low dose cohort is required to allow dosing of the high dose for the second and third cohorts and the determination of the rate of infusion for the third cohort. The dose and the infusion rate for Cohort 4 and 5 will be selected based on emerging clinical data analysis and is not expected to exceed the highest exposures seen in the FIH TAK-951-1001 study.

Sponsor is to remain blinded during the review of available safety and PK data. Once a decision is made to proceed to the next cohort, the Sponsor may be unblinded following dose escalation/safety meetings to allow additional analysis.

The dose and rate for Cohorts 4 and 5 will be determined by clinical data analysis so as not to exceed the highest exposure seen in the currently ongoing FIH study (TAK-951-1001). Cohorts 4 and 5 may run concurrently, sequentially or be omitted.

Safety will be assessed by monitoring for AEs, vital signs, safety 12-lead ECGs/telemetry, safety laboratory assessments, and physical examinations throughout the study.

Immunogenicity will be assessed prior to dosing and approximately 14 and 28 days after dosing.

In accordance with local regulatory guidance for the COVID-19 pandemic, the clinical study unit will implement standard COVID-19 procedures as per their internal guidance documents. Subjects may be admitted earlier than Day -2 for COVID-19 testing not related to study protocol as per CRU requirements.

The planned dose levels of TAK-951 to be evaluated are outlined in Table 6.a.

Table 6.a Planned Dose Levels of TAK-951

Cohort	Total Dose	Infusion Duration
Cohort 1	**20 µg and matching placebo**	60-minute
Cohort 2	1.0 mg **and matching placebo**	60-minute
Cohort 3	1.0 mg and matching placebo	120-minute

6.2 Dose Escalation

The sentinel subjects will be dosed at least 24-hours before the remaining 6 subjects in each cohort. After dosing the first 2 subjects (the sentinel group - 1 receiving TAK-951 and 1 receiving placebo) the Investigator will review all available blinded safety and tolerability data up to 8 hour post-dose. If after dosing the sentinel group, there are no significant safety/tolerability concerns, then the rest of the cohort will be dosed. There will be at least 1 hour between dosing of each subject in each cohort, except for the sentinel subjects. A dose-escalation/blinded safety review meeting will be held between the Investigator and Sponsor after each cohort is completed to review the safety and available PK data from samples taken up to 1-day post dose, in order to confirm the dose level and/or infusion rate for the subsequent cohort.

Cohort 1 will be administered a 20 µg dose of TAK-951 or matching placebo as a single 60-minute IV infusion.

Cohort 2 will receive a higher dose of TAK-951 or matching placebo as a 60-minute infusion. The dose will be determined based on the safety and the plasma concentrations from Cohort 1. The exposure from the selected dose is expected to not exceed the exposure seen at the highest dose deemed to be safe in the single ascending dose (SAD) portion of the FIH study (TAK-951-1001).

The dose and the infusion rate for Cohort 4 and 5 will be determined by emerging clinical data analysis and will not to exceed the highest exposure seen in the FIH study (TAK-951-1001).

6.3 Stopping Rules

The Investigator and/or the Sponsor may pause further dosing for safety review or discontinue the study if any of the stopping rules are met or safety concerns identified at one of the planned TAK-951 dose, as listed here:

- 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 the product, 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.
- Any notable Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher AE or a related SAE.
- One subject experiences a clinically significant arrhythmia.

6.4 Rationale for Study Design, Dose, and Endpoints

6.4.1 Rationale of Study Design

This study has been designed to examine the safety, tolerability, and PK of various doses of TAK-951 infused at least two different rates (slow and fast).

6.4.2 Rationale for Dose

Cohort 1 will be administered 20 µg TAK-951 or matching placebo in a single 60-minute IV infusion. Simulations using a fit for purpose population PK model predict plasma concentrations above the 20 pg/mL lower limit of quantitation for up to approximately 10-12 hours following a 60-minute infusion dose administration. The predicted concentration at end of infusion (C_{eoi}) with an assumed absolute bioavailability (F) of 90% was comparable to the C_{max} observed in the ongoing FIH study following a 20 µg subcutaneous administration. The predicted C_{eoi} with an assumed F of 30% was comparable to the observed C_{max} following a 60 µg subcutaneous administration. The current highest doses in the ongoing FIH are 4000 µg SAD and 450 µg twice daily, 8 hours apart for 5 days. Although the subcutaneous bioavailability of TAK-951 is assumed to be high (~90%) based on non-clinical data (minipig), starting with a low infusion dose of 20 µg allows for a potentially greater exposure following IV administration if the subcutaneous bioavailability is actually very low (~1%). In this hypothetical case, a potential 100-fold greater bioavailability would result in AUC and C_{max} exposures 100-fold greater than predicted at 20 µg. This would still be within the exposures seen at the 4000 µg subcutaneous dose level in TAK-951-1001.

Cohort 2 will receive a 1.0 mg as a 60-minute infusion.

Cohort 3 will receive a 1.0 mg dose as a 120-minute infusion.

Additional cohorts (Cohorts 4 and 5) may be added to explore additional IV dosing regimens ensuring the predicted exposure will not be exceeding the exposure seen at the highest dose deemed to be safe in SAD portion of the FIH study.

For Cohort 4 and 5, as applicable, PK sampling and time-matched vital sign assessments scheduled relative to infusion timing will be based on emerging clinical data analysis. As such, this timing will be provided in a separate document and will not exceed 30 hours post start of infusion. The number of planned samples may be less than or equal to those in the protocol.

Please refer to Section 6.2 for additional details on the dose and rate determination for Cohorts 2 and up.

6.4.3 Rationale for Endpoints

6.4.3.1 Safety Endpoints

The key safety endpoints are typical for phase 1 studies and also takes into consideration GIP pharmacology-related cardiovascular effects and will be assessed through monitoring of AEs, vital signs, safety ECGs/telemetry, safety laboratory assessments, and physical examinations.

6.4.3.2 Pharmacokinetic Endpoints

The PK endpoints are standard for this type of study.

6.4.3.3 Immunogenicity Endpoints

The anti-drug antibodies will be assessed with the baseline sample and the post baseline samples. The formation of anti-drug antibodies such as IgM can occur 7 to 14 days after study drug administration. In this study we will be evaluating anti-drug antibodies at 14 (±2) and 28 (±3) days post-dose administration to assess potential immunogenicity.

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6.4.4 Future Biomedical Research

Any residual PK plasma samples will be stored by the Sponsor or Bioanalytical facility for the maximal 5 years determined by the Sponsor following the dosing. Tubes or containers will be identified with a barcode using an appropriate label. Immunogenicity samples will not be stored.

The purpose for storing samples is not to identify pre-existing medical conditions using genetic/genomic analysis using deeoxyribonucleic acid (DNA), or ribonucleic acid (RNA) but rather to analyze GIP pharmacology-related or safety observation-related biomarkers. Samples will not be submitted to a public database. The Sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses, and PK and statistical analysis of the data will have access to the samples and/or the data that resulted from the analysis, if performed.

By signing the ICF, subjects agree to the possible future analysis of these samples (for metabolites). At any time, the subjects can contact the CRU staff to request destruction of the residual samples once PK assessments required to meet the current study's objectives of the study are completed. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

6.4.5 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the critical component is safety and tolerability. The assessment should be performed as described in Section 9.2.

6.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of TAK-951 to any subject may not be modified for Cohort 1. The doses for the subsequent cohorts (dose level and/or rate of infusion) will be determined as indicated in Section 9.2.8. If necessary, a subject may be discontinued for the reasons described in Section 7.5 and Section 7.6. If indicated, the plasma PK samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites.

6.6 Study Beginning and End/Completion

6.6.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (ie, signing of the ICF) of the first subject.

6.6.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3.0).

6.6.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in the last follow-up visit for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subject is lost to follow-up.

6.6.4 Definition of Study Discontinuation

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.6.5 Criteria for Premature Termination or Suspension of the Study

Refer to the Stopping Rules (see Section 6.3).

6.6.6 Criteria for Premature Termination or Suspension of a Site

Not applicable.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female (of non-childbearing potential only), 19-55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine- and tobacco-containing products and/or cannabis products for at least 3 months prior to dosing and throughout the study.
3. BMI $\geq$ 18.0 and $\leq$32.0 kg/m^2 at screening.
4. Medically healthy based on no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee.

5. Female must be of non-childbearing potential as described in Appendix D.
6. A non-vasectomized, male subject must agree to use a barrier contraception (eg, condom with spermicide) or abstain from sexual intercourse from dosing and until 90 days after dosing. No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to dosing of study drug. A male who has been vasectomized less than 4 months prior to dosing must follow the same restrictions as a non-vasectomized male (see Appendix D).
7. If male, must agree not to donate sperm from dosing until 90 days after dosing.
8. Understands the study procedures in the ICF and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. Has a documented history of any clinically significant disorders, including psychiatric, cardiovascular, nephrological, neurological, metabolic, or gastrointestinal disease.
3. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
5. Drink alcohol in excess of 21 glasses/units per week for males or 14 glasses/units per week for females, with one unit = 150 mL of wine or 360 mL of beer or 45 mL of 45% alcohol.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
7. Have any tattoos, scars or skin issue at planned IV infusion site which could interfere with dosing.
8. History or presence of:
   - Three (3) or more incidences of vasovagal syncope within the last 5 years prior to screening.
   - Family history of unexplained sudden death or channelopathy.
   - Brugada syndrome (ie, RBBB pattern with ST-elevation in leads V1-V3).
   - Cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, stroke, sick sinus syndrome, pulmonary congestion, symptomatic or significant cardiac arrhythmia, second-degree AV block type 2, third-degree AV block, prolonged QTcF interval, hypokalemia, hypomagnesemia, or conduction abnormalities;

- Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome);
- Any clinically significant ECG findings or medical history including: long or short QT interval with QTcF (over 450 msec or less than 360 msec), bifascicular block or QRS ≥120 msec or PR interval >200 msec at screening or Day -1 pre-Hour 0.
- Documented history of sinoatrial block or sinus pause ≥3 seconds.

9. Semi-recumbent blood pressure (average of duplicate) is less than 90/60 mmHg or greater than 140/90 mmHg at screening.
10. Has an average semi-recumbent heart rate <60 or >100 bpm (at screening, at Day -1 pre-Hour 0, or at pre-dose Day 1); athletic subjects with an average semi-recumbent heart rate <60 bpm can be enrolled only with medical monitor approval. If subject has heart rate <60 bpm Investigator should obtain medical approval from Sponsor.
11. Has orthostatic hypotension defined as a decrease in systolic blood pressure ≥20 mmHg or a decrease in diastolic blood pressure ≥10 mmHg after 2 minutes of standing when compared with blood pressure from the semi-recumbent position at screening and at Day -1 pre-Hour 0. The semi-recumbent blood pressure will be an average of duplicate measurements.
12. Has postural orthostatic tachycardia, defined as an increase of 30 bpm or heart rate >120 bpm after standing for 2 minutes.
13. Female subjects of childbearing potential.
14. Female subjects with a positive pregnancy test or who is lactating.
15. Positive urine drug or alcohol results at screening or check-in.
16. Positive urine cotinine at screening or check-in.
17. Positive results at screening for HIV, HBsAg, or HCV.
18. Unable to refrain from or anticipates the use of any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to dosing and throughout the study. Thyroid hormone replacement medication may be permitted if the subject has been on same stable dose for the last 3 months prior to study drug administration. After dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the Investigator or designee. Hormone replacement therapy will also be allowed.
19. Has been on a diet incompatible with the on-study diet, in the opinion of the Investigator or designee, within the 30 days prior to dosing and throughout the study.
20. Donation of blood or significant blood loss within 56 days prior to dosing.
21. Plasma donation within 7 days prior to dosing.

22. Participation in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.
23. Positive results for COVID-19 testing at screening or check-in.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. After dosing, acetaminophen (up to 2 g per 24 hour) may be administered at the discretion of the Investigator or designee. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the last 3 months prior to dosing. Hormone replacement therapy will also be allowed.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case by case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

Use of excluded agents (prescription or nonprescription) or dietary products is outlined in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and Dosing (Days -28 to predose [Day 1])	After Dosing (Day 1) to Follow-Up
Alcohol	Prohibited from 7 days prior to dosing	Prohibited from dosing until the last PK collection.
Xanthine and/or caffeine	Prohibited from 24 hours prior to dosing [a]	Prohibited from dosing until the last PK collection.[a]
Medications	See Sections 7.1 and 7.2	See Sections 7.1 and 7.2
Nicotine- and tobacco-containing and/or cannabis products	Prohibited from at least 3 months prior to dosing	Prohibited from dosing until last follow-up visit.
Food substance		
Grapefruit/Seville orange	Prohibited from 28 days prior to dosing	Prohibited from dosing until the last PK collection.

[a] small amounts of caffeine derived from normal foodstuffs (eg, 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction).

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

On Day -1 of each cohort, subjects will be fasted overnight (at least 8 hours) and will continue to fast for 4 hours after Hour 0 for the collection of baseline time-matched heart rate and blood

pressure assessments. On Day 1 of each cohort, TAK-951 will be administered following an overnight fast (at least 8 hours) and subjects will continue to fast for 4 hours (after Hour 0) post start of infusion.

On Day 1 of each cohort, meals and snacks must be completed at least 1 hour before any Holter recording extractions and/or safety ECG.

When confined, standard meals and snacks will be provided at appropriate times and water will be provided *ad libitum*. Subjects will be required to fast from all food and drink except water between meals and snacks.

7.4.2 Activity

Subjects will remain semi-recumbent position for the duration of the infusion and for the first 4 hours following the end of infusion, except when they are standing or seated for study procedures or AEs.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side. During the first 4 hours after the end of infusion, subjects may be allowed to rise for brief periods under supervision (eg, in order to use the toilet facilities).

Subjects must be awakened at least 1 hour prior to the start of the cardiodynamic ECGs on Day 1 and at least 1 hour prior to the start of the cardiodynamic ECG recording scheduled at the 24-hour (Day 2) post-dose time point. On Day 1, subjects will remain awake for at least 12 hours post dose as the QT-RR relationship is different during sleep. However, subjects must lie down for at least 10 minutes prior to ECG recordings to avoid tachycardia secondary to physical activity.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the CRF using the following categories.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Positive urine drug or alcohol or cotinine results.
3. Positive pregnancy test.
4. Difficulties in blood collection.
5. Liver function test (LFT) abnormalities:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) in conjunction with elevated total bilirubin >2 times the ULN with no alternate etiology, in the opinion of the Investigator.

If during the study any of the study stopping criteria are met, further dosing will be paused, and the safety data will be reviewed by the Sponsor along with the Investigator. A recommendation will be made to continue, modify, temporarily suspend, or terminate the study as described in Section 6.3.

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 end-of-study or early termination as described in Section 3.0.

7.7 Subject Replacement

Replacement of discontinued or withdrawn subjects due to any reason (does not include discontinuations due to drug related safety) will be assessed on a case by case basis by the Sponsor and Investigator to ensure a minimum of 6 PK-evaluable subjects complete the cohort.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

TAK-951 is formulated for immediate-release and is available in dose strengths of 0.1mg/mL, 1.0 mg/mL, and 10mg/mL in vials for injection. The matching placebo is normal saline. Refer to Section 9.2.8.

Details of the dosage form description and strengths, or composition for the extemporaneous preparation, can be found in the pharmacy manual.

8.1.1 Clinical Study Drug Labeling

TAK-951 will be provided to the site bearing a label in accordance with local regulatory requirements.

TAK-951 and placebo will be prepared by licensed pharmacy staff at the CRU according to the procedures outlined in the pharmacy manual.

See Section 9.2.8 for study drug administration details.

8.1.2 Clinical Study Drug Inventory and Storage

The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report. Study drugs will be stored according to the product labels provided with the product.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

8.1.3 Clinical Study Drug Blinding

This is a double-blind, placebo-controlled study.

8.1.4 Randomization Code Creation and Storage

A computerized randomization scheme will be created by a Celerion statistician and it shall be considered blinded (as per the following).

The randomization is available only to the CRU pharmacy staff that is preparing the drug who will not be involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, subjects, or members of the staff responsible for the monitoring and evaluation of safety assessments.

One set of sealed envelopes containing the randomization code will be supplied to the Investigator or designee at the start of the study.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject.

In the event of a medical emergency, it is requested that the Investigator or designee make every effort to contact the Study Monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the Investigator or designee, for that subject only. In the event that the emergency is one, in which it appears that the other subjects may be at imminent risk, the blind may be broken for all subjects dosed at that dose level. The unblinding will be properly documented in the study file.

In all cases where the code is broken, the Investigator or designee should record the date and reason for code breaking.

At the end of the study, envelopes will be retained according to site procedures unless specified otherwise by the Sponsor.

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, and the database is officially locked.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The Sponsor will supply sufficient quantities of the TAK-951 to allow completion of this study. Celerion will provide sufficient quantities of normal saline (placebo) for infusion to allow completion of the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drug will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. Any remaining supplies that were purchased

by Celerion will be destroyed, if appropriate. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign, and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of dosing, different from the screening number.

If replacement subjects are used, the replacement subject number will be 100 more than the original (ie, Subject No. 101 will replace Subject No. 1).

9.1.1.2 Study Drug Assignment

All subjects will receive the treatments as detailed in Section 9.2.8.

9.1.2 Inclusion and Exclusion

Please refer to Sections 7.1 and 7.2.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.3. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to subject safety.

For this study, safety and tolerability is the critical assessment. Procedures, as applicable, will be performed in the following the order below, with regard to the prescribed time (not applicable for the screening visit):

a. Blood sample(s) collection (to be collected at exact time point).

b. Vital Signs (to be collected as close to the exact time point as possible).

c. Safety ECG and Holter ECG recording extraction to be performed before or after items above, with priority for PK and then vital signs to be collected as close to exact time point as possible.

d. Standardized meal or snack (meal/snack must be completed at least 1 hour before any Holter recording extractions and/or safety ECG).

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.2.1 Physical Examination

Qualified site personnel will conduct full physical examinations.

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Height (cm) and body weight (kg) will be obtained with the subject's shoes off, and jacket or coat removed. Height and weight will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 Body Mass Index

The BMI equals a subject's weight in kilograms divided by height in meters squared ($BMI = kg/m^2$). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4, round down, and 0.5 to 0.9, round up.

9.2.4 Vital Signs

Measurements of body temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Body temperature will be measured with an oral (temperature taken at floor of the mouth) thermometer. The same method (ie, oral) must be used for all measurements for each individual subject and should be the same for all subjects.

Blood pressure and heart rate measurements will be performed with subjects in a semi-recumbent position, except when they are seated or standing because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee. Subjects should rest

in a semi-recumbent position for at least 3 minutes before vital signs are measured. Blood pressure and heart rate should be made in duplicate with an interval of approximately 2 minutes between the 2 assessments. A third blood pressure assessment will be taken if results are inconsistent, at PI discretion. Final blood pressure read out should be the average of these assessments.

At the predose or prior to Hour 0 time points, blood pressure and heart rate will be measured within 2 hour prior to dosing or Hour 0. When scheduled after the start of infusion, vital signs will be performed within approximately 15 minutes of the scheduled time point.

Subjects from each cohort will have baseline heart rate and blood pressure assessments performed on Day -1 which are time-matched (± 5 minutes) to the Day 1 assessments (ie, time-matched baseline).

Refer to Section 9.2.5 for when safety ECGs will trigger vital sign measurements.

For orthostatic vital signs, heart rate and blood pressure will be performed after the duplicate semi-recumbent assessment has been completed. The subject should stand still for approximately 2 minutes before the standing heart rate and blood pressure assessment. Standing assessments **must not** be performed if semi-recumbent systolic blood pressure is <85 mmHg or if the subject presents with signs or symptoms suggestive of postural hypotension after standing. Subjects should continue to rest in a semi-recumbent position from the time of dosing until 4 hours post-dose except to stand for the measurement of standing vital signs or other study-related procedure. The semi-recumbant vital sign measurements will be taken in duplicate and the average will be used.

9.2.5 12-Lead ECG

Triplicate 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Ad hoc 12-lead ECGs will also be required, if a subject complains of palpitations, dizziness, breathlessness, chest tightness or any other symptoms suggestive of arrhythmia, between Day 1 (post-dose) and discharge. The ECG, blood pressure and heart rate measurements will be reviewed by the Investigator or medically qualified designee. If a clinically relevant abnormality is detected, the Investigator will follow the appropriate clinical protocols to stabilize the subject and will contact the Sponsor to discuss further management.

The Investigator or designee 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 CRF from the subject's ECG trace: HR, RR interval, QRS interval, PR interval, QT interval, and QTcF.

The Investigator or designee 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 with the clinical study report.

ECGs will be performed with subjects in a semi-recumbent position. All ECG tracings will be reviewed by the Investigator or designee.

At the predose or prior to Hour 0 time points ECG will be measured within 2 hours prior to dosing and prior to Hour 0. When scheduled after the start of infusion, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Cardiodynamic ECGs

The 12-lead Holter ECG monitoring will be captured on Day 1 as indicated in in the Schedule of Study Procedures (Section 3.0). Continuous 12-lead Holter ECG monitoring will be performed from -0.75-hour until 24 hours after the start of infusion. For all pre- and post-dose ECG collections, three 10-second ECGs will be extracted at each extraction window time point.

ECG extraction time points will occur before or after PK blood draws. Accordingly, subjects will be supervised and quietly resting semi-recumbent beginning a minimum of 10 minutes before each actual ECG extraction window of 10 minutes, if possible. During the extractions that are less than 1 hour post start of infusion, subjects may not have been resting for 10 minutes due to the proximity of sample collection. The rest period prior to the early PK draws (<1 hour post start of infusion) may need to be shortened to accommodate the events schedule. At all other timepoints, subjects will be supervised while remaining at rest, quiet, and awake and in a semi-recumbent position from at least 10 minutes if possible before the beginning of each ECG extraction time point and will remain quiet, awake, motionless, and semi-recumbent for at least 10 minutes after the beginning of each ECG extraction time point.

ECG data from Holter monitoring are not intended to be analyzed for real-time safety monitoring.

CCI [redacted]

9.2.7 Telemetry

Cardiac monitoring (heart rate and ECG) will be assessed via telemetry and will be performed as indicated in the Schedule of Study Procedures (Section 3.0).

Telemetry data will be used for real time safety monitoring to alert site staff and will not be stored or recorded in the CRFs.

9.2.8 Study Drug Administration

TAK-951 for IV infusion will be supplied as immediate release injection solution in 0.1 mg/mL, 1.0 mg/mL, and 10 mg/mL vials.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject as per the randomization scheme.

For IV dosing, the times of the beginning and the end of infusion will be recorded. Dosing interuptions will be recorded.

Dosing regimen (frequency and food requirements). Single dose:

Cohort 1: a low dose (20 µg) TAK-951 or placebo administered as a 60-minute IV infusion on Day 1

Cohort 2: a high dose (1.0 mg) TAK-951 or placebo administered as a 60-minute IV infusion on Day 1

Cohort 3: 1.0 mg TAK-951 or placebo administered as a 120-minutes IV infusion on Day 1.

If dosed, Cohorts 4 and 5 dose(s) of TAK-951 and infusion rate(s) of TAK-951 and placebo will be decided based on emerging clinical data analysis from the previous cohorts.

The ratio of active:placebo in each cohort will be 6:2 according to the randomization scheme and in a double-blinded fashion.

Subjects will fast for at least 8 hours before Hour 0 on Day -1 and Day 1 and will continue to fast for an additional 4 hours after Hour 0 on Day -1 and Day 1. Water is permitted. Standard meals will be administered at approximately 4 (lunch), 6 (snack), 10 (dinner), and 13 (snack) hours after start of dosing on Day 1. The same fasting requirements and meal/snack schedule will be followed on Day -1.

9.2.9 AE Monitoring

AE monitoring begins after signing of the ICF. Subjects will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 10.0.

9.2.10 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.10.1 Clinical Laboratory Tests

9.2.10.1.1 Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

9.2.10.1.2 Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample being taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Blood Urea Nitrogen	Magnesium
Bilirubin (total and direct)	Sodium
Alkaline phosphatase (ALP)	Potassium
AST	Chloride
ALT	Glucose
Albumin	Creatinine *
Gamma-glutamyl transferase (GGT)	

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

9.2.10.1.3 Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

9.2.10.1.4 Other

HIV test	Urine drug screen:
HBsAg	Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone)
HCV *(if antibody positive, confirm RNA negative)*	Amphetamines
Urine alcohol screen	Barbiturates
Serum pregnancy test (for females only)	Benzodiazepines
FSH (for postmenopausal females only)	Cocaine
Urine cotinine	Cannabinoids
COVID-19 testing (performed according to CRU standard procedures, provided in a separate document[s])	

9.3 Pharmacokinetic Samples

Instructions for sample collection, processing, and shipping will be provided in separate documents.

To reflect plasma drug exposure more precisely, blood samples for determination of plasma TAK-951 will not be collected from the infusion line arm during study drug administration and the

physical set for drug administration will not be used to obtain PK samples. If the opposite arm is not available, blood samples should be collected at the site as distant to the infusion site as possible, and the site of the blood sampling should be documented.

Samples from all subjects who receive active drug will be assayed even if the subjects do not complete the study. Placebo samples will not be assayed. Samples for determination of plasma TAK-951 will be analyzed using validated bioanalytical methods.

Primary specimen collection parameters are provided in Table 9.a. If indicated, the plasma PK samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
TAK-951 sample for PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory
ADA sample for immunogenicity	Blood	Serum	Serum sample forADA	Mandatory

9.3.1 PK Measurements

Pharmacokinetic parameters of TAK-951 will be calculated using noncompartmental analysis methods from the individual concentration-time profiles from all evaluable subjects who received active drug. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

9.3.1.1 Plasma PK Measurements

PK parameters for plasma TAK-951 concentrations will be calculated as follows, as appropriate:

AUC_{last}: The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.

AUC_{∞}: The area under the concentration-time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_{last} plus the ratio of the last measurable blood concentration to the elimination rate constant.

$AUC_{extrap}\%$: Percent of AUC_{∞} extrapolated, represented as $(1 - AUC_{last}/AUC_{\infty})*100$.

CL: Total plasma clearance after IV administration, calculated as $Dose/AUC_{\infty}$.

C_{eoi}: Concentration at the end of infusion.

t_{max}: Time to reach C_{eoi}. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.

$t^{1}/_{2z}$: Terminal disposition phase half-life will be calculated as $0.693/\lambda_z$.

Where λ_z is the apparent first order terminal disposition phase rate constant calculated from a semilog plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (eg, three or more non-zero plasma concentrations).

V_z: Volume of distribution during the terminal disposition phase after IV administration.

No value for λ_z, AUC_∞, AUC_{extrap}%, CL, V_z, or $t^{1}/_{2z}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for subjects with detectable concentrations at 2 or fewer consecutive time points.

Individual and mean plasma concentration-curves (both linear and log-linear) will be included in the final report.

Additional PK parameters may be estimated as appropriate.

CCI [redacted]

9.3.2 Immunogenicity Measurements

The status of anti-drug antibodies, titer, prior to and approximately14 and 28 days after dosing will be assessed.

CCI [redacted]

9.3.4 PGx Measurements

Not applicable

9.3.5 Confinement

Subjects will be housed on Day -2, at the time indicated by the CRU, until the Day 2 study procedures are completed. In accordance with the local local regulatory requirements for the COVID-19 pandemic, the clinical study unit will implement standard COVID-19 procedures as per their internal guidance documents. Subjects may be admitted earlier than Day -2 for COVID-19 testing not related to study protocol as per CRU requirements. Subjects will return for

study procedures as indicated in Section 3.0. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (ie, 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.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered 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.

Diagnoses versus 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 an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (ie, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). 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 an 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 from Baseline in the condition (ie, "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an 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 (ie, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or 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 (ie, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, 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 AEs. However, if a preplanned procedure is performed early (ie as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as 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 AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

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. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 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
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

The adverse events of special interest (AESI)s for TAK-951 include injection site reactions, hypotension, and tachycardia (refer to Section 10.2.8.5).

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to National Cancer Institute CTCAE: NCI CTCAE (NCI CTCAE v5.0). AEs not listed by the NCI CTCAE will be graded as displayed in Table 10.b.

Table 10.b NCI CTCAE

Grade	Description
1 – Mild	asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2 – Moderate	minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3 - Severe or medically significant but not immediately life-threatening	hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
4 - Life-threatening consequences	urgent intervention indicated.
5 - Fatal	AE an event that results in the death of the subject.

10.2.2 Assigning 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 a causal relationship is at least a reasonable possibility, ie, the relationship 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 medications and concurrent treatments.

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

Episodic AEs (ie, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Study Treatment

- 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 had not yet started or dosing with study medication was already stopped before the onset of the AE).
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE 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 become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (ie, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, LFTs and ADA

10.2.8.1 Collection Period

Collection of AEs (eg, AEs, SAEs, AESI, LFTs, and ADA) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up visit on Day 15 (± 2 days) and on Day 29 (± 3 days). For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

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 an SAE prior to the first exposure to investigational product 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. Nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not 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 AEs will be documented in the AE page of the CRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

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

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

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

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Appendix 14.1.1.

If reporting by fax, the site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via E-mail within 1 business day.

If reporting by E-mail, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via E-mail within 1 business day.

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 SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

10.2.8.3.1 SAE Follow-Up

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.

10.2.8.4 Reporting Special Interest AEs

AEs of special interest for TAK-951 include injection site reactions, hypotension, and tachycardia (refer to Section 10.2.8.5) and will be monitored by the Investigator and Sponsor.

10.2.8.5 Management of Specific AEs

Sinus Tachycardia

CTCAE Grade	Management
CTCAE Grade 2 sinus tachycardia (ie, Symptomatic*; nonurgent medical intervention indicated) with HR 120 and above at rest for at least 5 minutes with no physical exertion.	Evaluate ECG for abnormalities, manage as per local guidelines and call the medical monitor immediately. In MRD, the subject may be rechallenged with the agreement of the sponsor and investigator. In MRD, if a subject develops a second episode of symptomatic tachycardia, discontinue treatment with study drug.
Any CTCAE Grade 3 sinus tachycardia (ie, urgent medical intervention indicated) or Grade 4 (life-threatening)	Evaluate ECG for abnormalities, manage as per local guidelines and call the medical monitor immediately. In all subjects, discontinue further treatment with study drug.

CTCAE: Common Terminology Criteria for Adverse Events; ECG: electrocardiogram; MRD: multiple rising dose.
* Symptoms may include dizziness, light headedness, chest pain, chest heaviness, palpitations, and shortness of breath.

Low Blood Pressure

If a subject develops symptoms suggestive of hypotension or postural hypotension, blood pressure should be assessed for evidence of hypotension, which should be managed as per local guidelines, and the medical monitor should be contacted.

Injection Site Reaction

If a subject develops a CTCAE Grade 3 (ulceration or necrosis; severe tissue damage, operative intervention need) or 4 (life-threatening consequences; urgent intervention indicated) discontinue administration of TAK-951, provide immediate treatment and contact medical monitor.

Hypersensitivity

If anaphylaxis or other serious allergic reactions occur, TAK-951 administration will be discontinued immediately and appropriate management initiated (eg, epinephrine, and antihistamines, and further immediate care as necessary).

10.2.8.6 Reporting of Abnormal LFTs

If subjects experience ALT or AST >3 times the ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, and GGT) should be performed 24 hours after the abnormality was noted, and the medical monitor should be contacted.

If ALT or AST remains elevated >3 times the ULN, the Investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug (if applicable), and discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE and reported as per Section 10.2.8.2.

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. Follow-up laboratory tests as described in Section 13 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 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 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 study. 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 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the SAP.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

The safety analysis set will consist of all subjects who are enrolled and received the full or partial dose of study drug or placebo.

11.1.1.2 PK Set

The PK analysis set will consist of all subjects who received the active study drug and have at least one measurable plasma concentration of TAK-951.

11.1.1.3 Immunogenicity Set

The immunogenicity analysis set will include those subjects from the safety set who have a baseline and at least 1 post-baseline immunogenicity sample assessment.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (eg, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics for each treatment (cohort) and by pooled placebo. Categorical demographic data (eg, gender, race, ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

All PK data will be summarized using PK analysis set.

The plasma concentration of TAK-951 will be summarized by TAK-951 dose and infusion rate over each scheduled sampling time using descriptive statistics. The PK parameters of TAK-951 will be determined from the concentration-time profiles for all evaluable subjects using noncompartmental analysis approach. Actual sampling times, rather than scheduled sampling times, will be involved in the derivation of PK parameters.

Additional PK parameters may be calculated as appropriate. Further details will be specified in the SAP.

Values will be calculated for the plasma concentrations and the PK parameters for plasma as listed in Section 9.3.1.1 using appropriate summary statistics to be fully outlined in the CPAP.

CCI

[redacted]

11.1.5 Immunogenicity Analysis

All immunogenicity data will be summarized using immunogenicity analysis set.

Immunogenicity information will be summarized by treatment and point of time collection using descriptive statistics as applicable. Additional analysis may be performed on immunogenicity, if deemed necessary, such as the relationship between immunogenicity responses and PK/safety.

11.1.6 Safety Analysis

All safety data will be summarized using safety analysis set. The placebo subjects from all cohorts will be pooled into a single placebo group for all summaries and presentations.

11.1.6.1 AEs

TEAEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by treatment (cohort) and pooled placebo for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, severity, and relationship to treatment will be provided.

11.1.6.2 Clinical Laboratory Evaluation

Baseline (check-in), postdose (after start of infusion), and change from baseline to postdose laboratory data will be summarized by treatment. Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal criteria will be summarized. All clinical laboratory data will be provided in the data listings. All summaries will be performed by treatment (cohort) and pooled placebo (placebos pooled from all cohorts).

11.1.6.3 Vital Signs

Baseline (time-match [Day -1]), post-dose (after start of infusion), and change from baseline to postdose vital signs data will be summarized by treatment. Individual vital signs results that meet Takeda's markedly abnormal criteria (according to CTCAE) will be summarized. All vital signs data will be provided in the data listings. All summaries will be performed by treatment (cohort) and pooled placebo (placebos pooled from all cohorts).

11.1.6.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

Baseline (predose), postdose (after start of infusion), and change from baseline to postdose ECGs data will be summarized by treatment (cohort) and pooled placebo (placebos polled from all cohorts).

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and will be listed by subject.

11.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned. Section 6.0 describes the safety, tolerability and PK review that will take place after completion of each cohort and before starting of next cohort in the study.

11.3 Determination of Sample Size

Up to approximately 40 adult subjects (8 per cohort) are planned to be randomized. A formal sample size calculation was not performed for this study. The current sample size is deemed appropriate to evaluate the safety, tolerability, PK, and PD of TAK-951 following IV administration. A minimum of 3 cohorts will be evaluated.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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 CRFs. Source documents are defined as original documents, data, and records. The Investigator and study site guarantee access to source documents by the Sponsor or its designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of CRFs 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.

12.2 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.

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.

12.3 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 guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harminsation (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 A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1 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 (ie, 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 study. Until the site receives drug/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.

13.2 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 subject 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.

13.3 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 13.2).

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

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 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.

13.4.2 Clinical Study Registration

In order to ensure that information on clinical studies reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical studies it Sponsors anywhere in the world on ClinicalTrials.gov and/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 study sites closest to their homes by providing the Investigator name, address, and phone number to the callers requesting study information. Once subjects receive Investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study enrollment, they should be referred to the Sponsor.

Any Investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

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

13.5 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 study subjects. Refer to the 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.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 224-554-1052 Email: PVSafetyAmericas@tpna.com

14.1.2 INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council 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 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

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/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

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

14.1.4 List of Abbreviations

μg	Microgram
λ_z	Terminal disposition phase rate constant
AE	Adverse event
AESI	Adverse events of special interest
ADA	Anti-drug antibodies
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{last}	Area under the serum concentration-time curve, from time 0 to the time of the last quantifiable concentration, as calculated by the linear trapezoidal.
AUC_{∞}	Area under the serum concentration versus time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_{last} plus the ratio of the last measurable serum concentration to the elimination rate constant.
AV	Atrioventricular
BMI	Body mass index
C_{eoi}	End of infusion
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
C_{max}	Maximum observed concentration
CPAP	Clinical Pharmacology Analysis Plan
CRF	Case report form
CRU	Clinical Research Unit
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
F	Absolute bioavailability
FDA	Food and Drug Administration
FIH	First in human
FSH	Follicle-stimulating hormone
g	Gram
GABA	Gamma aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GIP	Glucose insulinotropic peptide
HBsAg	Hepatitis B surface antigen

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International units
IV	Intravenous
kg	Kilogram
L	liters
LFT	Liver function test
ln	Natural log
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NCI	National Cancer Institute
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PTE	Pretreatment event
QTcF	Corrected QT interval by Frederica
RBBB	Right bundle branch block
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSARs	Suspected unexpected serious adverse reactions
$t_{½z}$	Terminal disposition phase half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to first occurrence of C_{max}
ULN	Upper limit of normal
US	United States
USA	United States of America
WHO	World Health Organization
X-minute	Duration of infusion

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA®. Drugs will be coded using the WHO Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the Investigator. The final signed CRFs are provided to the Sponsor in the format as decided upon between Celerion and the Sponsor (eg, CD, flashdrive, SFTP). This will be documented in the DMP (if applicable).

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

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

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

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

CRFs 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 CRFs. The completed CRFs 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.

15.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of CRFs, 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, ICH E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8.0) 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.

16.0 REFERENCES

1. National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Revised: Nov-2017 (v5.0). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

17.0 APPENDICES

Appendix A 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. If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the 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.

10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B 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 or the subject's legally acceptable representative 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. Male subjects must use highly effective contraception (as defined in the informed consent) from dosing, throughout the duration of the study, and until 90 days after dosing. If the female partner of the subject is found to be pregnant during the study, the Investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical study information from this study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the 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 study 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 D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects

From dosing, throughout the duration of the study, and until 90 days after dosing, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicide) or abstain from sexual intercourse. In addition, they must be advised not to donate sperm during this period.

Female Subjects and Their Male Partners

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, and bilateral tubal ligation or bilateral salpingectomy performed at least 6 months prior to dosing. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to dosing of study drug. A male who has been vasectomized less than 4 months prior to dosing must follow the same restrictions as a non-vasectomized male.

Pregnancy

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

If any subject is found to be pregnant during the study she should be withdrawn and any Sponsor-supplied drug should be immediately discontinued.

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.

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

All pregnancies, including female partners of male subjects, in subjects on active study drug (including comparator, if applicable) will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

Appendix E Detailed Description of Amendments to Text

Change 1. Flexible wording added to allow more or less cohorts than currently written in the protocol as clinical data emerges.	
The change occurs in the protocol in Section 1.0 – Study Summary and Section 6.1 – Study Design	
Initial wording:	none
Amended or new wording:	Cohort 4 and 5 may run concurrently, sequentially or be omitted. Additional cohorts may be enrolled however the cohorts will not exceed the highest exposure observed in the FIH study.

Change 2.	Remove language restrictions for infusion duration as clinical data for cohort 2 did not support a 1 mg over less than 60 minutes.
The change occurs in Section 1.0 – Study Summary, Section 6.1 – Study Design, Section 6.4.2 – Rationale for the Dose, and Section 9.2.8 - Study Drug Administration.	
Initial wording:	Cohort 3: a high dose (same as the Cohort 2) TAK-951 or placebo administered as an IV infusion over a period of less than 60 minutes (TBD) on Day 1. Cohort 3 will be administered the same dose as Cohort 2, but as a single rapid IV infusion administration (rapid rate; duration of X minutes)
Amended or new wording	1.0 mg TAK-951 or placebo administered as 120 minutes IV infusion of on Day 1. Cohort 3 will receive a 1.0 mg dose as a 120-minute infusion.

Change 3.	Change of modeling and simulation wording to a more accurate description of emerging clinical data analysis to determine the next cohort's dosing regimen
The change occurs in Section 1.0 – Study Summary, Section 3.0 – Schedule of Study Procedures, Section 6.1 – Study design, and Section 6.4.2 – Dose Rationale	
Initial wording:	…Modeling and simulation
Amended or new wording	…emerging clinical data analysis

Change 4.	Allowance for flexibility in timepoints for Cohort 4 and 5
The change occurs in Section 1.0 – Study Summary and Section 6.1 – Study Design,	

Initial wording:	none
Amended or new wording:	For Cohort 4 and 5 as applicable, PK sampling and time-matched vital sign assessments scheduled relative to infusion timing will be based on emerging clinical data analysis. As such, this timing will be provided in a separate document and will not exceed 30 hours post start of infusion. The number of planned samples may be less than or equal to those in the protocol.

Change 5.	A second Schedule of Study Procedures table was added for Cohort 3 and any infusion longer than 60 minutes with associated footnotes. The original Schedule of Study Procedures was retained as it was used for Cohort 1 and 2 and would be used if the dosing regimen is less than or equal to 60 minutes. Footnotes were added or updated.
The change occurs in Section 3.0 – Schedule of Study Procedures.	
Initial wording:	None
Amended or new wording:	Table titled "Cohort 3 and any Cohort with an Infusion less than or Equal to 60 minutes"

Change 6.	The following change indicated in the protocol clarification letter (PCL) dated 30 Jul 2020 was incorporated: The blood collection and the vital sign measurements are to be as close as possible to the exact time point.
The change occurs in Section 9.2 – Clinical Procedures and Assessments	
Initial wording:	For this study, safety and tolerability is the critical assessment. Procedures, as applicable, will be performed in the following the order below, with regard to the prescribed time (not applicable for the screening visit). a. Holter ECG recording extraction b. Safety ECGs c. Vital Signs (to be collected as close to the exact time point as possible) d. Blood sample(s) collection e. Standardized meal or snack (meal/snack must be completed at least 1 hour before any Holter recording extractions and/or safety ECG)
Amended or new wording:	For this study, PK, safety and tolerability is the critical assessment. Procedures, as applicable, will be performed with regard to the prescribed time (not applicable for the screening visit):

	a. Blood sample collection (to be collected at exact time point) b. Vital signs (to be collected as close to exact time point as possible) c. Safety ECG and Holter ECG recording extraction to be performed before or after items above, with priority for PK and then vital signs to be collected as close to exact time point as possible. d. Standardized meal or snack (meal/snack must be completed at least 1 hour before any Holter recording extractions and/or safety ECG).
The change occurs in Section 3.0 – Schedule of Study Procedures	
Initial wording:	The study events at the end of infusion will proceed in this order: Holter ECGs, safety ECGs, vital signs, blood samples, meals and snacks.
Admended or new wording:	The study events at the end of infusion will proceed in this order: blood samples, vital signs, safety ECGs and Holter ECGs, meals and snacks.

Change 7.	The following change indicated in the PCL dated 30 Jul 2020 was incorporated: For logistical reasons, the Holter monitoring resting and extraction periods after dosing up to the 1 hour time point may have a shorter resting period than the 10 minutes stipulated in this section.
The change occurs in Section 9.2.6 – Cardiodynamic ECGs	
Initial wording:	ECG extraction time points will occur before PK blood draws.
Amended or new wording:	ECG extraction time points will occur before or after PK blood draws.
Initial wording:	none
Amended or new wording:	"During the extractions that are less than 1 hour post start of infusion subjects may not have been resting for 10 minutes due to the proximity of sample collection."

Change 8.	The following change indicated in the protocol clarification letter (PCL) dated 30 Jul 2020 was incorporated: Added language for COVID-19 related safety procedures.
The change occurs in Section 1.0 – Study Summary, Section 3.0 – Schedule of Study Procedures, Section 6.1 – Study Design, and Section 9.3.5 - Confinement	
Initial wording:	none

Amended or new wording:	In accordance with local regulatory guidance for the COVID-19 pandemic, the clinical study unit will implement standard COVID-19 procedures as per their internal guidance documents. Subjects may be admitted earlier than Day -2 for COVID-19 testing not related to study protocol as per CRU requirements.
The change occurs in Section 1.0 – Study Summary and Section 7.2 – Exclusion Criteria	
Initial wording:	None
Amended or new wording:	23. Positive results for COVID-19 testing at screening or check-in.
The change occurs in Section 9.2.10 - Laboratory Procedures and Assessments	
Initial wording:	none
Amended or new wording:	COVID-19 testing (performed according to CRU standard procedures, provided in a separate document[s])

Change 9.	The dose in Cohort 2 was specified based on the actual dose administered in this cohort was dosed prior to the writing of this amendment.
The change occurs in Section 1.0 – Study Summary, Section 6.4.2 – Rationale for the Proposed Study, Section 6.1 – Study Design and Section 9.2.8 – Study Drug Administration	
Initial wording:	"TBD" or "To be determined"
Amended or new wording:	1.0 mg
Initial wording:	The dose level in Cohort 2 and 3 will be the same. The duration (X-minute) of Cohort 3 infusion will be less than 60 minutes.
Amended or new wording:	none

Change 10.	Clarifying infusion duration
In the protocol in Section 4.2 - Ratoinal for the proposed study.	
Initial wording:	Infusion duration for subsequent cohorts may be faster or slower than 60 minutes and will be determined based upon data from previous cohorts
Amended or new wording:	Infusion duration for subsequent cohorts may be longer or shorter than 60 minutes and will be determined based upon emerging clinical data analysis

	from previous cohorts

Change 12.	The rationales for proposed study and dose were updated to match the known dose levels.
In the protocol Section 4.2 – Rationale for the Proposed Study	
Initial wording:	To that end, this study is designed as a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of TAK-951 in at least 3 cohorts of healthy adult subjects following a single IV infusion administration with at least two dose levels and different infusion rates, slow infusion, 60-minute, and a rapid rate(s).
Amended or updated wording:	To that end, this study is designed as a phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of TAK-951 in at least 3 cohorts of healthy adult subjects following a single IV infusion administration with at least two dose levels. Infusion duration for the first two cohorts will be 60 minutes. Infusion duration for subsequent cohorts may be faster or slower than 60 minutes and will be determined based upon data from previous cohorts.
In the protocol Section 6.4.2 –Rationale for Dose	
Intial wording:	Cohort 2 will receive a higher dose as a 60-minute infusion. Cohort 3 will be administered the same dose as Cohort 2, but as a single rapid IV infusion administration (rapid rate; duration of X-minute). Additional cohorts (Cohorts 4 and 5) may be added to explore additional IV dosing regimens ensuring the predicted exposure (based on modeling and simulation with all previous PK data) will not be exceeding the exposure seen at the highest dose deemed to be safe in SAD portion of the FIH study.

Amended or updated wording:	Cohort 2 will receive a 1.0 mg as a 60-minute infusion. Cohort 3 will receive a 1.0 mg dose as a 120-minute infusion. Additional cohorts (Cohorts 4 and 5) may be added to explore additional IV dosing regimens ensuring the predicted exposure will not be exceeding the exposure seen at the highest dose deemed to be safe in SAD portion of the FIH study. For Cohort 4 and 5, as applicable, PK sampling and time-matched vital sign assessments scheduled relative to infusion timing will be based on emerging clinical data analysis. As such, this timing will be provided in a separate document and will not exceed 30 hours post start of infusion. The number of planned samples may be less than or equal to those in the protocol.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	08-Jan-2021 16:06 UTC
	Clinical Pharmacology Approval	08-Jan-2021 16:06 UTC
	Clinical Science Approval	08-Jan-2021 19:39 UTC