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

NCT Number: NCT05567393

SAP Approve Date: 12 October 2020

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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.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-951-1001

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

PHASE 1

Version: **3.0**

Date: 12 October 2020

Prepared by:

PPD

Based on:

Protocol Version: Amendment 4.0

Protocol Date: 23 September 2020

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

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3.0 LIST OF ABBREVIATIONS

%CV	coefficient of variation
λ_z	terminal disposition phase rate constant
AE	adverse event
Ae_t	amount of drug excreted in urine from time 0 to time t
Ae_τ	amount of drug excreted in urine during a dosing interval
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC_∞	area under the concentration-time curve from time 0 to infinity
AUC_τ	area under the concentration-time curve during a dosing interval
AUC_{last}	area under the CSF concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{24}	area under the concentration-time curve from time 0 to time 24 hours
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance after extravascular administration
CL_R	renal clearance
C_{max}	maximum observed concentration
$C_{max, ss}$	maximum observed concentration during a dosing interval, at steady state
CSF	cerebrospinal fluid
CV	conventional units
ECG	Electrocardiogram
eCRF	electronic case report form
fe, t	fraction of administered dose of drug excreted in urine from time 0 to time t
IA	interim analysis
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple-rising dose
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
PTE	pretreatment event
QD	once daily
R	Accumulation ratio (index)
$R_{ac(AUC)}$	accumulation ratio based on AUC
$R_{ac(Cmax)}$	accumulation ratio based on C_{max}
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

SI	International System of Units
SOC	system organ class
SRD	single-rising dose
TEAE	treatment emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
t_{lag}	Lag time to first quantifiable concentration
t_{max}	time of first occurrence of C_{max}
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objective

- Parts 1
  - To characterize the safety (including immunogenicity) and tolerability of single SC doses of TAK-951 in healthy subjects.
- Part 3
  - To characterize the safety (including immunogenicity) and tolerability of multiple SC doses of TAK-951 in healthy subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- Parts 1
  - To characterize the plasma PK of TAK-951 following single SC doses in healthy subjects.
- Part 3
  - To characterize the plasma PK of TAK-951 following multiple SC doses in healthy subjects.

4.3 Exploratory Objectives

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4.4 Study Design

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

The study will consist of 2 parts:

- Part 1 is a FIH, randomized, double-blind, placebo-controlled, SRD study to assess the safety, tolerability and PK of TAK-951 in healthy volunteers. Up to 13 cohorts will be enrolled. Subjects will be randomized to receive TAK-951 or matching placebo.
- Part 2 of the study has been removed in Protocol Amendment 04.
- Part 3 is a randomized, double-blind, placebo-controlled, multiple rising dose (MRD) study. CCI [redacted]

TAK-951 and matching placebo will be administered subcutaneously. Any part of the study may not be conducted at the discretion of the sponsor. Safety will be assessed by monitoring for AEs, vital signs, ECG/telemetry, safety laboratory assessments after each dose and immunogenicity. Sampling times may vary based on emerging PK data, but the maximal number of samples or the maximum time point will not change.

An overview of treatment cohorts is presented in Table 4.a.

Table 4.a Overview of Treatment Cohorts

Cohort	Regimen	Treatment	
Part 1			
		TAK-951	**Placebo**
1	SRD	6	2
2		6	2
3		6	2
4		6	2
5		6	2
6		6	2
13		6	2
14		6	2
15		6	2
16		6	2
17		6	2
18		6	2
19		6	2
Part 3			
		TAK-951	**Placebo**
10	MRD	6	2
11		6	2
12		6	2
20		6	2

IV: intravenous; MRD: multiple rising dose; SC: subcutaneous; SD: single dose; SRD: single rising dose
Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

4.4.1 Part 1: SRD Cohorts 1 to 6 and 13 to 19

Part 1 will consist of up to 13 cohorts of 8 healthy subjects. Subjects in each cohort will be randomly assigned to receive a single dose of TAK-951 or placebo in a 3:1 ratio in a double-blind manner. Up to approximately 104 healthy subjects will be randomized in Part 1 (see Table 4.b).

Table 4.b Part 1: Schematic Representation and Planned Doses – Cohorts 1-6

TAK-951 Dose 1	TAK-951 Dose 2[a]	TAK-951 Dose 3[a]	TAK-951 Dose 4[a]	TAK-951 Dose 5[a]	TAK-951 Dose 6[a]
CCI [redacted]					
Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
6 active	6 active	6 active	6 active	6 active	6 active
2 placebo	2 placebo	2 placebo	2 placebo	2 placebo	2 placebo

[a] Dose may be subject to change based on emerging data.

Subjects from each cohort will be admitted into the study unit on Day -1 and will be dosed with TAK-951 or matching placebo on Day 1 after a minimum of 8 hours of fasting. Subjects will be confined for a minimum of 30 hours after dosing (can be discharged after the 30-hour PK sample) and may be confined for up to 48 hours postdose at the discretion of the investigator, if needed to ensure subject safety. After discharge, subjects will return to the study unit for additional assessments as indicated in the schedule of assessments. Blood samples for assessment of TAK-951 plasma concentrations will be collected up to 48 hours postdose. Urine will be collected up to 24 hours post TAK-951 dose.

A staggered dosing approach may be used for cohorts in Part 1. After dosing the first 2 subjects of each cohort (1 receiving TAK-951 and 1 receiving placebo) the investigator will review all available safety and tolerability data prior to dosing the remaining subjects in the cohort. The investigator will also consult Takeda as needed at any time.

CCI [redacted] Doses may be subject to change based on emerging PK and safety data. The sponsor may decide to administer lower doses, repeat doses, and cancel or add cohort(s) if deemed necessary. Subjects who drop out of the study for nonsafety reasons may be replaced at the discretion of the sponsor after discussion with the investigator.

After completion of each dosing cohort, and before selecting the next evaluable dose, a fully blinded assessment of the safety and tolerability, laboratory results of at least 24 hours, and available PK data will be performed by the site and select sponsor safety team.

Following each full blinded dose cohort review, while the site personnel and study subjects will be blinded to study drug assignment, the sponsor and select sponsor representatives may be unblinded to the completed cohort treatments. However, precautions will be taken not to unblind the study staff, including the investigator and subject, until the study is completed. The blind

may be broken before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety concerns.

Study Drug Administration

In Part 1, all attempts should be made to administer the single SC dose of TAK-951 in the abdomen. In all cases, care should be taken to avoid areas of scars or moles. TAK-951 must not be administered into an area where the skin appears to be tender to touch, signs of bruising/bleeding are noted, or the area seems indurated or erythematous. When locating injection sites on the abdomen, avoid giving the injection in the umbilicus, ribs, hip bone. For additional information on study drug administration, please refer to the Study Pharmacy Manual.

Part 2 of study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

4.4.2 Part 3: MRD Cohorts 10 to 12 and 20

Part 3 may start before completion of Part 1. If Part 3 is started before the completion of Part 1, the starting dose in Part 3 will be at a dose level below that currently being studied in Part 1. Similarly to Part 1, a staggered dosing approach may be used for cohorts in Part 3. Site personnel and study subjects will be blinded to study drug assignment, but selected sponsor vendors (third-party open) may be unblinded. Part 3 consists of up to 4 sequential ascending cohorts of healthy subjects. In each cohort, 8 healthy subjects will be randomly assigned to receive TAK-951 or matching placebo in a 3:1 ratio in a double-blind manner. Up to approximately 32 healthy subjects will be randomized in Part 3.

Subjects will be admitted to the study unit on Day -1 and will be dosed on Day 1 in each cohort/period after a minimum of 8 hours of fasting. Subjects will be confined until Day 6, 30 hours after last dose on Day 5 to assess safety, tolerability and PK. Subjects will return after discharge for additional assessments including PK sampling as indicated in the study flow chart.

Four safe and tolerable doses from Part 1 CCI [redacted] will be studied in Part 3 in an ascending manner. Based on emerging PK data from Part 1, adjustment to dose, dosing frequency, and repeat dosing duration may be implemented. CCI [redacted]

After completion of each cohort and before selecting the next evaluable dose, a blinded assessment of the safety and tolerability, laboratory at least 24 hours, and available PK data will be performed by the site and select sponsor safety team.

Following each fully blinded dose cohort review, while the site personnel and study subjects will remain blinded to study drug assignment, the sponsor and select sponsor vendor (third-party open) may be unblinded to the completed cohort treatments. Precautions will be taken not to unblind the study staff, including the investigator and subject, until the study is completed. The blind may be broken before each blinded cohort review and/or dose escalation meeting, if necessary, due to safety concerns.

Subjects who drop out may be replaced at the discretion of the sponsor after discussion with the investigator.

Study Drug Administration

In Part 3, when administering TAK-951, injection sites must be rotated. All attempts should be made to administer the single SC dose of TAK-951 in the abdomen first, followed by upper arms, then thigh as alternative sites, avoiding areas of scars or moles. If repeat injections of TAK-951 are given in the same spot, this may cause scarring and hardening of fatty tissue, which may interfere with the absorption of the drug; if feasible, injections should not be given at the same location repeatedly. Each TAK-951 injection must be administered approximately 2 inches (5 centimeters) apart and must not be administered into an area where the skin appears to be tender to touch, signs of bruising/bleeding are noted, or the area seems indurated or erythematous. If locating injection sites on the abdomen, avoid giving the injection in the umbilicus, ribs, hip bone. If injecting in the thighs, use the outer areas, below the groin and above the knee. For additional information on study drug administration, please refer to the Study Pharmacy Manual.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- Parts 1and 3
  - The primary safety endpoint of the study is safety and tolerability as assessed through physical examinations, vital signs, ECG/telemetry, laboratory assessments, AEs and immunogenicity.

5.2 Secondary Endpoints

- Part 1: plasma PK parameters for TAK-951
  - Maximum observed plasma concentration (C_{max}).
  - Area under the plasma concentration time curve from time 0 to infinity (AUC_{∞}).
- Part 3: plasma PK parameters for TAK-951
  - C_{max} on Day 1.
  - Area under the plasma concentration-time curve during a dosing interval ($AUC\tau$), where tau (τ) is the length of the dosing interval on Day 1.

5.3 Exploratory Endpoints

- CCI [redacted]

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

For Parts 1 and 3, the selected sample sizes are considered sufficient for evaluation of safety, tolerability, PK, and PD. The study is not statistically powered to perform hypothesis testing in Parts 1 and 3.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All study-related raw and derived data for randomized subjects will be presented in listings by cohort. All summaries will be presented for each study part separately.

Continuous data will be summarized using the following descriptive statistics: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, the coefficient of variation (%CV) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percent of subjects for each category, where appropriate. Percentages will be reported to 1 decimal place.

Data from Study Parts 1 and 3 will analyzed separately. Summaries for Study Parts 1 and 3 will be presented by pooled placebo, each TAK-951 dose level, TAK-951 overall and overall.

All statistical analyses will be performed using the SAS System Version 9.4 or higher.

7.1.1 Definition of Study Day, Baseline and Study Visit Windows

Study day will be calculated relative to the date of the first dose of the study drug in each study part. Study days prior to the first dose of study drug in each study part will be calculated as: {date of assessment/event – date of first dose of study drug in that study part}. Study days on or after the first dose of study drug in each study part will be calculated as: {date of assessment/event – date of first dose of study drug in that study part + 1}.

There will be no visit windowing.

In Study Parts 1 and 3, Baseline values is defined as the last observed value before the first dose of study medication, unless otherwise stated.

7.1.2 Conventions for Missing Data

There will be no imputation of incomplete or missing data.

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

7.2 Analysis Sets

Safety Set

The Safety Set will include all randomized subjects who receive at least 1 dose of investigational products in a given part of the study. Subjects in this set will be used for demographic, baseline characteristics, and safety summaries.

Pharmacokinetic Set

The PK analysis set will consist of all subjects who receive TAK-951 and have at least 1 measurable plasma concentration of TAK-951. All subjects with valid PK parameter estimates will be included in the summaries and analyses for that parameter.

Pharmacodynamic Set

The PD analysis set for Parts 1 and 3 will include all subjects who are randomized and received study drug and have at least 1 non-missing PD measurement. Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

7.3 Disposition of Subjects

Disposition of all screened subjects (denominator) will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

For Study Parts 1 and 3, summaries will be presented by pooled placebo, each TAK-951 dose level, TAK-951 overall and overall.

Disposition of all randomized subjects will be tabulated for each part of the study:

- All treated subjects (denominator)
- Subjects who were randomized but not treated, if applicable
- Subjects who completed the study investigational products
- Subjects who prematurely discontinued study investigational products
- Subjects who completed all study visits
- Subjects who prematurely discontinued study visits.

Primary reasons for discontinuation of study drug/visits, as entered on the electronic case report form (eCRF), will be tabulated. Reasons for discontinuation include adverse event, significant protocol deviation, lost to follow-up, voluntary withdrawal, sponsor study termination, IRB study termination, regulatory agency study termination, pregnancy, and other. The date of first dose, date of last dose, duration of treatment and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by study part for subjects in the Safety Set.

For Study Parts 1 and 3, summaries will be presented by pooled placebo, each TAK-951 dose level, TAK-951 overall and overall.

Summary statistics will be presented for continuous variables (age, height, weight, and body mass index [BMI]). The number and percentage subjects within each category will be presented for categorical variables (gender, race, etc). Individual subject demographic and baseline characteristic data will be listed.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 18 or higher) coding system.

Medical history includes any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions.

All medical history and concurrent medical condition data will be listed by site (study center) and subject number. The listing will contain subject identifier, treatment, system organ class (SOC), preferred term (PT), whether there was any medical history or concurrent condition, and, if yes, a detail of the medical history or concurrent condition. No inferential statistics will be presented.

7.6 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent. Concomitant medications are recorded on the eCRF and include any medications, other than study drug, taken at any time between informed consent and the end of the study.

All medication history and concomitant medications will be listed by site (study center) and subject number. The listings will contain subject identifier, treatment, preferred medication name, dose, unit, frequency, route, start date, stop date, whether the medication was ongoing, and reason for use. No inferential statistics will be presented.

Medication history and concomitant medications will be coded using the WHODrug Version 01March 2015 or higher.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing for all subjects. Summaries of PK data will be provided by dose in Study Parts 1 and 3. No other summary statistics for the extent of exposure to study investigational products or compliance calculations will be performed for this study.

7.8 Efficacy Analysis

Not applicable

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

All PK summaries and analyses will be based on the PK set. PK parameters of TAK-951 will be derived using non-compartmental analysis methods. The PK parameters of TAK-951 will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

CCI [redacted]

Blood samples for determination of TAK-951 will be collected according to the following schedule:

Study Part	Analyte	Matrix	Day	Scheduled Times (Hours)
1	TAK-951	Plasma	1	Predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 30, 48 hours postdose
3	TAK-951	Plasma	1	Predose and at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours postdose
			2, 3, 4	Predose
			5	Predose and at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours postdose
			6	Discharge

Concentrations of TAK-951 in plasma will be summarized by study part, dose, and day over each scheduled sampling time using descriptive statistics. Individual plasma TAK-951 concentration data will be presented in a data listing.

The following plasma PK parameters will be determined after SD and at steady state:

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

Descriptive statistics (N, arithmetic mean, geometric mean, SD, %CV, median, minimum, and maximum) will be used to summarize the plasma PK parameters for TAK-951 by dose for Study Parts 1 and 3. In addition, geometric mean will be computed for C_{max} and AUCs. Individual plasma PK parameters will be presented in a data listing.

Serial urine samples for determination of TAK-951 will be collected according to the following schedule:

Study Part	Analyte	Matrix	Day	Scheduled Times (Hours)
1	TAK-951	Urine	1	Predose and at 0-4, 4-8, 8-12, 12-16, and 16-24 hours postdose
3	TAK-951	Urine	1, 5	Predose and at 0-4, 4-8, 8-12, 12-16, and 16-24 hours postdose

The urine volume and the urine concentrations of TAK-9511 will be summarized by dose over each scheduled sampling interval using descriptive statistics. Individual urine TAK-951 excretion data will be presented in a data listing.

The following urine PK parameters of TAK-951 will be determined in Part 1 and part 3:

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

Descriptive statistics (N, arithmetic mean, geometric mean, SD, %CV, median, minimum, and maximum) will be used to summarize the urine PK parameters for TAK-951. Individual urine PK parameters will be presented in a data listing.

In Study Parts 1 and 3, the relationship between dose and key PK parameters (C_{max} and AUCs) will be assessed using the power model. The power model can be described by the following equation:

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

where β_o is the intercept and β_1 is the slope with random error ε. Dose proportionality will be declared if the 90% confidence interval (CI) for β_1 lies entirely within the critical region,

$$\left(1 + \frac{\ln(0.80)}{\ln(r)}, 1 + \frac{\ln(1.25)}{\ln(r)}\right)$$

where r is the ratio of the highest and the lowest dose in a given part of the study. Dose proportionality for subjects who are administered all of the study drug will be tested for TAK-951 C_{max} and AUCs on Day 1 for Study Part 1 and on Days 1 and 5 separately for Study Part 3.

7.9.2 Pharmacodynamic Analysis

Part 2 of Study TAK-951-1001 has been removed from the study in Protocol Amendment 04.

7.10 Other Outcomes

CCI

[redacted]

7.11 Safety Analysis

The Safety Set will be used for all summaries of safety and tolerability assessment including AEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters.

The safety summaries for Study Parts 1 and 3 will be presented separately by pooled placebo, each TAK-951 dose level, TAK-951 overall, and overall.

7.11.1 Adverse Events

All adverse events will be coded using MedDRA latest version. In this dictionary, each verbatim term is coded to a lower level term, and then mapped to a preferred MedDRA term, which is then mapped to an SOC. All adverse events will be included in the data listings but only treatment emergent adverse events will be included in the summary tables.

A treatment-emergent adverse event (TEAE) is defined as an AE that started or worsened after first study drug administration and within 30 days of last dose of study drug (AE onset date – date of last dose ≤30). AEs with missing onset dates will be summarized with TEAEs regardless of toxicity grade and relationship to study medication.

The following summaries will be presented:

- Overview of TEAEs during the study - number and percentage of subjects, number of events.
- TEAEs by SOC and PT - number and percentage of subjects.
- TEAEs by PT - number and percentage of subjects.
- Toxicity grade of TEAEs by SOC and PT - number and percentage of subjects.
- Relationship of TEAEs by SOC and PT - number and percentage of subjects.
- Drug-related TEAEs by SOC and PT - number and percentage of subjects.
- TEAEs Related to Study Procedure by SOC and PT - number and percentage of subjects.
- TEAEs leading to study discontinuation by SOC and PT - number and percentage of subjects.
- Serious TEAEs by SOC and PT - number and percentage of subjects, number of events.

SOCs will be sorted in alphabetical order. Within an SOC, adverse events will be sorted in descending order of total number of subjects with the preferred term among all the treatment groups.

In the high-level adverse event summary tables, TEAEs will be summarized regardless of severity and relationship to study drug. Within each subject, multiple reports of events that map to a common MedDRA term will be counted only once.

At the adverse event level, the summary tables will present the number of subjects reporting each of these MedDRA events, ie, the number of subjects reporting 1 or more events that map to the given MedDRA term.

At the SOC level, the summary tables will present the number of subjects reporting 1 or more events that map to the given SOC. That is, the number of subjects reported at the SOC level will be less than or equal to the sum of the subject counts across all adverse events within that SOC.

In selected summaries (see above), adverse events will be summarized by the number of events reported in addition to the number and percentage of subjects with events.

For the summary of TEAEs by SOC, preferred term and maximum toxicity grade, if a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the maximum toxicity grade of the episode (preferred term). Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once by the maximum toxicity grade in that SOC.

TEAEs classified in the eCRF as related to the study medication will also be summarized by preferred term and SOC. If a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once for the preferred term. Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once in that SOC. Adverse events with missing relationship will be classified as related to study drug.

Listings for TEAEs, TEAEs leading to study discontinuation, SAEs, deaths, and AE of special interest will be presented.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be evaluated and presented using International System of Units (SI) units unless otherwise stated. Only observations within 7 days of the last dose of study drug will be included in the tables. No inferential statistics will be presented unless otherwise stated.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical laboratory variables will be summarized for baseline, postbaseline values, and change from baseline by treatment group and overall at each measurement. Only the scheduled measurements will be included in the summary.

Individual results for hematology laboratory tests and serum chemistry tests will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix A). All subjects that meet the MAV criteria will be presented in a data listing. If a subject has a MAV for a particular laboratory test, all values for that subject and for that parameter will be listed. The number and percentage of subjects with at least 1 postbaseline markedly abnormal laboratory test result will be presented by treatment group and overall. All postbaseline clinical lab results within 7 days of the last dose, including scheduled and unscheduled measurements will be included in the MAV summaries. The mapping of the subjects with postbaseline results which meet the MAV criteria will be listed as a table.

Listings of all clinical laboratory data will be provided. Laboratory data outside of the normal reference range will be flagged on the listing along with values meeting MAV criteria

7.11.3 Vital Signs and Weight

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to summarize vital sign parameters at baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Only observations within 7 days of the study drug will be included in the tables.

All individual vital signs that meet Takeda's predefined criteria for markedly abnormal values (Appendix B) will be listed. The number and percentage of subjects with at least 1 postbaseline markedly abnormal vital sign measurement will be summarized. All postbaseline vital signs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries. The mapping of the subjects with postbaseline results which meet the MAV criteria will be listed as a table.

Orthostatic hypotension, identified by the criteria defined in Appendix C, will be calculated at every time point where sitting/standing and semi-recumbent measurements are available using the formula: sitting/standing vital measurement – semi-recumbent vital measurement at 1 minute and 3 minutes. The mapping of the subjects who meet the criteria for orthostatic hypotension will be listed by study visit as a table. All orthostatic hypotension observations, including ones at unscheduled visits, will be included in the subject mappings.

All vital sign data will be presented in the listings. Vital sign MAVs will be flagged in the listings.

7.11.4 12-Lead ECGs

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to summarize the ECG parameters including heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (Fridericia's) for baseline, each post-baseline visit, and change from baseline to each post-baseline visit. Only the scheduled measurements will be included in the summary. Only observations within 7 days of the study drug will be included in the tables. No inferential statistics will be presented.

A shift table for the investigator's ECG interpretation will provide the number of subjects in each of the appropriate categories (Normal, Abnormal but not clinically significant, or Abnormal and clinically significant) at the scheduled visit relative to the Baseline status.

All individual ECGs that meet Takeda's predefined criteria for markedly abnormal values (Appendix D) will be listed. The number and percentage of subjects with at least one markedly abnormal ECG measurement will be summarized. All post dose ECGs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries. The mapping of the subjects who meet the MAV criteria will be listed as a table.

All ECG data will be presented in the listings. ECG MAVs will be flagged in the listings.

7.11.5 Other Observations Related to Safety

Immunogenicity will be summarized using the safety set. Descriptive statistics will be used to summarize subjects in the following categories: ADA negative, ADA positive, low or high ADA titer.

The injection site assessment for local tolerability will be summarized by the severity level for each assessment (Erythema, Ecchymosis, Induration, Tenderness, Warmth, Swelling, and Lipoatrophy) by the assessment timepoints.

7.12 Interim Analysis

An interim analysis (IA) will be conducted after the completion of Part 1 SRD portion of study to support the safety review and regulatory interactions. Takeda personnel will be unblinded to the treatment assignments of individual subjects of Part 1 SRD portion of data, while the site personnel and study subjects will remain blinded to study treatment assignment. The details of IA data access and distribution will be described in a separate document (i.e., data access management plan).

The statistical methodologies to be used in the interim analysis are as described in this SAP. In particular,

- Only the data/cohort(s) from Part 1 SRD portion of study will be included in the IA.
- The IA will focus on key safety data including subject disposition, demographic and baseline characteristics, TEAEs, lab, vital signs, and ECG.

7.13 Changes in the Statistical Analysis Plan

The following changes from the protocol have been made in this SAP:

- An IA after the completion of Part 1 SRD portion of study is added in the SAP version 2.0. Refer to Section 7.12 for details.
- All references to Part 2 of the study were removed in this version of SAP per Protocol Amendment 4 dated 23Sept2020.

7.13.1 Revision History

Version	Date	Description of Changes
1.0	April 12, 2019	N/A
2.0	April 3, 2020	Updated the texts for study design in Section 4.4 based on Protocol Amendment 3 dated 28Jun2019. Clarified the data from Part 1 and Part 3 will analyzed separately in Section 7.1. Added an IA after the completion of SRD portion of study in Section 7.12.
3.0	October 12, 2020	Removed all references to Part 2 of the study throughout the SAP per Protocol Amendment 4 dated 23Sept2020. Added urine PK sample timepoints for Part 3 in Section 7.9.1. Updated high abnormal criteria for markedly abnormal laboratory values for GGT, Alkaline phosphatase, Total Bilirubin in Appendix A.

8.0 REFERENCES

1. Bruce G. Wolff, MD, et al. Alvimopan, a Novel, Peripherally Acting μ Opioid Antagonist. Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Major Abdominal Surgery and Postoperative Ileus.
2. Irinel Popescu, et al. The Ghrelin Agonist TZP-101 for Management of Postoperative Ileus After Partial Colectomy: A Randomized, Dose-Ranging, Placebo-Controlled Clinical Trial.
3. Grant Bochicchio, et al. Ghrelin Agonist TZP-101/Ulimorelin Accelerates Gastrointestinal Recovery Independently of Opioid Use and Surgery Type: Covariate Analysis of Phase 2 Data.
4. Justin T Brady, et al. The use of alvimopan for postoperative ileus in small and large bowel resections.
5. Conor P. Delaney, et al. Postoperative upper and lower gastrointestinal recovery and gastrointestinal morbidity in patients undergoing bowel resection: pooled analysis of placebo data from 3 randomized controlled trials.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	SI	<0.8 × LLN	>1.2 × ULN
Hematocrit	SI	<0.8 × LLN	>1.2 × ULN
RBC count	SI	<0.8 × LLN	>1.2 × ULN
WBC count	SI	<0.5 x LLN	>1.5 × ULN
Platelet Count	SI	$<75 \times 10^9$/L	$>600 \times 10^9$/L

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

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	SI	--	>3 × ULN
AST	SI	--	>3 × ULN
GGT	SI	--	>3 × ULN, if baseline is normal; >2 × baseline, if baseline is high abnormal
Alkaline phosphatase	SI	--	>3 × ULN, if baseline is normal; >2 × baseline, if baseline is high abnormal
Total Bilirubin	SI	--	>1.5 × ULN, if baseline is normal; >1.5 × baseline, if baseline is high abnormal
Albumin	SI	<25 g/L	--
Total protein	SI	<0.8x LLN	>1.2 × ULN
Creatinine	SI		>177 µmol/L
Blood urea nitrogen	SI		>10.7 mmol/L
Sodium	SI	<130 mmol/L	>150 mmol/L
Potassium	SI	<3.0 mmol/L	>5.5 mmol/L
Glucose	SI	<3 mmol/L	>10 mmol/L*
Chloride	SI	<75 mmol/L	>126 mmol/L
Calcium	SI	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	
Bicarbonate	SI	<8.0 mmol/L	

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

Appendix B Criteria for Abnormal Vital Signs

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

Appendix C Criteria for Identification of Markedly Abnormal Orthostatic Changes

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

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

Appendix D Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

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