Statistical Analysis Plan

NCT Number:

Title: A Randomized, Double-Blind, Placebo-Controlled Repeated Crossover Study to Evaluate the Safety and Tolerability of Intermittent Single Doses of TAK-951 in the Abortive Treatment of Subjects with Cyclic Vomiting Syndrome.

Study Number: TAK-951_1501

Document Version and Date: Version 1.0 09-SEPT-2021

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-951-1501

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Phase: 1

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Prepared by: [redacted]

Based on:

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REVISION HISTORY

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Original version	09-AUG-2021	Not Applicable

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BOCF	baseline observation carried forward
BMI	body mass index
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CVS	Cyclical vomiting syndrome
DMC	Data Monitoring Committee
IRC	Internal Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
HR	hazard ratio
ITT	intention-to-treat
KM	Kaplan-Meier
LLN	lower limit of normal
LOCF	last observation carried forward
MAR	missing at random
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model for repeated measures
MNAR	missing not at random
OC	observed cases
OR	odds ratio
PD	pharmacodynamic
PFS	progression free survival
PK	pharmacokinetic
PPAS	per-protocol analysis set
PRO	patient-reported outcomes
PT	Preferred Term (MedDRA)
Q1	25th percentile
Q3	75th percentile
RD	risk difference
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan

SOC	System Organ Class
TEAE	treatment-emergent adverse event]
WHODrug	WHO drug dictionary

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of intermittent single SC doses of TAK-951 in subjects with CVS during the prodromal/early emetic phase at home.

1.1.2 Secondary Objective(s)

The secondary objective(s) of the study are:

- *To evaluate the efficacy of intermittent single SC doses of TAK-951 in subjects with CVS.*
- *To assess the immunogenicity after intermittent single SC doses of TAK-951 in subjects with CVS.*

1.1.3 Exploratory Objective(s)

Exploratory endpoints of this study include:

- *To evaluate the PK of TAK-951 following intermittent single SC doses in subjects with CVS.*
- *To evaluate additional efficacy parameters of intermittent single SC doses of TAK-951 in subjects with CVS.*

1.2 Endpoints

1.2.1 Primary Endpoint(s)

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

1.2.2 Secondary Endpoint(s)

The secondary endpoints exclude the first 30 minutes immediately following TAK-951/placebo administration.

The following endpoints will be assessed within 2, 4, 8, 12 and 24 hours postdose:

- *Total response (Yes/No), defined as no emesis, no nausea (verbal rating scale [VRS] "none") and no need for rescue therapy before each timepoint (by both electronic reported patient-outcomes [ePRO] and electronic observer-reported outcomes [eObsRO] inclusive).*
- *Absence of emesis (Yes/No), defined as no emesis and no need for rescue medication before each timepoint (by both ePRO and eObsRO, inclusive).*
- *Absence of significant nausea (Yes/No), defined as VRS of "none" or "mild" and no need for rescue medication before the evaluation timepoint (ePRO).*

- *Peak nausea verbal rating scale (VRS) score at 0, 1, 2 hours in all subjects and 4, 8, 12, 24 hours postdose without receiving rescue medication before the evaluation timepoint (ePRO). Data will also be collected at 3, 5, 6, and 7 hours postdose as able.*
- *Change in nausea VRS score at 1 and 2 hours in all subjects and 4, 8, 12, 24 hours postdose as compared with predose score without receiving rescue medication before the evaluation timepoint. Data will also be collected at 3, 5, 6, and 7 hours postdose as able (ePRO).*
- *Status of subject's antidrug antibody (ADA) assessment (ie, ADA-negative or ADA-positive, and low or high ADA titer).*

1.2.3 Exploratory Endpoint(s)

All exploratory endpoints exclude the first 30 min immediately following TAK-951/placebo administration.

Exploratory endpoints will be assessed through the following parameters:

1. *Efficacy*
   - *Number of emeses by hour (eg 0-1h, 1-2h, 2-3h, etc) (ePRO, eObsRO, event marker, audio recording).*
   - *Absence of emesis within 2 hours postdose (Yes/No) (event marker, audio recording).*
   - *Absence of emesis within 4 hours postdose (Yes/No) in subjects who have not received rescue medication before the evaluation timepoint (event marker, audio recording).*
   - *Absence of emesis within 8 hours postdose (Yes/No) in subjects who have not received rescue medication before the evaluation timepoint (event marker, audio recording).*
   - *Time from dose to first emetic event (vomiting or retching), within each episode—(ePRO, eObsRO, event marker, audio recording).*
   - *Total duration (min) of CVS episode, defined as time from study dose to subject-determined resolution of episode (i.e., back to baseline status) (ePRO)*
   - *Abdominal pain (peak score) at 0, 1, and 2 hours in all subjects and 4, 8, 12, and 24 hours postdose in subjects who have not received rescue medication before the evaluation timepoint (ePRO). Data will also be collected at 3, 5, 6, and 7 hours postdose as able.*
   - *Headache (peak score) at 0, 1, 2 hours in all subjects and 4, 8, 12, 24 hours postdose in subjects who have not received rescue medication before the evaluation timepoint (ePRO). Data will also be collected at 3, 5, 6, and 7 hours postdose as able.*
   - *Health-related quality of life (HRQOL) PROMIS-29 at baseline and in inter-episodic phase every 4 weeks (ePRO).*
   - *Number of emergency department visits for CVS per CVS episode (Yes/No) (as defined by onset of prodrome in 1 study episode to subject's definition of resolution of that episode).*

- *Number of hospitalizations for CVS per CVS episode (as defined by onset of prodrome in 1 study episode to subject's definition of resolution of that episode) (ePRO).*
- *Rescue medication usage per CVS episode (as defined by onset of prodrome in 1 study episode to subject's definition of resolution of that episode) (Yes/No) (ePRO, eObsRO).*
- *Time from dosing to first use of rescue medication within each CVS episode (as defined by onset of prodrome in 1 study episode to subject's definition of resolution of that episode) (ePRO, eObsRO).*
- *Missed days of school/work due to CVS per CVS episode (as defined by onset of prodrome in 1 study episode to subject's definition of resolution of that episode) (ePRO).*
- *Usability and feasibility of ePRO, eObsRO and audio monitor recording (embedded interviews after the 1st episode with patients and HHC, and study interviews after the completion of this study with patients). Participation to interviews are all on voluntary basis.*
- *Subject activity as a proxy for functional disability* [redacted]
- [redacted] *from baseline (predose) to first emesis in those subjects who receive prodromal dosing (wearable event marker).*

2. *Individual plasma concentrations for TAK-951.*

2.0 STUDY DESIGN

This is a randomized, double-blind, repeat crossover placebo-controlled study to evaluate the safety, tolerability, efficacy, PK, and feasibility of episodic administration at home of TAK-951/placebo in subjects aged 18 to 50 years, inclusive, during the prodromal and early emetic phase in subjects with moderate to severe CVS. Approximately 20 subjects will be randomized to treatment sequence in this study.

Consented subjects will be screened for eligibility before randomization. Of note, data from Study TAK-951-1001 FIH study showed that 34% of healthy volunteers experienced orthostatic tachycardia (<5% symptomatic) as defined as >120 beats per minute (bmp) or an increase in HR upon standing of >30 bpm, and approximately 13% experienced orthostatic hypotension (<5% symptomatic) defined as a decrease upon standing of >20 mm Hg systolic, 10 mm Hg diastolic, or both at any time point after dosing with effects lasting approximately 2 to 4 hours. It is hypothesized that TAK-951 causes vasodilation that leads to these observed hemodynamic changes. At the screening visit, baseline physical examination, medical history including cardiovascular history and any history of autonomic dysfunction, safety laboratory tests, ECG, vital signs, orthostatic BP and HR will be assessed. Given that CVS may also be associated with comorbidities involving autonomic dysfunction, subjects will be screened to exclude baseline orthostatic hypotension and postural tachycardia as part of their cardiovascular history and vital sign assessments. Before randomization, a telehealth visit with the investigator/home health provider/study staff will evaluate the at-home setting for proximity to a visiting home health provider, potential drug storage conditions will be assessed for study feasibility, and safety of the

home setting. The remote home screening may not occur same day as physical screening but randomization may not occur until both physical and home screening are complete and the subject is eligible. Those subjects who are eligible will then be randomized into the study. Randomized subjects will use a variety of devices to facilitate their participation in this decentralized study including: tablet or hand-held mobile device for ePRO diary, wearable patch and accompanying bedside monitor tablet, wrist-worn event marker, audio recording device, BP cuff, and glucometer, as well as a small temperature-monitored freezer for drug/placebo home storage.

The at-home portions of the study will be supported by home HCPs (registered nurse, nurse practitioner, etc.) who will have a skill set including but not limited to the ability to: monitor vital signs, draw/prepare samples for clinical laboratory assessment, place an intravenous line if necessary, administer intravenous fluids if indicated, and review a digital rhythm strip if indicated.

Approximately 20 subjects will be randomized to treatment sequence in 1 of 4 groups with 5 subjects per group as outlined in Figure 2.a. in this 4 episode, 12 month randomized, double-blind, repeat crossover, placebo-controlled study to evaluate the safety, tolerability, efficacy, PK, and feasibility of episodic administration at home of TAK-951/placebo. Subjects will receive a single dose of TAK 951 or placebo at each of the 4 anticipated CVS episodes over a maximum 52-week study period in a double-blind manner (subject, sponsor and investigator blinded). Subjects who meet stopping criteria will be discontinued from the study and may be replaced by another subject. Subjects who do not have a CVS episode within 10 weeks of randomization and subjects who withdraw may be replaced in order for approximately 20 subjects to complete the study.

At the initiation of the prodrome (ie, first recognition by the subject of 1 or more of their usual symptoms of CVS prodrome) in each of the assessed CVS episodes, the subject will immediately contact a study HCP, produce a urine sample if necessary, and remove the blinded dose from the freezer to thaw at room temperature. Temperature excursion data supports dose stability up to 4 hours and dose thaw within 20 minutes at room temperature.

The HCP will arrive at the subject's home as rapidly as possible following contact from the subject to allow for dosing no later than 1 hour after onset of the emetic phase. The HCP will complete predose checks as outlined in the Schedule of Assessments (Section 3.0), initiate the wearable patch and wrist-worn wearable device (event marker) and administer double-blind study drug/placebo to eligible subjects based on predose vital signs during the continued prodrome or no later than 1 hour after the onset of the emetic phase. Upon arrival, the HCP will also activate a passive recording device for exploratory audio data collection of retching and emesis during the study period. Immediately before dosing in each CVS episode, subjects who meet any cardiovascular criteria will be excluded from dosing during that episode as follows: subjects who have a BP of ≤90/60 or ≥150/95 mm Hg, or HR ≤50 or ≥110 bpm. Athletic subjects with a HR <55 bpm may be enrolled based upon the investigator's judgement provided that HR is >45 bpm and rhythm is sinus bradycardia.

Postural hypotension is an identified risk for TAK-951 and data from the FIH study TAK-951-1001 suggest that orthostatic BP and HR changes may occur in some subjects in the first 2 hours postdose as described above. To mitigate this risk, following study drug administration, the subject will remain continuously supine or semirecumbent for at least 2 hours with assistance (including repositioning in use of emesis basin and bedpan as needed) and monitoring by the visiting HCP. No orthostatic vital signs will be assessed immediately before dosing given that some subjects may already be in the emetic phase of a CVS episode at the time of dosing, thereby limiting their ability to safely and accurately complete them. Orthostatic vital sign measurements will be assessed at 2, 4, and 8 hours following dosing as safety assessments for ambulation and at the end of HCP monitoring. No orthostatic vital signs will be completed during the first 2 hours after study drug administration for the first 20 aggregate doses of study drug/placebo. If asymptomatic (for example, no dizziness, lightheadedness, or palpitations) with normal supine/semirecumbent BP and HR at 2 hours after study drug administration, the subject will be allowed to mobilize if desired with the assistance of the HCP, and orthostatic HR/BP will be measured if tolerated. However, if a subject reports symptoms consistent with hypotension (for example, light-headedness, dizziness, palpitations, or pre-syncope) upon standing, the HCP will immediately assist the subject back to a sitting, semirecumbent, or supine position for an additional 1 to 2 hours. If no subjects meet criteria for hypotension or orthostatic hypotension (as defined above) after the first 20 aggregate doses in the study, then orthostatic BP will be assessed at 90 minutes after dosing and eligible subjects will be allowed to mobilize as desired with assistance of the HCP as above at that time point for the next 20 aggregate doses. If no subjects meet criteria for hypotension or orthostatic hypotension after the first 40 doses in the study with assessments at both 120 and 90 minutes postdose, then the first postdose orthostatic BP will be assessed at 60 minutes after dosing and eligible subjects will be allowed to mobilize as desired with assistance of the HCP as above at that time point.

If a subject develops symptoms suggestive of hypotension or postural hypotension at any time following study drug administration, BP and HR will be assessed by the HCP for evidence of hypotension and/or tachycardia, which should be managed as per protocol (see Section 10.2.8.4.) and local standard of care. The HCP will remain with the subject for continued observation and frequent monitoring of vital signs and cardiovascular side effects for at least 8 hours following the dose, as specified in Section 3.0. Should the subject experience persistent, stereotypic emesis or retching >2 hours after dosing, rescue with eligible medication(s), as defined in Section 7.4, will be allowed by self-administration. The informed consent form will detail potential combinatorial cardiovascular effects of commonly prescribed rescue medications (as used off-label for CVS in standard of care) and TAK-951.

Blinded study drug will not be administered more than 1 hour after the onset of the emetic phase. A subject who does not receive a dose due to closure of this 1-hour post-emesis onset dosing window for 1 episode will remain eligible for dosing in future episodes if all other dosing criteria are met. Subjects who fail to be dosed 2 or more times for any reason may be replaced.

The HCP will remain at the subject's home for at least 8 hours after dosing to monitor the subject and collect additional data. The wearable patch will provide real-time remote continuous single lead ECG, vital signs (temperature, HR), and [redacted] *for 8 hours after application. If*

needed, a telemedicine visit with the investigator/study staff will be scheduled to provide further support to the subject and/or HCP during or following the monitoring period. At the close of the 8 hour HCP monitoring period, a final set of vital signs will be obtained to assist in the decision for disposition of the subject as described in Sections 9.2.4 and 10.2.8.4.

To evaluate the secondary and exploratory efficacy endpoints, a variety of clinical outcome assessment (COA) measures are proposed. Validated COA measures specific to CVS do not currently exist but are under development. Please refer to the associated COA contents (v1.0) for full text and design of the COA.

Briefly, subjects will report their symptoms, signs, HRQOL and other outcomes using an ePRO diary device.

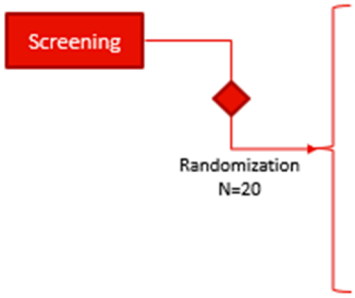
- *During inter-episodic phases, subjects may report entries on CVS related symptoms/signs on weekly basis, and HRQOL of physical, mental, and social functioning every 4 weeks.*
- *During prodromal/emetic phases, subjects may make diary entries approximately hourly, as able, to record changes in symptoms (eg. vomiting/retching, nausea, abdominal pain and headache) over time.*
- *During recovery phases (in the absence of emesis), subjects may make diary entries on daily basis, to record their remaining symptoms and to respond to check-in question daily on resolution (ie. whether back to baseline as defined by the subject).*
- *At the resolution of each episode, as defined by the subject, the subject will complete a global assessment of episode severity, and impact (eg. work/school absence), and return to inter-episodic mode for regular (weekly/monthly) entries.*

During the HCP observation period (8 hours), the HCP will also complete an eObsRO diary for symptoms and signs associated with CVS. Additionally as an exploratory tool, a passive audio data recorder as described above, activated by the HCP upon arrival, will collect audio data of emesis (vomiting/retching) for approximately 8 hours, the period of HCP monitoring in each CVS episode. Patients will also be asked to press a button on a wrist worn wearable device to mark each instance of vomiting or retching they experience during the HCP observation period. The association between patient and HCP-reported vomiting/retching (via eObsRO and ePRO) and audio-recorded vomiting/retching will be assessed to evaluate the feasibility of audio data collection as a potential endpoint for future studies. The audio data collected will not be used to inform any treatment recommendations or decisions. The association between patient and HCP-reported vomiting/retching (via eObsRO and ePRO) and event marker recorded vomiting/retching will be assessed to evaluate the feasibility of event marker data collection as a potential endpoint for future studies. The event marker data collected will not be used to inform any treatment recommendations or decisions.

As there are many unknowns associated with this first interventional study in CVS patients, study-embedded interviews are planned for first 5 subjects and HCPs after the patients' first CVS episode, to assess to what extent the COA plan and approaches meet the needs of patients and HCPs and whether there are any significant gaps in design and execution.

Subjects will be evaluated for safety, tolerability, and efficacy associated with TAK-951 or placebo following all CVS episodes. No subject will be dosed more frequently than every 7 days. Sparse PK sampling will occur during the times specified in Section 3.0 An optional DNA sample [redacted] *will also be collected from subjects that provide consent for collection through a separate procedure at the end of study visit.*

Safety will be assessed by monitoring for AEs, vital signs, continuous HR and ECG monitoring (using wearable patch), and safety laboratory assessments. PK sampling times and scheme may vary based on emerging safety, tolerability and available PK data, but the maximal number of samples or the maximum time point will not change. Efficacy assessments will be descriptive without predefined hypothesis testing.



Abortive therapy (at home)

	Randomization Sequence	Episode 1	Episode 2	Episode 3	Episode 4
N=5	Seq. ABBA	A (placebo)	B (TAK-951)	B	A
N=5	Seq. BAAB	B	A	A	B
N=5	Seq. AABB	A	A	B	B
N=5	Seq. BBAA	B	B	A	A

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

No formal statistical hypothesis testing is planned in this study.

3.2 Statistical Decision Rules

No formal statistical decisions are planned in this study.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

The sample size is based on feasibility. The chosen sample size is deemed adequate to assess the primary objective of safety in this study.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set will include all subjects who were randomized and received at least 1 dose of study medication. Subjects will be analyzed according to the treatment they actually received.

5.2 Full Analysis Set

The full analysis set (FAS) will include all subjects who were randomized and received at least 1 dose of study medication. Subjects will be analyzed according to their randomized treatment, regardless of whether they receive an investigational product that is different from that to which they were randomized. Subjects who were randomized but never dosed and were replaced will be excluded from the efficacy analysis.

5.3 Per-Protocol Analysis Set

The per protocol analysis set (PPAS) will include all subjects who are in the FAS and do not violate the terms of the protocol in a way that would impact the study output significantly. All decisions to exclude subjects for the per protocol analysis set will be made before the unblinding of the study. Analyses using the per protocol analysis set will be provided as a sensitivity analysis.

5.4 Pharmacokinetic Analysis Set

The PK analysis set will consist of all subjects who receive at least 1 dose of study medication and have at least 1 measurable plasma concentration sample.

5.5 Immunogenicity Set

The immunogenicity analysis set consists of subjects who receive at least 1 dose of study medication and have ADA status assessment at baseline, and at least 1 postbaseline sample.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All data for randomized subjects will be presented in by-subjects listings, sorted by sequence, subject ID, treatment, period, and timepoint.

Data listings and summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/FAS/PPS/PK/Immunogenicity). Summary statistics and statistical analyses will be based on protocol defined nominal visit/timepoint. The data collected at the unscheduled visit/timepoint will be excluded from by-visit summary statistics and statistical analyses, but will be displayed in the data listings.

The following conventions will be applied to present the analyses results, unless otherwise specified.

- Descriptive statistics:
  - For continuous data (study drug exposure and compliance, clinical laboratory data, vital signs, ECGs, etc.):
    - n, mean, standard deviation, median, minimum, and maximum.
  - For categorical data:
    - frequency counts and percentages.
  - Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate. Percentages will be reported to 1 decimal place. For the calculation of summary statistics and statistical analysis, unrounded data will be used.
  - Where appropriate, variables will be summarized descriptively by treatment, visit, and timepoint. The denominator for the percentage will be based on the number of subjects in each treatment group (column total) unless otherwise specified. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be presented.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model Version 2.1, and CDISC ADaM Implementation Guide Version 1.2. Pinnacle 21 Version 2.1.0 or higher will be utilized to ensure compliance with CDISC standards.

6.1.1 Handling of Treatment Misallocations

For all efficacy endpoints, subjects will be analyzed as randomized. For all safety endpoints, subjects will be analyzed as treated.

6.1.2 Analysis Approach for Continuous Variables

The longitudinal continuous endpoints will be analyzed using MMRM as observed. This MMRM model will include treatment, sequence, period, timepoint, treatment-by-timepoint interaction and treatment-by-timepoint-by-period interaction as fixed effects, and subject-within-sequence as a random effect. Covariance structure may be selected from: Autoregressive(1), Compound Symmetry, Unstructured, and Toeplitz. A model with each covariance structure will be fit, the models which converge will be compared using AIC_C.

$$AIC_C = AIC + \frac{2(k+2)(k+3)}{T-k-3},$$

Where T is the number of observations and k is the number of predictors.

Point estimates, the associated 95% CIs and nominal p-values for treatment difference between TAK-951 and placebo will be presented at 0, 1, 2, 4, 8, 12, 24 hours postdose for peak nausea VRS score, and at 1, 2, 4, 8, 12, 24 hours postdose for change in nausea VRS score.

If the above MMRM model does not converge the endpoints will be analyzed using matched pairs t-tests. Multiple imputation for missing data will be used with the matched pairs t-test.

6.1.3 Analysis Approach for Binary Variables

The binary secondary efficacy endpoints will be summarized by treatment groups as observed. Treatment difference between TAK-951 and placebo at each scheduled timepoint will be estimated and the associated 95% CI will be constructed using normal approximation. These binary efficacy endpoints will be analyzed using a nonlinear mixed effects model with repeated measures (NMMRM) with treatment, sequence, period, timepoint, treatment-by-timepoint interaction, and treatment-by-timepoint-by-period interaction as fixed effects and subject-within-sequence as a random effect based on the observed data as the main analysis method. The odds ratio between TAK-951 and placebo at each scheduled timepoint (i.e., 2, 4, 8, 12, and 24 hours postdose), the associated 95% CI and nominal p-value obtained from the nonlinear mixed effects model will be presented.

If the above NMMRM model fails to converge, binary efficacy endpoints will be analyzed using McNemar's test, where subjects who have missing information to determine endpoint status will be considered as treatment failures. Count, percentage, treatment difference and p-value will be reported in this instance.

6.1.4 Analysis Approach for Time-to-Event Variables

The time-to-event endpoints (time from dose to first emetic event) will be summarized by treatment groups. Subjects without documented events will be censored at the last visit. Kaplan-Meier (KM) estimates and KM plots for appropriate endpoints will be provided.

6.2 Disposition of Subjects

Disposition of all randomized subjects (denominator) will be tabulated (count and percent). The summaries of disposition will be presented by treatment arm.

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

- Subjects who were randomized but not treated, if applicable;
- Subjects who completed the study investigational products;
- Subjects who prematurely discontinued or withdrew study investigational products;
- Subjects who completed all planned 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 or withdrawal include pre-treatment even, adverse event, LFT abnormalities, lost to follow-up, pregnancy, protocol deviation, study terminated by sponsor, voluntary withdrawal by subject, subject identified with COVID-19

infection, and Other. The date of first dose, date of last dose, number of dose received, and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (eg, age, height, weight, and body mass index (BMI)) for placebo group and TAK-951. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (eg, gender, ethnicity, race) will be tabulated. Individual subject demographic and baseline characteristics data will be listed.

BMI equals a subject's weight in kilograms divided by height in meters squared (BMI = kg/m2). The values should be reported to 1 decimal place by rounding.

6.3.2 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 24 or higher) coding system.

During the screening period and prior to randomizarion, a complete medical history will be compiled for each subject. The history will be summarized by system organ class (SOC), preferred term (PT) and by each treatment group and overall based on the Safety Analysis Set.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the screening examination according to the judgment of the investigator. The condition (ie, diagnosis) should be described and will be summarized by system organ class and preferred term based on the Safety Analysis Set.

Individual subject medical history and concurrent medical condition data will be listed.

6.4 Medication History and Concomitant Medications

Medication history includes all medications, other than study treatment, which was stopped at or prior to the first dose of study treatment. Only medications taken 6 months prior to study entry (ICF signing) will be included. Concomitant medication includes all medication, other than study treatment, which was started after the first dose of study treatment, through the end of the safety follow-up period.

Medication history and concomitant medication will be coded using the World Health Organization Drug Dictionary (WHODrug, March, 2020 or higher) coding system.

The summary of concomitant medication will include the number and percentage of subjects by preferred term within each Anatomical Therapeutic Chemical (ATC) class level 2 by treatment arm using safety analysis set. The summary table will be presented with ATC class sorted in

alphabetical order and preferred term sorted in decreasing frequency based on the total number of subjects. A subject will be counted only once within a given ATC class and within a given preferred term, even if he/she received the same concomitant medication at different times.

All medication history and concomitant medication data will be provided in by-subject listings using safety analysis set.

6.5 Efficacy Analysis

The efficacy analyses will be conducted using the FAS. Sensitivity analyses based on PPAS will be performed for selected secondary efficacy endpoints (eg, data collected via ePRO diary, eObsRO diary). Selected secondary efficacy endpoints will be defined in a subsequent version of the SAP. Nominal p-values will be presented when appropriate. The efficacy data within the first 30 minutes immediately following TAK-951/placebo administration will be excluded from the efficacy analysis as the dosing window allows for study drug/placebo to be given up to 1 hour into the emetic phase where subjects may already be experiencing severe, repeated bouts of emesis.

In addition to this SAP, a separate psychometric analysis plan will be developed to detail the COA evaluation methods of the COA endpoints.

6.5.1 Secondary Endpoint(s) Analysis

6.5.1.1 Derivation of Endpoint(s)

Endpoint	Definition
Total response (Yes/No) by ePRO and eObsRO	No emesis, no nausea (verbal rating scale [VRS] "none") and no need for rescue therapy before each timepoint (by electronic reported patient-outcomes [ePRO and eObsRO]). Both ePRO and eObsRO must confirm the definition. If there is any disagreement or if either the ePRO or eObsRO are missing, then the value will be "No".
Absence of emesis (Yes/No) by ePRO and eObsRO	No emesis and no need for rescue medication before each timepoint (ePRO and eObsRO]). Both ePRO and eObsRO must confirm the definition. If there is any disagreement or if either the ePRO or eObsRO are missing, then the value will be "No".
Absence of significant nausea (Yes/No)	VRS of "none" or "mild" and no need for rescue medication before the evaluation timepoint (ePRO).
Peak nausea verbal rating scale (VRS) score at 0, 1, 2 hours in all subjects and 4, 8, 12, 24 hours postdose without receiving rescue medication before the evaluation timepoint (ePRO). Data will also be collected at 3, 5, 6, and 7 hours postdose as able	Nausea has a lead in question of: "Did you experience nausea yes/no?" If the response to this is "No", then the subject will be listed as "none" for the VRS. If the subject responded "Yes": Nausea (defined as the desire to vomit without the presence of expulsive muscular movements) will be scored using a self-reported, 4-point VRS of "none", "mild", "moderate" or "severe." Significant nausea is defined as a VRS ≥"moderate". The presence and severity of subject-reported nausea will be recorded in the ePRO and/or reported by the subject to the HCP and recorded in the eObsRO. The VRS scores for subjects after receiving rescue medication before the evaluation timepoint (ePRO) will be considered as missing data. Data collected at 3, 5, 6, and 7 hours postdose will be included in the summary statistics and data listings but excluded from the statistical modeling.
Change in nausea VRS score at 1 and 2 hours in all subjects and 4, 8, 12, 24 hours postdose as compared with predose score without receiving rescue medication before the evaluation timepoint.	Value at given time (1,2,4,8,12,24) – predose value. The VRS scores for subjects after receiving rescue medication before the evaluation timepoint (ePRO) will be considered as missing data. Data collected at 3, 5, 6, and 7 hours postdose will be included in the summary statistics and data listings but excluded from the statistical modeling.

6.5.1.2 Main Analytical Approach

Binary secondary efficacy endpoints to be assessed at 2, 4, 8, 12 and 24 hours include:

- Total response (Yes/No), defined as no emesis, no nausea (verbal rating scale [VRS] "none") and no need for rescue therapy before each timepoint (by both ePRO and eObsRO inclusive).
- Absence of significant nausea (Yes/No), defined as VRS of "none" or "mild", before each endpoint (ePRO).
- Absence of emesis (Yes/No), defined as no emesis and no need for rescue medication before each timepoint (by both ePRO and eObsRO inclusive).

Binary Endpoints will be analyzed as described in Section 6.1.3.

Longitudinal continuous secondary endpoints include:

- Peak nausea VRS score at 0, 1, 2 hours in all subjects and 4, 8, 12, 24 hours postdose in subjects who have not received rescue medication before the evaluation timepoint (ePRO).
- Change in nausea VRS score at 1, 2 hours in all subjects and 4, 8, 12, 24 hours postdose as compared to predose score in subjects who have not received rescue medication before the evaluation timepoint
- Status of subject's ADA assessment (ie, ADA-negative or ADA positive, and low or high ADA titer).

Longitudinal continuous endpoints will be analyzed as described in Section 6.1.2.

6.5.2 Exploratory Endpoint(s) Analysis

6.5.2.1 Derivation of Endpoint(s)

Endpoint	Definition
Number of emeses by hour (eg 0-1h, 1-2h, 2-3h, etc)	Count of emeses (vomiting or retching) by hour (eg 0-1h, 1-2h, 2-3h, etc)
Absence of emesis within 2 hours postdose (Yes/No)	Emeses (vomiting or retching) within 2 hours postdose.
Absence of emesis within 4 hours postdose (Yes/No) in subjects who have not received rescue medication before the evaluation timepoint	Absence of emeses (vomiting or retching) within 4 hours postdose.
Absence of emesis within 8 hours postdose (Yes/No) in subjects who have not received rescue medication before the evaluation timepoint	Absence of emeses (vomiting or retching) within 8 hours postdose.
Time from dose to first emetic event (vomiting or retching), within each episode	Time of first emetic event – Start time of episode
Total duration (min) of CVS episode	Time from study dose to subject-determined resolution of episode (i.e., back to baseline status) defined based on ePRO.
Abdominal pain (peak score) at 0, 1, and 2 hours in all subjects and 4, 8, 12, and 24 hours postdose in subjects who have not received rescue medication before the evaluation timepoint	Max abdominal pain score at each timepoint (0, 1, and 2 hours in all subjects and 4, 8, 12, and 24 hours postdose) in subjects who have not received rescue medication before the evaluation timepoint
Headache (peak score) at 0, 1, 2 hours in all subjects and 4, 8, 12, 24 hours postdose in subjects who have not received rescue medication before the evaluation timepoint	Max headache pain score at each timepoint (0, 1, and 2 hours in all subjects and 4, 8, 12, and 24 hours postdose) in subjects who have not received rescue medication before the evaluation timepoint
Health-related quality of life (HRQOL) PROMIS-29 at baseline and in inter-episodic phase every 4 weeks	Score determined off of ePRO and Clinical Outcome Assessment Scales and Questionnaires v1.0.
Number of emergency department visits for CVS per CVS episode (Yes/No)	Count of emergency department visits per CVS episode defined below. CVS episode defined as: Onset of prodrome in 1 study episode to subject's definition of resolution of that episode
Number of hospitalizations for CVS per CVS episode	Count of hospitalizations for CVS per CVS episode defined above.
Rescue medication usage (Yes/No) per CVS episode	Rescue medication usage per CVS episode as defined above.
Time from dosing to first use of rescue medication within each CVS episode	Date of Rescue Medication Administration - Date of First Dose + 1 CVS Episode defined above.
Missed days of school/work due to CVS per CVS episode	Count of missed days of school/work due to CVS per CVS episode
Usability and feasibility of ePRO, eObsRO and audio monitor recording (embedded and exit interviews with patients and nurse practitioners)	This will be defined and the analysis will be described in a separate Biomarker Analysis Plan.
Subject activity as a proxy for functional disability	This will be defined and the analysis will be described

Endpoint	Definition
([redacted]	in a separate Biomarker Analysis Plan.
Change [redacted] from baseline (predose) to first emesis in those subjects who receive prodromal dosing (wearable event marker).	This will be defined and the analysis will be described in a separate Biomarker Analysis Plan.

6.5.2.2 Main Analytical Approach

The exploratory endpoints will be summarized descriptively by treatment groups as observed.

Descriptive statistics for continuous endpoints will include number of subjects, number of observations, mean, standard deviation, median, minimum, and maximum.

Descriptive statistics for binary or categorical endpoints will include count and percentage. The time-to-event endpoints (time from dose to first emetic event), will be summarized by treatment groups. Subjects without documented events will be censored at the last visit. Kaplan-Meier (KM) estimates and KM plots for appropriate endpoints will be provided.

The analysis of exploratory biomarkers and audio markers will be described in a separate analysis plan and will be reported separately.

6.6 Safety Analysis

Safety data will be summarized by treatment groups using the safety analysis set. No formal statistical testing or inference will be made.

6.6.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or higher and will be summarized by System Organ Class and Preferred Term by treatment groups. Treatment-emergent adverse events will be summarized by treatment groups and. The number and percentage of subjects with treatment-emergent adverse events and SAEs will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term overall, by severity, and by relationship to study drug for each treatment group.

A treatment-emergent adverse event (TEAE) is defined as an AE that started or worsened after first dose of the study treatment and up to the date of the last follow-up visit. AEs with missing onset dates will be summarized with TEAEs regardless of toxicity grade and relationship to study medication.

The intensity of all AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0 or higher). AEs not listed by the NCI CTCAE will be graded as displayed in Table 6.a.

Table 6.a 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 (ADL).
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the subject.

In summary, AEs will be summarized by each treatment group and overall using the Safety Analysis Set as follows:

- Overview of TEAEs - number and percentage of subjects, number of events;
- Pretreatment AEs by system organ class (SOC), high level term (HLT), and preferred term (PT) - number and percentage of subjects;
- TEAEs by system organ class (SOC), high level term (HLT), and preferred term (PT) - number and percentage of subjects;
- Most frequent TEAEs by PT (sorted by frequency, occurring in ≥5% of subjects in any treatment arm) - number and percentage of subjects;
- TEAEs by relationship to study drug and by SOC, HLT and PT - number and percentage of subjects;
- TEAEs for toxicity grade 3 or higher by relationship and by SOC, HLT and PT - number and percentage of subjects;
- TEAEs leading to treatment discontinuation by SOC, HLT, and PT - number and percentage of subjects;
- Serious TEAEs by SOC, HLT and PT - number and percentage of subjects;
- Serious TEAEs by relationship to study drug and by SOC, HLT and PT - number and percentage of subjects;
- Serious TEAEs by intensity (toxicity grade) and by SOC, HLT and PT - number and percentage of subjects;
- TEAEs resulting in death by PT - number and percentage of subjects;
- TEAEs of special interest (AESI) by SOC, HLT, and PT - number and percentage of subjects.

Key guidelines for determining the incidence of AEs are as follows:

- AEs with missing or unknown intensity will be considered as severe (or Grade 3).
- AEs with missing or unknown relationship to study drug will be counted as related.
- A subject with 2 or more AEs within the same level of the MedDRA term will be counted only once in that level.
- 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.
- For the summary of TEAEs by SOC, HLT and PT and intensity (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.
- In selected summaries, adverse events will be summarized by the number of events reported in addition to the number and percentage of subjects with events.

Data listings for TEAEs, TEAEs leading to study discontinuation, SAEs, deaths, and AESI will be presented. The AEs will be listed by treatment, subject number and onset date of the adverse event. The listing will contain: subject identifier, age, sex, body weight, race, adverse event (preferred term and reported term), SOC, onset date, end date or whether the event was ongoing, duration, frequency, intensity, action taken concerning study drug, causality to study drug, the outcome, whether the adverse event was an SAE and whether the event was an AESI.

Based on the mechanism of action of TAK-951, certain AESIs have been predefined. The categories of AESIs, are described below. AESI will be summarized by investigator-indicated AESI in the eCRF and derived-AESI per the MedDRA terms or definition below.

AESIs	MedDRA Terms or definitions
Injection site reaction	Injection Site Reaction (HLT)
Hypotension	Hypotension (PT)
Tachycardia	Tachycardia (PT)
Orthostatic Hypotension	Orthostatic Hypotension (PT)

6.6.2 Clinical Laboratory Evaluation

The analysis of the laboratory data will include parameters tabulation for each assessment visit by treatment group using the Safety Analysis Set, using the following:

- Number of subjects with non-missing values (n),
- Arithmetic mean,
- Median,

- Standard deviation (SD),
- Minimum and maximum observed values (Min, Max).

For the post-baseline assessments, the summary will also include the change from baseline values. Subjects with markedly abnormal values for laboratory tests will be tabulated (see Section 9.3 for details).

Individual subject clinical laboratory data will be listed by timepoint.

Blood samples for analysis of the Hematology, Serum Chemistry, Serum and Urine parameters are shown below:

6.6.2.1 Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cells [RBCs])	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells [WBCs] with absolute differential	

6.6.2.2 Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride and lipase
Creatinine	Glucose
Gamma-glutamyl transferase	Sodium
Potassium	Bilirubin (total) if above the upper limit of normal, total bilirubin will be fractionated
Protein (total)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase

6.6.2.3 Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrate
For Females only: hCG (for pregnancy)	

6.6.2.4 Diagnostic Screening

Other

HIV	Hepatitis screen (hepatitis B surface antigen, hepatitis C virus antibody)
FSH	βhCG (pregnancy) test

6.6.3 Vital Signs

Vital signs will include HR (bpm), respiratory rate, and systolic blood pressure and diastolic blood pressure in all parts of the study.

Absolute values and changes from baseline in vital signs parameters will be summarized descriptively for each treatment group. Individual vital sign results meeting the Takeda's markedly abnormal criteria will be flagged and tabulated (see Section 9.4 for details).

6.6.4 ECG

ECG parameters (i.e., heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (Fridericia's)) will be summarized using descriptive statistics for baseline, postbaseline value, and change from baseline by treatment arm based on safety analysis set. The ECG parameters will be only summarized at the scheduled visits.

In addition, individual result for ECG parameters (heart rate, PR interval, QRS interval, and QTc interval) will be evaluated against the Takeda's predefined markedly abnormal value (MAV) criteria (Criteria for Identification of Markedly Abnormal Values for the 12-Lead ECG Parameters). All postbaseline ECG data including scheduled and unscheduled measurements will be included in the MAV evaluation. For the ECG parameter of interest, the number and percentage of subjects with at least 1 postdose value meeting Takeda's MAV criteria for ECG parameters will be presented by treatment arm based on safety analysis set.

The investigator's ECG interpretation (Normal, Abnormal but not clinically significant, or Abnormal and clinically significant, Not evaluable) will be summarized using a shift table as cross-tabulations (baseline versus each scheduled postbaseline visit) of numbers and percentage of subjects in each of appropriate categories by treatment arm based on safety analysis set.

All ECG data along with values meeting MAV criteria will be presented in the by-subject listings based on safety analysis set.

6.6.5 Other Safety Parameters

Physical examination findings will be presented in the data listings.

Depending on the prevalence of COVID-19 infections and illness in regions where the study is conducted, additional analysis may be performed to evaluate the impact of COVID on the safety of all participating subjects.

6.6.6 Extent of Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing for all subjects in the Safety Analysis Set. No other summary statistics for the extent of exposure to study investigational products or compliance calculations will be performed for this study.

6.7 Immunogenicity Analysis

ADA positive is defined as subjects who have confirmed positive ADA status in at least 1 postbaseline assessments. ADA negative is defined as subjects who do not have a confirmed positive ADA status in any postbaseline assessment.

For ADA positive only, high ADA titer is defined as subject who has at least 1 postbaseline ADA titer >16; low ADA titer is defined as subject whose postbaseline ADA titers are all ≤16.

Immunogenicity will be summarized using the number and percentage of subjects in the following categories: ADA status (ADA negative, ADA positive), ADA titer (low or high) at baseline and postbaseline visits by treatment arm based on immunogenicity analysis set.

The summary of TEAE by PT and immunogenicity categories (ADA status (ADA negative, ADA positive), ADA titer (low or high)) and treatment arm based on immunogenicity analysis set may be provided to explore the relationship between immunogenicity status and safety, if deemed necessary.

The summary of PK parameters (including but not limited to C_{max}, AUCs and CL/F where appropriate) by immunogenicity categories (ADA status (ADA negative, ADA positive), ADA titer (low or high)) and treatment arm based on immunogenicity analysis set may be provided to explore the relationship between immunogenicity status and PK, if deemed necessary.

All immunogenicity data will be provided in by-subject listings based on immunogenicity analysis set.

6.8 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

No formal noncompartmental PK analysis will be performed on concentration-time data. Summary statistics of plasma concentrations will be summarized using the PK set. Individual concentration data will be included in the listings using the PK set.

A population PK analysis may be conducted, and a more detailed description of these analyses may be given in a separate analysis plan. The results of these analyses will not be included in the clinical study report and may be a standalone report, if needed.

6.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.9.1 PRO Analysis

There will be both electronic patient reported outcomes (ePRO) and electronic observer-reported outcomes [eObsRO]). Both will be used to evaluate endpoints as described early. A separate psychometric analysis plan will detail the analysis and evaluation of ePRO and eObsRO.

6.9.2 Health Care Utilization Analysis

Health-related quality of life (HRQOL) PROMIS-29 at baseline, monthly and at the end of every CVS episode. The data for this will be collected via the ePRO and the analysis and evaluation of this will be detailed in a separate psychometric analysis plan.

6.10 Interim Analyses

An interim analysis (IA) may be conducted when approximately 50% of the total planned number of subjects have completed the study or withdrawn. Data for the selected secondary endpoints will be analyzed as part of the IA for internal decision making purposes. The sponsor personnel will not have access to the treatment assignment of individual subjects but only the aggregated IA results. Study site personnel and the study subjects will remain blinded to the treatment assignment for individual subjects and to the outcome of the IA until final database lock. Since this is a phase 1b study, the IA is intended to assist internal decision making and does not include a possibility to stop the study for efficacy or futility; there will not be alpha level adjustment for the final analysis.

Should the sponsor decide to conduct the IA, the study team would identify relevant TLFs for the purpose of the IA. Complete details related to the unblinding and analysis of interim data will be described in a subsequent version of SAP and data access management plan (DAMP). Further details will follow in a subsequent version of this analysis plan.

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

An external independent DMC will conduct ongoing reviews of safety data. The DMC will make recommendations to the study team as described in the DMC charter. Details of the DMC, including meeting frequency, approach to maintaining the study blind through appropriate firewalls, will be captured in the DMC charter before the start of the study.

7.0 REFERENCES

Burnham, K.P. and Anderson, D.R. (2002) Model Selection and Inference: A Practical Information-Theoretic Approach. 2nd Edition, Springer-Verlag, New York.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not Applicable

9.0 APPENDIX

9.1 Data Handling Conventions

9.1.1 Missing Data Handling

9.1.1.1 Conventions for Missing Adverse Event Dates

Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

For AEs or serious adverse events (SAEs), a missing or incomplete onset date will be imputed according to the following conventions:

1. If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
   - First study drug date.
   - Consent date (for SAEs only).
2. If an onset date is incomplete, the derived onset date will be calculated following:
   - Missing day, but month and year present: the day will be imputed as the 1st of the month. If the first study drug dose occurs in the same month and year but after the imputed date, the derived onset date will be set equal to the first study drug date.
   - Missing day and month, but year present: the day and month will be imputed as the 30th June of the year. If the first study drug dose occurs in the same year but after the imputed date, the derived onset date will be set equal to the first study drug date. If the EOS date occurs in the same year but before the imputed date, the derived onset date will be set equal to the first study drug date.

For AEs or SAEs, a missing or incomplete end date will be imputed according to the following conventions:

1. If an end date is missing, the derived end date will be imputed the last assessment date.
2. If an end date is incomplete, the derived end date will be calculated following:
   - Missing day, but month and year present: the day will be imputed as the last date (for example February 2009 will be imputed as 28 February 2009) of the month. Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.

9.1.1.2 Conventions for Missing Concomitant Medication Dates

Start and stop dates for all concomitant medications are collected on the case report form (CRF). However, in case of missing or partial information in these dates, the following rules will be used:

If the start date is unknown or partial:

- If the day is missing, the start day will be the first day of the month.
- If the month is missing,
  - If the year is the same as the date of first dose of study drug, the start month will be the month of the dose first study drug.
  - If the year is not the same as the date of first dose of study drug, the start month will be January.
- If the year is missing, the start year will be the minimum of the year of the first clinic visit or the year of the informed consent date.
- If the entire start date is unknown, the start date will be the date of first study drug administration.

If the stop date is missing, partial or "ongoing:"

- If the day is missing, the stop day will be the last day of the month reported.
- If the month is missing,
  - If the year is the same as the date of last assessment, the stop month will be the month during which the last assessment occurred.
  - If the year is not the same as the year of the last assessment, then the end month will be December.
- If the year is missing, the stop year will be the year in which the last assessment occurred.
- If the entire stop date is unknown or if the medication is "ongoing", the stop date will be the date of last assessment.

9.1.1.3 Methods for Handling of Missing Efficacy Data

Missing data for longitudinal dichotomous efficacy endpoints will not be imputed, but handled using a nonlinear mixed effects model with repeated measures (NMMRM) assuming missing at random (MAR) mechanism. Other missing data handling method maybe explored such as the non-responder imputation method, ie, any subject with missing information for determination of endpoint status will be considered as having an undesirable outcome in the analysis.

Missing data for longitudinal continuous endpoints will not be imputed, but handled using a MMRM assuming MAR. Other missing data handling method maybe explored such as the multiple imputation method.

Missing data for time to event endpoints will not be imputed.

Other missing data handling method may be explored.

9.1.2 Definition of Baseline

Baseline is defined as the last non-missing measurement prior to the first dose of study drug.

All data will be analyzed using the protocol defined nominal visits, unless otherwise stated. Missing baseline values will not be imputed.

9.1.3 Definition of Visit Windows

Study visits do not have a set schedule but are based on nominal individual patient CVS episodes. Date and time of the Episode will be recorded. For purposes of time-to-event data visit day can be calculated as:

Date of event – Date of baseline + 1

9.1.4 Definition of Hour Window

For each hour, the questionaire is initiated 1 minute after the hour and is available for 15 minute. It asks patients about their experience in the prior hour.

The event marker and audio are available in real time. They will be cut off at the completion time of the questionaire. Then the next hour for these markers will continue.

9.2 Analysis Software

SAS 9.4 or greater

9.3 Criteria for Identification of Markedly Abnormal Laboratory Values and Vital Sign 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 x ULN
Platelet Count	SI	<75 x 10^9/L	>600 x 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	--	>3x ULN
AST	SI	--	>3x 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	>1.2x 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.

9.4 Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Systolic blood pressure	mm Hg	<85	>140
Diastolic blood pressure	mm Hg	<50	>90
Body temperature	^{o}C	<35.6	>37.7
	^{o}F	<96.1	>99.9
Heart rate (traditional clinical consensus)	bpm	<60	>100
Respiratory Rate	breath per minute	<12	>16
BMI		<18.5	>25.0 • Class 1: BMI of 30 to <35 • Class 2: BMI of 35 to <40 • Class 3: BMI of 40 or higher.

9.5 Criteria for Identification of Markedly Abnormal Orthostatic Changes

Parameter	Criteria
Orthostatic Hypotension	Decrease in SBP ≥20 mm Hg or a decrease in DBP ≥10 mm Hg on standing
Orthostatic Tachycardia	Defined as an increase of >30 bpm or HR >120 bpm on standing

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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	10-Sep-2021 17:49 UTC