Protocol

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: Amendment 1 19 November 2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL

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 Identifier: TAK-951-1501

Compound: TAK-951

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19 November 2021	Amendment 1	Substantial	United States
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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceuticals	**Compound:** TAK-951
Study Identifier: TAK-951-1501	**Phase:** 1b
Protocol 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 Design: This is a randomized, double-blind placebo-controlled repeated crossover study to evaluate the safety, tolerability, efficacy, pharmacokinetics (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 cyclic vomiting syndrome (CVS).	
Study Primary Objective: To evaluate the safety and tolerability of intermittent single subcutaneous (SC) doses of TAK-951 in subjects with moderate to severe CVS during the prodromal/early emetic phase at home. **Secondary Objectives:** • 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.	
Study Subject Population: Subjects with moderate to severe CVS based on the ROME IV diagnostic criteria, aged 18 to 50 years, inclusive at screening.	
Planned Number of Subjects: Approximately 20 subjects	**Planned Number of Sites:** Approximately 10 sites within the United States
Dose Levels: [redacted] intermittent single dose	**Route of Administration:** SC
Duration of Treatment: Subjects completing the study will receive a single dose of either placebo or [redacted] TAK-951 in each of 4 CVS episodes for a total of 2 doses of TAK-951 and 2 doses of placebo over a 52-week period.	**Planned Study Duration:** ~18 months
Main Criteria for Inclusion: Subject eligibility is determined according to the following criteria before entry into the study: 1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements and is eligible for the study. 2. The subject or, when applicable, the subject's legally acceptable representative, signs and dates a written or electronic informed consent form and any required privacy authorization before the initiation of any study procedures. 3. The subject is male or female and aged 18 to 50 years, inclusive. 4. The subject has at least a 1-year history of CVS diagnosis based on the Rome IV diagnostic criteria. 5. The subject has had at least 4 CVS episodes over 6 months before screening during the last 12 months. 6. If taking medications prescribed for the prophylaxis or abortive management of CVS, the subject must be receiving a stable dose for at least 3 months before screening. 7. The subject is willing and able to exclusively use the protocol rescue medications if needed. 8. The subject has a stereotypic prodrome with onset ≤4 hours before CVS emetic phases.	

9. The subject has a body mass index (BMI) between 18 and 32 kg/m^2, inclusive.
10. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (eg, condom with or without spermicide) from signing of informed consent throughout the duration of the study and for 30 days after last dose OR a surgically sterile female subject, or females of nonchildbearing potential with laboratory confirmation of postmenopausal status (ie, follicle-stimulating hormone levels >40 mIU/mL) or one of childbearing potential who is sexually active with a nonsterilized male partner agrees to use a highly effective method of contraception from signing of informed consent throughout the duration of the study and for 30 days after the last dose as defined in Section 9.5.

Main Criteria for Exclusion:

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

1. The subject has participated in another interventional study within 4 weeks or 5 half -lives of the investigational study drug, whichever is longer, before the screening visit. The 4-week window will be derived from the date of the last study procedure and/or adverse event (AE) related to the study procedure in the previous study to the screening visit of the current study.
2. The subject has potentially received TAK-951 in a previous clinical study, or has previously completed, discontinued, or withdrawn from this study.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or is unable to provide consent (eg, incapacity or potential duress or undue influence on informed consent process).
4. The subject has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance (including medication-induced emesis) to prescription or nonprescription drugs or food, or allergic reactions to allowed rescue medication(s).
5. The subject has any condition or abnormality (including laboratory abnormalities), current or past, that, in the opinion of the investigator or medical monitor, would compromise the safety of the subject or interfere with or complicate the assessment of signs or symptoms of CVS.
6. The subject uses medical or recreational cannabis more than 3 days/week or its usage triggers nausea and/or vomiting.
7. The subject has a history of hypotension, autonomic instability, orthostatic hypotension (excluding in the context of concurrent dehydration), postural orthostatic tachycardia syndrome or a history or presence of 2 or more incidents of syncope within the last 5 years before screening.
8. The subject has a history of long corrected QT interval (QTc) syndrome, history of significant cardia arrhythmia, or a history or presence of:
   a) A family history of unexplained sudden death or channelopathy; or
   b) Brugada syndrome (ie, right bundle branch block pattern with ST-elevation in leads V1-V3); or
   c) Second-degree atrioventricular block type 2, third degree atrioventricular block, prolonged QT interval with Fridericia correction method (QTcF) interval, hypokalemia, hypomagnesemia, or conduction abnormalities; or
   d) Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome); or
   e) Any clinically significant electrocardiogram (ECG) findings or medical history including: long or short QTcF (over 450 msec or less than 360 msec), bifascicular block or QRS ≥120 msec or PR interval >210 msec at screening; subjects with QTcF ≥450 msec (up to 470 msec) taking chronic tricyclic antidepressants (>3 months) may be enrolled after consultation with the medical monitor or
   f) The subject has a documented history of sinus bradycardia (<45 beats per minute [bpm]), sinoatrial block, sinus pause ≥3 seconds, or sinus node dysfunction.
9. The subject has a history of other cardiovascular or cerebrovascular disease as assessed by the investigator including: hypertension requiring therapy or a history or presence of diseases such as cardiac valvulopathy, myocardial infarction, stroke.

10. The subject has average semirecumbent systolic blood pressure (SBP) <95 or >140 or a diastolic blood pressure (DBP) <65 mm Hg or >90 mm Hg at screening. Note: See Section 6.1 for specific cardiovascular criteria that must be met immediately before the dose for dosing eligibility.
11. The subject has a screening average heart rate (HR) <55 or >100 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. Note: See Section 6.1 for specific cardiovascular criteria that must be met immediately before the dose for dosing eligibility.
12. The subject has orthostatic hypotension defined as a decrease in systolic BP ≥20 mm Hg or a decrease in diastolic BP ≥10 mm Hg after approximately 3 minutes of standing when compared with BP from the semirecumbent position, at screening.
13. The subject has postural orthostatic tachycardia, defined as an increase of 30 bpm or HR >120 bpm after standing for approximately 3 minutes, at screening.
14. The subject is taking medications commonly associated with tachycardia, palpitations, hypotension, or QTc prolongation as potential adverse effects (eg, beta blockers, nitrates, sildenafil).
15. The subject is taking medications prescribed for the prophylactic management of CVS with possible safety or tolerability interactions with TAK-951 as determined by the investigator(s). As above, chronic (>3 months) consistent doses of tricyclic antidepressants are allowed after consultation with the medical monitor if QTcF is ≤470. The use of prochlorperazine/or promethazine as a rescue medication is explicitly prohibited until ≥30 hours (5 half-lives of TAK-951) after IP administration.
16. Subject has a history of autonomic dysfunction.
17. The subject has active neoplastic disease or history of neoplastic disease within 5 years of screening visit (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix that has been definitively treated with standard of care approaches) and has received treatment in the last 5 years.
18. The subject has a history of requiring emergency room/urgent medical treatment and intravenous fluid therapy for management of dehydration associated with clinically relevant hypotension for ≥2 CVS episodes in the last 6 months.
19. The subject has a history of other conditions associated with episodic emesis including: type 1 diabetes mellitus, type 2 diabetes mellitus, gastroparesis, gastrointestinal dysmotility, inflammatory bowel disease, eosinophilic esophagitis, rumination, severe functional dyspepsia, severe gastroesophageal reflux disease, large (>3 cm) hiatal hernia, or unrepaired intestinal malrotation.
20. The subject has taken opiate medications for more than 3 days in the last month.
21. The subject has a progressive neurological disorder or a structural disorder of the brain from birth, trauma or past infection.
22. The subject has an uncontrolled psychiatric disorder, to include history of suicide attempt, active major depressive disorder or severe panic disorder, or at the discretion of the investigator(s), for any clinically significant psychiatric history that would likely interfere with full participation in the study.
23. The subject has started a nonpharmacologic prophylactic approach (eg, acupuncture, biofeedback, chiropractic methods) within 1 month before initiation of the treatment period.
24. The subject has a history of substance abuse.
25. The subject has a positive pregnancy test or plans to become pregnant during the study period.
26. The subject is a pregnant or lactating/nursing female.
27. The subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to TAK 951 (or any other glucose-dependent insulinotropic polypeptide receptor agonist investigational products) or to any other ingredients of the investigational product.
28. The subject has a clinically unstable disease or condition.
29. The subject has any disease or condition that could compromise the function of those body systems as assessed by the investigator that could result in altered absorption, excess accumulation, or impaired metabolism or excretion

of the test medications (eg, mild, moderate or severe renal impairment [ie, estimated creatinine clearance <90 mL/min, CrCL]) and/or altered hepatic function as assessed by the investigator (eg, alanine aminotransferase >2× the upper limit of normal [ULN], total bilirubin [TB]>1.5× ULN, alkaline phosphatase >1.5× ULN).

30. The subject has known or suspected active coronavirus disease 2019 infection as assessed by the investigator.

Main Criteria for Evaluation and Analyses:

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

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

The following secondary endpoints will be assessed within 2, 4, and 8 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).
- 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 VRS score at 0, 1, 2 hours in all subjects and 4, 8 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 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).

The following endpoint will be assessed across the entirety of the study.

- Status of subject's antidrug antibody (ADA) assessment (ie, ADA-negative or ADA positive, and low or high ADA titer).

Statistical Considerations:

This is a repeated crossover design and all analysis will adjust for treatment and sequence. For summarizations on or prior to randomization tables will be summarized by sequence. For safety and efficacy summarizations after randomization, tables will be summarized by Treatment and administration of treatment (ie first and second). More complex analysis are described below and further detailed in the statistical analysis plan (SAP).

Analysis Sets

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 without any CVS episode within the first 10 weeks and were replaced will be excluded from the efficacy analysis.

The per protocol analysis set (PPS) 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 PPS will be made before the unblinding of the study. Analyses using the PPS will be provided as a sensitivity analysis.

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.

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

The immunogenicity 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.

Safety Analysis

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

inference will be made.

AEs will be coded using the Medical Dictionary for Regulatory Activities, Version 23.0 or higher and will be summarized by System Organ Class and Preferred Term by treatment groups. Absolute values and changes from baseline in clinical safety laboratory tests, vital signs, and ECG parameters will be summarized descriptively for each treatment group. Values outside normal ranges and potentially clinically significant values will be flagged and tabulated.

Efficacy Analysis

Efficacy analyses will be conducted using the FAS. Sensitivity analyses based on the PPS will be performed for selected secondary efficacy endpoints (data collected via ePRO and eObsRO devices). Nominal p-values will be presented when appropriate. All efficacy data within the first 30 minutes immediately following TAK- 951/placebo administration will be excluded from the efficacy analysis to allow for inclusion of those subjects who are dosed after the onset of the emetic phase. Clinical laboratory data will be summarized by treatment and administration using the following: n, mean, median, standard deviation, minimum and maximum observed values. Post-baseline assessments will also contain average change from the baseline values. Vital signs will include HR (bpm), respiratory rate, systolic and diastolic blood pressure which will be summarized descriptively by treatment and administration.

Secondary Efficacy Endpoints

Binary secondary efficacy endpoints (total response, absence of emesis, absence of nausea and no need for rescue medication at 2, 4, and 8 hours postdose). These endpoints will be summarized by treatment groups as observed. Treatment difference between TAK-951 and placebo will be estimated and the associated 95% CI will be constructed using normal approximation. Binary efficacy endpoints will be analyzed using a nonlinear mixed effects model (NLMEM) with repeated measures with treatment, sequence, period, 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, the associated 95% CI, and nominal p-value obtained from the nonlinear mixed effects model will be presented. Binary efficacy endpoints may also be analyzed using generalized linear mixed effects model with fixed effects of sequence, treatment and period with random effect of subject modeled with a no diagonal factor analytic (FA0(2)) covariance structure with residual covariance matrix modeled by variance component grouped by treatment. Model based estimates comparing treatments along with corresponding CI in case the NLMEM model does not fit.

Longitudinal continuous secondary endpoints (peak nausea VRS at 0, 1, 2, 4, and 8 hours postdose and change in nausea VRS at 1, 2, 4, and 8 hours postdose [on a verbal response scale]), will be analyzed using a mixed model for repeated measures (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. Point estimates, the associated 95% CIs, and nominal p-values for treatment difference between TAK-951 and placebo by timepoint will be presented.

Missing data by patient and observer may be examined at each timepoint as well as by treatment assignment.

Exploratory Efficacy Endpoints

The exploratory endpoint assessments 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 will be summarized by treatment groups. Subjects without documented events will be censored. Kaplan-Meier estimates and plots will be provided.

PK Analysis

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.

Immunogenicity Analysis

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

ADA Negative – defined as subjects who do not have a confirmed positive ADA status in any postbaseline assessment.

ADA positive – defined as subjects who have confirmed positive ADA status in any postbaseline assessment.

High ADA titer – defined as subjects who have at least 1 postbaseline ADA titer greater than a cutoff to be determined based on the actual titer data.

Low ADA titer – defined as subjects whose postbaseline ADA titer numbers are all less than or equal to a cutoff to be determined based on the actual titer data.

ADA status and titer will be listed by subjects.

For effect of ADA on efficacy, subjects may be summarized within each ADA response status (negative, positive, high and low titer).

For effect of ADA on safety, subjects' incidence of AEs by ADA response status (negative, positive, high and low titer) may be provided. Injection-site reactions (preferred term) may also be summarized by ADA status. The same analysis may be repeated based on ADA titer.

The relationship between immunogenicity status (ADA and ADA titer) and PK may be explored.

Sample Size Justification:

A total sample size of ~20 subjects is considered sufficient for evaluation of safety and tolerability of intermittent single SC doses of TAK-951 in subjects with moderate to severe CVS during the prodromal/early emetic phase at home. The study is not statistically powered to perform any hypothesis testing in the study.

1.1 Protocol Amendment 1 Summary of Changes

Protocol Amendment 1 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are:

- Minor wording, editorial, formatting and grammatical changes to improve clarity.
- Increased number of sites to accommodate revised recruitment rate estimates.
- To modify study sequences (ie, from 4 to 2 randomized sequences with the same 2-treatment repeated crossover design) to improve anticipated study retention rates to reduce impact of missing data for early discontinuation.
- To address Food and Drug Administration (FDA) comments regarding definitions of sterility and contraceptive duration.
- To remove efficacy timepoints at 12 and 24 hours from the protocol.

In this amendment, minor grammatical, editorial, formatting, style and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 1.0 STUDY SUMMARY	Planned number of sites changed from 4 to 10.	Further evaluation of the recruitment rate and site feedback led to revised estimates for the number of sites needed.
2.	Section 1.0 STUDY SUMMARY Section 1.0 STUDY SUMMARY	Changed '6 months' to 30 days' for contraception requirement postdose, added postmenopausal follicle-stimulating hormone criteria in Inclusion Criterion # 10	Modified for consistency across informed consent form (ICF) and protocol as per Food and Drug Administration (FDA) comments.
3.	Section 1.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Clarified prohibition of prochlorperazine or promethazine as a rescue medication until >30 hours (5 half-lives of TAK-951) after IP administration.	Combinatorial cardiovascular risk is anticipated to be minimal after 5 half-lives of TAK-951.
4.	Section 1.0 STUDY SUMMARY	Added to Efficacy Analysis "Clinical laboratory data will be summarized by treatment and administration using the following: n, mean, median, standard deviation, minimum and maximum observed values."	Clarification of analysis plan for clinical laboratory data.

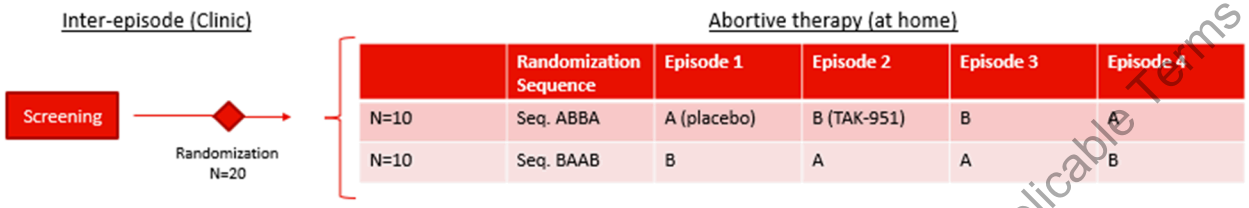
Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5.	Section 2.0 Study Schematic	Simplified study sequences from 4 to 2. Replaced Figure 2.a. with an updated figure.	Simplification of the study design to a 2-sequence, 4-period, 2-treatment repeated crossover design to reduce the drop out risk from certain sequences in original design.
6.	Section 3.0 Schedule of Study Procedures	Addition of twice monthly site calls to subject as mechanism to collect interepisode adverse events (AEs) and healthcare encounters.	Supports subject safety and enhances AE data collection. Healthcare encounters eCRF has been added to collect information relating to hospitalizations and/or outpatient clinic visits.
7.	Section 5.2 Endpoints Section 1.0 STUDY SUMMARY Section 12.0 STATISTICAL Methods	Removed 12- and 24-hour efficacy timepoints throughout.	Revised electronic clinical outcome assessments and removed the 12- and 24-hour timepoints based on recommendations of experts in cyclic vomiting syndrome (CVS).
8.	Section 6.1 Study Design	Changed last 6 lines of the fourth paragraph to "No episodes will be eligible for dosing in the study until ≥14 days after randomization. A 14 day washout begins immediately following study drug/placebo dosing. 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 or their last dosed CVS episode and subjects who withdraw may be replaced in order for approximately 20 subjects to complete the study".	Expansion of washout period between doses from 7 to 14 days to provide additional buffer between CVS episodes. Clarification of rules for subject replacement.
9.	Section 6.1 Study Design	Added to the fourth paragraph: "The randomization sequencing will not advance if the subject is not dosed for a CVS episode (eg, if the subject is scheduled to receive placebo during that episode and is not dosed, they will still be scheduled to receive placebo as per the randomization sequence for the next episode that is eligible for dosing)." "For spontaneously aborted episodes (eg, 'false' prodromes where symptoms	Clarifies scenarios in which sequence randomization should not advance.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		have resolved and the subject no longer believes that they are having an impending CVS emetic episode by the time the HCP arrives), the subject may decline dosing and the randomization sequence will not advance."	
10.	Section 9.1.1.1 Assignment of Screening and Randomization Numbers	Added "Sponsor or sponsor delegate approval is required for rescreening subjects," to the end of the first paragraph.	Addition to assure sponsor oversight of rescreening.
11.	Section 9.3.2 Chemistry	Added "Estimated Creatinine Clearance" to chemistry evaluations table.	Addition to support renal exclusion criteria [redacted].
12.	Section 9.4 PK, Immunogenicity, and DNA Samples	Added a row in the specimen table for whole blood sample for DNA.	Additional optional collection of whole blood for DNA sequencing to allow data bridging as the biomarker program moves to this preferred method of collection for improved sequencing accuracy.
13.	Section 9.5.5 Pregnancy	Removed "5 half-lives or" from first paragraph	Harmonizing language across documents (protocol and ICF) [redacted]
14.	Section 10.2.8.2 Reporting AEs	Added "All hospitalizations, including those deemed to be related to CVS but not TAK-951/placebo as well as reasons for admission (ie, intractable nausea/vomiting due to CVS, tachycardia, hypotension etc), should be reported to the sponsor however AEs related to the underlying study disease (CVS) will not be reported as AEs unless they are deemed to be treatment-related SAEs" to end of first paragraph.	Clarification.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
15.	Section 10.2.8.4 Management of Specific AEs	Removed "In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9)." from last paragraph under Abnormal LFTs.	Clarification: abnormal liver function test (LFT) results meeting a Hy's Law event (eg, alanine aminotransferase or aspartate aminotransferase >3× upper limit of normal (ULN) and total bilirubin >2× ULN for which an alternative etiology has not been identified) will be reported as part of SAE documentation rather than in LFT increase electronic case report form.

2.0 STUDY SCHEMATIC

Figure 2.a Study Schematic



	Randomization Sequence	Episode 1	Episode 2	Episode 3	Episode 4
N=10	Seq. ABBA	A (placebo)	B (TAK-951)	B	A
N=10	Seq. BAAB	B	A	A	B

3.0 SCHEDULE OF STUDY PROCEDURES

				Episodes 1 - 4																												End of treatment/ end of study visit [d]
				Scheduled Time (in hours) [b]																												
	Screening	Randomization Day ≥-14 [a]	Prodrome	Pre-dose	0	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.5	3	3.5	4	4.5	5	6	7	8	24	Wash-out Period [c]	Inter-episode	
Procedures/ Assessments																																
Informed consent	X																															
Inclusion/exclusion criteria	X																															
Medical history/demographics	X																															
Prior/concomitant medication review	X			X																												X
Medication storage/ procedure review	X																															
Physical examination [e]	X			X																												X
BMI	X																															
Remote home screening [a]	X																															
Randomization [f]		X																														
HCP contacted			X [g]																													
HCP arrives				X [h]																												
HCP departs																						X										
TAK-951/placebo administration					X [i]																											
Rescue medication self-administration [j]													X																			
Safety Assessments																																
AE monitoring [k]		X----------Continuous Monitoring----------X																														
Semirecumbent HR/BP [l]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X									X
Standing HR/BP [m]	X													X				X					X									X
12-lead ECG [n]	X																															X
Temperature [o]	X			X																		X										
Continuous single lead ECG (patch)				X----------Continuous Monitoring----------X																												
HR (patch)				X----------Continuous Monitoring----------X																												

	Screening	Randomization Day ≥-14 [a]	Prodrome	Episodes 1 - 4																					Inter-episode	End of treatment/ end of study visit [d]
				Scheduled Time (in hours)[b]																						
				Pre-dose	0	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.5	3	3.5	4	4.5	5	6	7	8	24	Wash-out Period [c]		
Interepisode telephone contact [p]																									X	
Clinical Outcome Assessments																										
ePRO [q]		X	X						X				X		X		X		X	X	X	X	X		X	
eObsRO [q]			X	X					X				X		X		X		X	X	X	X				
Post episode interview [r]																									X	
Event marker				X----------Continuous Monitoring----------X																						
[redacted]				X----------Continuous Monitoring----------X																						
Audio data recording [s]				X----------Continuous Monitoring----------X																						
Laboratory Procedures/Assessments																										
Safety laboratory collection (hematology and serum chemistry)	X																					X				
Urinalysis	X																					X				
Urine drug screen	X																									
Alcohol breath test	X																									
Hepatitis screen [t]	X																									
HIV screen	X																									
Beta-hCG (pregnancy) test [u]	X																									
Urine pregnancy test [v]				X																						
Serum FSH test [v]	X																									
Blood glucose level (finger stick)				X																						
PK Assessments																										
Plasma sample for TAK-951 PK (venipuncture)				X									X [w]									X				
Immunogenicity and Biomarker Evaluations																										
Serum sample for immunogenicity	X																									X
Buccal epithelial cell sample for DNA (optional)[y]																										X

	Screening	Randomization Day ≥-14 [a]	Prodrome	Episodes 1 - 4																					Inter-episode	End of treatment/ end of study visit [d]
				Scheduled Time (in hours)[b]																						
				Pre-dose	0	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.5	3	3.5	4	4.5	5	6	7	8	24	Wash-out Period [c]		
Blood sample for DNA (optional) [y]																										X
[redacted]				X----------Continuous Monitoring----------X																						
Other																										
Supine/semirecumbent position [z]					X---------Continuous Monitoring----------X																					
Location	Site		Subject's home																							Site

AE: adverse event; anti-HCV: antibodies to hepatitis C virus; beta-hCG: beta human chorionic gonadotropin; BMI: body mass index; BP: blood pressure; bpm: beats per minute; CVS: cyclic vomiting syndrome; ECG: electrocardiogram; eCRF: electronic case report form; eObsRO: electronic observer-reported outcomes; ePRO: electronic patient reported outcome; ET: early termination; FSH: follicle-stimulating hormone; HBsAg: hepatitis B surface antigen; HCP: healthcare professional; HR: heart rate; PK: pharmacokinetic.

[a] Home screening to assess the subject's home will take place before randomization. The home screening does not have to occur on the same day as physical screening but randomization may not occur until both physical and home screening are complete and the subject is eligible.

[b] All scheduled measurements may occur within ±5 minutes of the scheduled episode timepoints until the 4-hour timepoint, and within ±10 minutes for all subsequent episode timepoints.

[c] The 14 day washout begins immediately following study drug/placebo dosing.

[d] Visit should occur between 7 to 10 days after the last dose or when the subject is terminated from the study.

[e] Physical examination at the indicated visit will be symptom driven.

[f] Subjects will be randomized to study treatment after the screening visit is complete. No episodes will be eligible for dosing in the study until >14 days after randomization.

[g] At the initiation of the prodrome, the subject will contact a study HCP who will arrive at the subject's home as rapidly as possible.

[h] On arrival, the HCP will complete initial vital signs, initiate the remote wearable patch and event marker, and activate the audio data recorder.

[i] TAK-951/placebo administration by the HCP will occur in the specified window and no later than 1 hour after the onset of the emetic phase. Postdose monitoring will occur relative to when the dose was administered within the administration window.

[j] Should the subject experience continued, persistent, stereotypic emesis ≥2 hour postdose, rescue medication will be allowed for self-administration.

[k] Collection of AEs will commence at the time the subject signs informed consent. A Healthcare Encounters eCRF will be utilized as part of the AE collection.

[l] All BP and pulse assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The HCP can take a third measurement if there is inconsistency between assessments. The final recorded number should be the averaged and decimals should be rounded up to whole numbers based on standard rounding rules. For pre-dose HR/BP assessments, all 3 potential measurements should be obtained within 5-25 minutes of each other in total, with the final set occurring immediately before dosing.

[m] For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment.Standing assessments must not be performed if semirecumbent systolic BP is <85 mm Hg, or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision). Orthostatic BP/HR assessments may occur earlier than 2 hours postdose if supported by ongoing review of safety data as detailed in Section 6.1.

[n] 12-lead ECG will occur as shown and ad hoc per protocol during HCP monitoring period.

[o] Temperature measurements to be completed as able.

[p] Site will contact subject by phone/televisit to collect any inter-episode AEs and Healthcare encounters every 14d ±4d.

[q] Refer to TAK-951-1501 Clinical Outcome Assessment Scales and Questionnaires.

[r] Timing of interview to be determined based on subject's report of episode resolution via ePRO. There are up to 2 interviews: 1) embedded interview, which takes place after the end of 1st episode for the first 5 voluntary patients and their associated HCPs, 2) study exit interview, which takes place after study completion for up to all 20 subjects (participation is on voluntary basis).

[s] Continuous audio data recording will be initiated by the HCP upon arrival at the subject's home and will be discontinued at the HCP's departure.

[t] Hepatitis panel, including HBsAg and anti-HCV.

[u] Serum/urine pregnancy test for female subjects of childbearing potential only.

[v] Serum FSH level will be obtained for postmenopausal women. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those aged <45 years) or women who are not using hormonal contraception or hormonal replacement therapy.

[w] PK sample will be collected ±1 hour of the scheduled PK timepoint. The actual time of sample collection must be recorded.

[x] Dosed subjects only.

[y] Buccal swabs and whole blood collection for the DNA sample can be collected at any time on the day of the end-of-treatment/end-of-study visit for those subjects that consent to the optional DNA sample collection. Both buccal swabs and whole blood are to be collected from each of the consenting subjects.

[z] Subjects are required to remain supine/semirecumbent for ~2 hours following study drug administration, however the subject may be mobilized at 2 hours or earlier following study drug administration if desired and asymptomatic as defined in Section 6.1.

4.0 INTRODUCTION

4.1 Background

Cyclic vomiting syndrome (CVS) is a chronic, disabling, functional disorder of unknown etiology for which there are no approved treatments to date for adults or children. The disease course is characterized by recurrent, stereotypical episodes of primarily incapacitating nausea and vomiting lasting hours to days, interspersed with varying lengths of symptom-free intervals between emetic episodes. During the prodromal and emetic phases, many symptoms other than nausea are often experienced by patients including headache, abdominal pain and sweating.

CVS is characterized by 4 phases; the inter-episode phase when patients are at their baseline health between episodes; the prodromal phase lasting on average 55 minute (window), where the patient senses an approach of an episode and can experience a variety of symptoms including: panic, lethargy, pallor, anorexia, and nausea of varying intensity; the emetic phase characterized by repeated, unrelenting nausea, vomiting, retching, and abdominal pain lasting hours to days; and the recovery phase with resolution of nausea and vomiting and return of energy, strength and appetite. Many CVS patients occasionally require emergency services for supportive care during severe episodes and may even require hospitalization for symptom management.

On average, patients with CVS experience 6 to 12 cycles per year. CVS affects both children and adults: 1) in children, estimated prevalence is approximately 0.05% to 1.9%, with median age of onset 5 to 6 years old; 2) in adults, estimated prevalence is approximately 1% to 2%, with mean age of onset 22 to 35 years old [1,2]. Migraine, autonomic instability, and psychological conditions (such as anxiety and depression) are common comorbidities.

Diagnosis of CVS is based on the Rome IV criteria (adults and children) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition criteria (pediatric only) and must include stereotypic episodes of vomiting over the preceding 6 months with intervening periods of wellness [3,4]. Recent guidelines also discriminate between mild disease (<4 episodes/year) and moderate to severe (≥4 episodes/year) [5]. CVS is associated with greater impairment of health status and worse quality of life than other functional gastrointestinal disorders.

[redacted]

4.2 Rationale for the Proposed Study

Unmet need in moderate to severe CVS is high due to the lack of regulatory approved therapies, poor or unknown efficacy of off-label agents, and unrelenting CVS episodes that result in costly emergency room (ER) visits/hospitalizations. For prodrome or emetic phases, off-label abortive options typically administered at home include: 1) antiemetics (eg, ondansetron, aprepitant), 2) triptans for those patients with clear migraine overlay, and 3) anxiolytics (benzodiazepines). If these efforts fail and the patient requires ER management, 1) intravenous antiemetics, 2) sedatives (eg, benzodiazepines, antihistamines) if treatment failure with antiemetics, and 3) supportive care including intravenous fluids and pain control to diminish patient discomfort until the episode self-resolves are provided. While multiple classes of medications are recommended off-label by guidelines for abortive treatment, evidence of efficacy is limited to uncontrolled retrospective studies and case series. The lack of data from prospective, placebo-controlled studies and the fact that all of these treatments are used off-label due to lack of approved treatment results in a high unmet medical need for approved treatments.

For CVS prophylaxis, which is typically prescribed to patients with moderate to severe CVS, off-label prophylactic options include antihistamines, tricyclic anti-depressants, anti-epileptics, anti-psychotics, selective natural killer 1 receptor antagonists, β-blockers, vitamins and supplements. CVS prophylaxis may be avoided as the current options have significant side effects, a key issue for a chronic reoccurring condition.

[redacted]

The safety, tolerability and pharmacokinetics (PK) of single TAK-951 doses [redacted] subcutaneous (SC) was evaluated in healthy volunteers in the first-in-human (FIH) Study (TAK- 951-1001) [redacted].

TAK-951 is proposed for the treatment of conditions associated with nausea and vomiting and is currently being investigated in PONV. Based on data from the completed FIH study TAK-951-1001, nonclinical findings from studies conducted with TAK-951, [redacted] and the known mechanism of action of GIP postural hypotension is an identified risk and potential risks include heart rate (HR) increase, hypotension, hypersensitivity, injection site

reactions, immunogenicity, synergistic effect when combined with beta-blockers, and effects on lipid metabolism and bone resorption.

TAK-951 is being developed as a potential first line, fast-acting therapy to abort the impending emetic episode if taken during the prodromal phase or terminate the episode if taken in the early emetic phase, in the at-home setting. Further understanding of the cardiovascular effects [redacted] along with efficacy results from ongoing TAK-951 clinical studies will inform the appropriateness of use of this fast-acting agent in aborting CVS prodrome or emesis at home.

4.3 Benefit/Risk Profile

The main purpose of this is to evaluate the safety and tolerability of intermittent single doses of TAK-951 in the abortive treatment of subjects with CVS.

As published studies have described increased HR and decreased blood pressure (BP) [redacted] and a proposed mechanism of vasodilation (refer to investigator's brochure), it is hypothesized that TAK-951 causes vasodilation, which leads to decreased BP, tachycardia and orthostatic findings in some individuals.

Based on the safety findings from nonclinical studies conducted with TAK-951, increased HR, decreased BP, and synergistic effect when combined with beta blockers are potential risks. Safety results from the FIH study indicated a trend of increase in HR and decrease in diastolic BP observed in TAK-951 groups. No observed trend in systolic blood pressure was noted. Additionally, orthostatic changes in HR and BP were observed in some individuals in the TAK-951 group. Orthostatic hypotension is considered an identified risk. After receiving TAK-951 in Part 1 or Part 3 of Study TAK-951-1001, 5 subjects experienced orthostatic hypotension, including 1 subject with a Grade 3 event and 2 subjects with Grade 2 events. Postural dizziness was reported by 7 subjects. For peptide-based therapeutics administered SC, immunogenicity and injection site reactions and more serious hypersensitivity reactions are always possible; no events were reported in Part 1, 2 subjects reported injection site pain and 1 subject reported injection site induration in Part 3.

Safety will be assessed by monitoring for adverse events (AEs), vital signs (pulse, and both semirecumbent and standing BP [after 2 hours as tolerated]), remote continuous single-lead electrocardiogram (ECG), safety laboratory assessments (serum chemistry, hematology, urinalysis), and immunogenicity.

The following risk mitigation plan will be employed:

- Exclusion of subjects with cardiovascular conditions and cardiovascular history as specified in Section 7.2.
- Exclusion of subjects with a history of frequent dehydration due to CVS episodes requiring ER or intravenous fluid management as specified in Section 7.2.
- Exclusion of subjects who do not meet vital sign criteria immediately before each dose as specified in Section 7.2.

- Well defined stopping criteria in the study to manage the cardiovascular risk related to TAK-951 as specified in Section 6.4.4.
- Exclusion of medications with known hypotensive side effects.
- Inclusion in the investigator's brochure of detailed guidance to investigators for management of potential HR and BP effects (including understanding of the potential underlying vasodilatory actions of TAK-951).
- Crossover study design to reduce the total number of subjects needed.
- Healthcare professional (HCP), such as registered nurse or nurse practitioner, monitoring in the home setting including vital signs, placing intravenous lines and administering intravenous fluids as indicated, drawing samples for clinical laboratory assessment, and interpreting digital rhythm strips as necessary.
- HCP administration of the study drug/placebo in the supine/semirecumbent position with subsequent observation and monitoring in that position following administration to mitigate the risk of orthostatic hypotension and other cardiovascular AEs with additional continued monitoring for 8 hours postdose.

An external Data Monitoring Committee (DMC) will be used for safeguarding the interest of study participants and assessing safety while maintaining the integrity of the study. The DMC will meet on a periodic basis during the conduct of the study as well as ad hoc for any safety concerns or in case any one of the stopping criteria are met. The sponsor may pause or stop enrollment at any time. Study drug dosing may resume if no safety concern is identified.

Overall, the proposed risk mitigation plan is adequate to monitor subjects enrolled in the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Study 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.

5.1.2 Study Secondary Objective

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.

5.1.3 Study Exploratory Objectives

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.

5.2 Endpoints

5.2.1 Primary Endpoint

5.2.2 The primary endpoint is the assessment of vital signs, laboratory values, and AEs. Secondary Endpoints

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

The following endpoints will be assessed within 2, 4, and 8 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 VRS score at 0, 1, 2 hours in all subjects and 4, 8 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 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).

The following endpoint will be assessed across the entirety of the study.

- Status of subject's antidrug antibody (ADA) assessment (ie, ADA-negative or ADA-positive, and low or high ADA titer).

5.2.3 Exploratory Endpoints

All exploratory endpoints exclude the first 30 minutes 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 (ie, back to baseline status) (ePRO).
   - Abdominal pain (peak score) at 0, 1, and 2 hours in all subjects and 4, and 8 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, and 8 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) (ePRO, electronic case report form [eCRF]).
   - 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, eCRF).
   - 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 HCP 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]).
- Change [redacted] from baseline (predose) to first emesis in those subjects who receive prodromal dosing (wearable event marker).

2. Individual plasma concentrations for TAK-951.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 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, the at-home setting will be evaluated for proximity to a visiting home health provider, potential drug storage conditions will be assessed for study feasibility and safety. The home screening does not have to 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 2 groups with 10 subjects per group as outlined in Figure 2.a. In this 4 episode, 52-week 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). No episodes will be eligible for dosing in the study until ≥14 days after randomization. A 14 day washout period begins immediately following study drug/placebo dosing. 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 or their last dosed CVS episode 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 the home health provider company, 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 Study Procedures (Section 3.0), initiate the wearable patch and wrist-worn wearable device (event marker). Additionally, the HCP will activate a passive recording device for exploratory audio data collection of retching and emesis during the study period. The double-blind study drug/placebo will be administered 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. Immediately before dosing in each CVS episode, any subjects who meet any cardiovascular criteria detailed below upon vital sign assessment during the Predose time period, the planned dose will not be administered during that episode. The randomization sequencing will not advance if the subject is not dosed for a CVS episode (eg, if the subject is scheduled to receive placebo during that episode and is not dosed, they will still be scheduled to receive placebo as per the randomization sequence for the next episode that is eligible for dosing). Subjects will not be dosed during that episode if one or more of the following is found: subjects who have a SBP of ≤90 or ≥150 or a diastolic (DBP) ≤60 or ≥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 at screening but are required to meet the same dosing criteria as above. For spontaneously aborted episodes (eg, 'false' prodromes where symptoms have resolved and the subject no longer believes that they are having an impending CVS emetic episode by the time the HCP arrives), the subject may decline dosing and the randomization sequence will not advance.

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 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 will 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 will 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 will 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 (Appendix D).

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 14 days. Sparse PK sampling will occur during the times specified in Section 3.0 optional DNA samples [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. The site will contact the subject every ~2 weeks (14 days +/- 4 days) to record any treatment related AEs.

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.

6.2 Rationale for Study Design, Dose, and Endpoints

6.2.1 Rationale of Study Design

The proposed randomized double-blind, 2-sequence, 4-period repeated crossover design which evaluates safety and tolerability of TAK-951 in CVS prodrome mitigates the overall cardiovascular safety risk of the study as a whole by limiting the number of required subjects, but doubles the amount of data as compared to a typical 2-sequence, 2-period crossover study with a balanced design, assuming subjects can complete all 4 periods. This design minimizes both inter- and intra-subject variability which is unknown but assumed to be high in a heterogenous syndrome such as CVS by allowing each subject to serve as their own control. Additionally, the design will provide an initial understanding of the rates of placebo effect for CVS that are as yet unknown. Expert consultant feedback and clinical guidelines [3,4,8,9] suggest that abortive therapies for CVS episodes are generally recommended to be used as early in the prodromal phase as possible; however, they are thought to have potential efficacy at preventing or attenuating an attack up to approximately 1 hour into the emetic phase. There is significant heterogeneity across the CVS patient population both in the duration of prodromes (minutes to hours) with an average of approximately 1 hour, and in the reliability and predictability of patients' prodromes. The primary goal of the proposed study is to optimize safety by having the subject closely monitored for safety immediately following dosing with active compound or placebo; therefore, we have proposed to allow for a window of dosing from late prodrome up to 1 hour after initiation of the emetic phase to facilitate the logistics of close monitoring in a decentralized study. Finally, medical and recreational cannabis use is prevalent in the adult CVS community (>80%) [9] raising the risk of confounding with cannabinoid hyperemesis syndrome (CHS), a controversial clinical entity which is not yet clearly accepted in the field as either: 1) a subtype of CVS with a known trigger, or 2) a separate syndrome. Rome IV criteria currently define CHS as a related but separate syndrome [1]. Heavy cannabis use is typically defined in the field as daily use. Therefore, due to the prevalence of cannabis use in this patient population, those subjects who report using cannabis >3 days/week will be excluded to limit confounding with CHS.

6.2.2 Rationale for Dose

The PK and tolerability of TAK-951 single doses [redacted] in healthy volunteers was evaluated and well tolerated in the phase 1 study TAK-951-1001 [redacted]

6.2.3 Rationale for Endpoints

The PK and safety endpoints are standard for this type of study, are used widely, and are recognized as reliable, accurate, and relevant. Additional PK parameters may be calculated if deemed necessary for the interpretation of the data. The secondary and exploratory efficacy endpoints are based on patient experience data and are designed to provide insight into the optimal timing and modality for capturing key signs and symptoms of acute CVS episodes while balancing subject burden.

6.2.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the following procedures are critical:

- Timing of dose, BP (semirecumbent and standing), HR (semirecumbent and standing), and timing of PK assessments.

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

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

This is a phase 1b study of TAK-951 in humans, and the PK and safety, tolerability profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures, as outlined below, may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study subjects. As such, the following alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily exposure, may not exceed that currently outlined in Section 6.2.2:

- If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional markers.
- The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECGs, safety laboratory tests) may be modified during the study based on newly available safety, tolerability, and PK. These changes will not increase the number of study procedures for a given subject during his/her participation in the entire study.

- Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the sponsor with a protocol amendment and institutional review board (IRB)/ ethics committee approval.

6.4 Study Beginning and End/Completion

6.4.1 Definition of Beginning of the Study

The overall study begins when the first subject signs the study informed consent form.

6.4.2 Definition of End of the Study

The overall study ends when the last subject completes the last planned visit/interaction (this can be a phone contact), discontinues from the study, is lost to follow-up (ie, the investigator is unable to contact the subject) or withdraws consent.

6.4.3 Definition of Study Discontinuation

The sponsor may stop the study for any reason.

Study discontinuation because of nonsafety reasons, such as the following:

- A finding (eg, PK, efficacy) from another nonclinical or clinical study using the study treatment(s) results in the study being stopped for a non-safety related reason.
- Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this study become available and results in the study being stopped for a non-safety-related reason.
- The study is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.

Study discontinuation because of safety reasons:

- Early study termination because of unanticipated concerns of safety to the study subjects arising from clinical or nonclinical studies with the study treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

6.4.4 Criteria for Premature Termination or Suspension of the Study

6.4.4.1 Criteria for Premature Termination or Suspension of Study

Stopping rules included for the study for events suspected to be related to TAK-951:

- Two or more subjects experience a sinus tachycardia with HR >120 bpm with symptoms of palpitations or light-headedness requiring medical intervention, or

- Two or more subjects experience a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale (v5.0) Grade ≥3 hypotension (ie, requiring medical intervention), or
- Two or more subjects experience any particular event that is a NCI CTCAE Version 5.0 Grade ≥3 or,
- One subject reports a NCI CTCAE Version 5.0 Grade ≥3 vasovagal syncope (fainting or orthostatic collapse), or
- One subject reports a serious adverse event (SAE) or
- One subject experiences a NCI CTCAE Version 5.0 Grade 4 event.

If during the study any of the study stopping criteria are met, further dosing in the study will be paused and subject will be discontinued from the study. The safety data will be reviewed by the unblinded DMC. A recommendation will be made to continue, modify, temporarily suspend, or terminate the study.

6.4.4.2 Procedures for Premature Termination or Suspension of the Study

In the event that the sponsor, an IRB, or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.4.4.3 Possible Changes to the Procedures to Address Interruptions due to Pandemic Outbreak

The following is intended to give guidance about which changes to the procedures could be accepted in case any study participants or study sites are impacted by the coronavirus disease 2019 (COVID-19) pandemic outbreak. The guidance takes references from the Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards, March 2020 and the update from 11 May 2020, and the European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 3 (28/04/2020). As the COVID-19 pandemic outbreak may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case by case basis following consultation with the medical monitor, with patient safety as the priority. The study is currently designed with most procedures (excluding screening and end of study visit) occurring in the subject's home with the assistance of a HCP.

Study sites will maintain site-specific plans to maintain the health and safety study subjects, site staff and other study personnel (ie, including the home HCP) as related to the COVID-19 pandemic.

In case there are restrictions to conduct procedures as originally planned in consequence to the COVID-19 pandemic:

- Sites will employ all efforts to see subjects as described in the clinical assessments.
- In unavoidable circumstances, such as the COVID-19 pandemic, exceptions may be granted for:
  - Alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such instances will be documented in the study records.
  - These data collected with alternative methods may be handled differently in the final data analysis, with this documented in the statistical analysis plan (SAP).
- Procedures for clinical laboratory samples:
  - Allow blood draws or other diagnostic tests to be conducted at a local laboratory (or relevant clinical or office facility) authorized/certified to perform such tests routinely.
  - Allow the use of web-based back-up system on electronic devices.
  - Deviations from the protocol (eg, missing required bloodwork, visit performed outside of window) will be noted as a protocol deviation related to COVID-19.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including laboratory test results, need to be confirmed before the first dose of study drug as outlined in the Schedule of Study Procedures in Section 3.0.

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements and is eligible for the study.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written or electronic, informed consent form and any required privacy authorization before the initiation of any study procedures.
3. The subject is male or female and aged 18 to 50 years, inclusive.
4. The subject has at least a 1-year history of CVS diagnosis based on the Rome IV diagnostic criteria.
5. The subject has had at least 4 CVS episodes over 6 months before screening during the last 12 months.
6. If taking eligible medications prescribed for the prophylaxis of CVS, the subject must be receiving a stable dose for at least 3 months before screening.
7. The subject is willing and able to exclusively use the protocol rescue medications if needed.

8. The subject has a stereotypic prodrome with onset ≤4 hours before CVS emetic events.
9. The subject has a body mass index (BMI) between 18 and 32 kg/m^2, inclusive.
10. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use barrier method of contraception (eg, condom with or without spermicide) from signing of informed consent throughout the duration of the study and for 30 days after last dose OR a surgically sterile female subject, or females of nonchildbearing potential with laboratory confirmation of postmenopausal status (ie, follicle-stimulating hormone levels >40 mIU/mL) or one of childbearing potential who is sexually active with a nonsterilized male partner agrees to use a highly effective method of contraception from signing of informed consent throughout the duration of the study and for 30 days after the last dose as defined in Section 9.5.

7.2 Exclusion Criteria

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

1. The subject has participated in another interventional study within 4 weeks or 5 half-lives of the investigational study drug, whichever is longer, before the screening visit. The 4-week window will be derived from the date of the last study procedure and/or AE related to the study procedure in the previous study to the screening visit of the current study.
2. The subject has potentially received TAK-951 in a previous clinical study, or has previously completed, discontinued, or withdrawn from this study.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or is unable to provide consent (eg, incapacity or potential duress or undue influence on informed consent process).
4. The subject has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance (including medication-induced emesis) to prescription or nonprescription drugs or food, or allergic reactions to allowed rescue medication(s).
5. The subject has any condition or abnormality (including laboratory abnormalities), current or past, that, in the opinion of the investigator or medical monitor, would compromise the safety of the subject or interfere with or complicate the assessment of signs or symptoms of CVS.
6. The subject uses medical or recreational cannabis more than 3 days/week or its usage triggers nausea and/or vomiting.
7. The subject has a history of hypotension, autonomic instability, orthostatic hypotension (excluding in the context of concurrent dehydration), postural orthostatic tachycardia syndrome or a history or presence of 2 or more incidents of syncope within the last 5 years before screening.

8. The subject has a history of long corrected QT interval QTc, history of significant cardiac arrhythmia, or a history or presence of:
   a) A family history of unexplained sudden death or channelopathy; or
   b) Brugada syndrome (ie, right bundle branch block pattern with ST-elevation in leads V1-V3); or
   c) Second-degree atrioventricular block type 2, third degree atrioventricular block, prolonged QT interval with Fridericia correction method (QTcF) interval, hypokalemia, hypomagnesemia, or conduction abnormalities; or
   d) Risk factors for Torsade de Pointes (eg, heart failure, cardiomyopathy, or family history of Long QT Syndrome); or
   e) Any clinically significant ECG findings or medical history including: long or short QTcF (over 450 msec or less than 360 msec), bifascicular block or QRS ≥120 msec or PR interval >210 msec at screening; subjects with QTcF ≥450 msec (up to 470 msec) taking chronic tricyclic antidepressants (>3 months) may be enrolled after consultation with the medical monitor; or
   f) The subject has a documented history of sinus bradycardia (<45 bpm), sinoatrial block, sinus pause ≥3 seconds, or sinus node dysfunction.
9. The subject has a history of other cardiovascular or cerebrovascular disease as assessed by the investigator including: hypertension requiring therapy, or a history or presence of disease such as cardiac valvulopathy, myocardial infarction, or stroke.
10. The subject has average semirecumbent SBP <95 or >140 or a DBP <65 mm Hg or >90 mm Hg at screening. Note: See Section 6.1 for specific cardiovascular criteria that must be met immediately before the dose for dosing eligibility.
11. The subject has a screening average HR <55 or >100 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. See Section 6.1 for specific cardiovascular criteria that must be met immediately before the dose for dosing eligibility.
12. The subject has orthostatic hypotension defined as a decrease in systolic BP ≥20 mm Hg or a decrease in diastolic BP ≥10 mm Hg after approximately 3 minutes of standing when compared with BP from the semirecumbent position, at screening.
13. The subject has postural orthostatic tachycardia, defined as an increase of 30 bpm or HR >120 bpm after standing for approximately 3 minutes, at screening.
14. The subject is taking medications commonly associated with tachycardia, palpitations, or hypotension as potential adverse effects (eg, beta blockers, nitrates, sildenafil).
15. The subject is taking medications prescribed for the prophylactic management of CVS with possible safety or tolerability interactions with TAK-951 as determined by the investigator(s). As above, chronic (>3 months) consistent doses of tricyclic antidepressants are allowed after

consultation with the medical monitor if QTcF is <470. The use of prochlorperazine and/or promethazine as a rescue medication is explicitly prohibited until >30 hours (5 half-lives of TAK-951) after IP administration.

16. Subject has a history of or suspected autonomic dysfunction.
17. The subject has active neoplastic disease or history of neoplastic disease within 5 years of screening visit (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix that has been definitively treated with standard of care approaches) and has received treatment in the last 5 years.
18. The subject has a history of requiring ER/urgent medical treatment and intravenous fluid therapy for management of dehydration associated with clinically relevant hypotension for >2 CVS episodes in the last 6 months.
19. The subject has a history of other conditions associated with episodic emesis including: type 1 diabetes mellitus, type 2 diabetes mellitus, gastroparesis, gastrointestinal dysmotility, inflammatory bowel disease, eosinophilic esophagitis, rumination, severe functional dyspepsia, severe gastrointestinal reflux disease, large (>3 cm) hiatal hernia, or unrepaired intestinal malrotation.
20. The subject has taken opiate medications for more than 3 days in the last month.
21. The subject has a progressive neurological disorder or a structural disorder of the brain from birth, trauma or past infection.
22. The subject has an uncontrolled psychiatric disorder, to include history of suicide attempt, active major depressive disorder or severe panic disorder, or at the discretion of the investigator(s), for any clinically significant psychiatric history that would likely interfere with full participation in the study.
23. The subject has started a nonpharmacologic prophylactic approach (eg, acupuncture, biofeedback, chiropractic methods) within 1 month before initiation of the treatment period.
24. The subject has a history of substance abuse.
25. The subject has a positive pregnancy test or plans to become pregnant during the study period.
26. The subject is a pregnant or lactating/nursing female.
27. The subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to TAK-951 [redacted] r to any other ingredients of the investigational product.
28. The subject has a clinically unstable disease or condition.
29. The subject has any disease or condition that could compromise the function of those body systems as assessed by the investigator that could result in altered absorption, excess accumulation, or impaired metabolism or excretion of the test medications (eg, mild, moderate or severe renal impairment [ie, estimated creatinine clearance <90 ml/min, CrCL]) and/or hepatic function as assessed by the investigator (eg, alanine aminotransferase [ALT] >2× the

upper limit of normal [ULN], total bilirubin [TB] >1.5× ULN, alkaline phosphatase >1.5× ULN).

30. The subject has known or suspected active COVID-19 infection as assessed by the investigator.

7.3 Excluded Medications, Supplements, Dietary Products

Subjects must be instructed not to take any new medications without first consulting with the investigator. Intermittent triptan therapy (eg, sumatriptan) for management of acute migraine headache is allowed but subjects will not be eligible for dosing during a CVS episode if a triptan has been taken within 24 hours of a CVS prodrome onset. See Section 7.2 for other excluded medications including: medications commonly associated with tachycardia, palpitations, or hypotension as potential adverse effects (eg, beta blockers, nitrates, sildenafil),any medications prescribed for the prophylactic management of CVS with possible safety or tolerability interactions with TAK-951 as determined by the investigator(s). As above, chronic (>3 months) consistent dose of tricyclic antidepressants is allowed. The use of prochlorperazine and/or promethazine as a rescue medication is explicitly prohibited until >30 hours after IP dosing.

7.3.1 Caffeine

Caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 6 units per day (1 unit = 120 mg of caffeine).

7.3.2 Diet, Fluid and Activity

There are no specific restrictions on diet and fluids associated with this study.

7.4 Rescue Therapy

If deemed necessary to manage ongoing CVS symptoms more than 2 hours after TAK-951/placebo is given, the subject may elect to self-administer guideline-recommended CVS abortive medications as prescribed including: ondansetron 8 mg orally/sublingual OR aprepitant 125 mg orally, and/or sumatriptan 20 mg nasal spray/SC [9]. The use of prochlorperazine and/or promethazine is explicitly excluded due to associated risks of falls and/or orthostatic hypotension until >30 hours (5 half-lives of TAK-951) after IP administration. After the completion of the HCP monitoring period, the subject may self-administer sedative medications (eg. diphenhydramine, benzodiazepines) as prescribed by their CVS provider. Date, timing, dose and medication name will be recorded in the eCRF and/or ePRO.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

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

- Pretreatment event or AE. The subject has experienced a pretreatment event or AE that requires early termination because continued participation imposes an unacceptable risk to the

subject's health or the subject is unwilling to continue because of the pretreatment event or AE.

- Liver function test (LFT) abnormalities that meet the following criteria:
  - ALT or aspartate aminotransferase (AST) >3 times the ULN in conjunction with elevated total bilirubin >2 times the ULN deemed to be treatment-related.
- Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
- Lost to follow-up. The subject did not report to the HCP and at least 3 attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
- Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
- Protocolized withdrawal. The subject may be removed from the study due to no CVS episode within 10 weeks following randomization or each subsequent study episode, or the subject has 2 or more episodes that do not meet criteria for dosing.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category.

- Study termination. The sponsor, IRB, or regulatory agency terminates the study.
- Pregnancy. The subject is found to be pregnant. Note: If the subject is found to be pregnant, the subject must be withdrawn immediately.
- Any subject identified with COVID-19 infection during the study.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit.

7.7 Subject Replacement

If a subject discontinues from the study, does not have a CVS episode within 10 weeks of randomization or the most recent study episode, or is unable to receive timely dosing per protocol for ≥2 episodes, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The study site should contact the sponsor for the replacement subject's treatment assignment and allocation number.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

In this protocol, the term study medication refers to all or any of the drugs defined below. TAK-951 SC injection and matching placebo injection will be provided to the site by the sponsor.

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation, of the active drug and placebo can be found in the pharmacy manual. Study drug will be packaged to support enrollment and replacement of subjects as required.

The study site will be supplied by the sponsor with the following medication in a double-blinded manner:

8.1.1 TAK-951

TAK-951 will be supplied [redacted] in an appropriately labeled carton with a single panel label that will contain, but not be limited to, the sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, caution statement, and storage conditions. Additional reference information and administration instructions can be found in the pharmacy manual.

The study site will provide the subject with a kit that will contain the next episode's randomized blinded dose. The HCP will have materials for administration (needle and syringe, alcohol pads and sharps container). As necessary, resupply should be provided as soon as practical after the subject recovers from the prior episode (ie, to ensure that subject has study drug for the next episode).

Additional reference information and administration instructions can be found in the pharmacy manual.

8.1.2 Placebo

Matching placebo vial for TAK-951 will be provided by the sponsor.

8.1.3 Clinical Study Drug Labeling

A clinical label will be affixed to study drug containers in accordance with local regulatory requirements.

8.1.4 Clinical Study Drug Inventory and Storage

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and must remain in the original container until dispensed. The blinded study drug/placebo will be dispensed at the site and then provided to the subject and maintained at -25 degrees C to -15 degrees C with protection from light in the subject's home until use.

Refer to the pharmacy manual for detailed information and instruction about the storage and handling of study drug at investigational sites and the subject's home.

The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the study site.

8.1.5 Clinical Study Drug Blinding

This is a double-blind study: the investigator, HCP, sponsor, and subjects are blinded to treatment assignment. Randomization code/disclosure envelopes or lists will be provided per the standard operating procedures of the study site.

8.1.6 Randomization Code Creation and Storage

All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.7 Clinical Study Blind Maintenance/Unblinding Procedure

The study drug blind will be maintained through a randomization schedule held by the unblinded pharmacist or their delegate at the study site or by the sponsor. The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. If possible, the medical monitor should be contacted before the blind is broken. Unblinding will be performed per the standard operating procedures of the study site.

8.1.8 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator and investigator's designated site pharmacy must ensure that the sponsor or contract research organization supplied drug is used in accordance with the protocol and pharmacy manual and is dispensed only to subjects enrolled in the study. To document appropriate use of the sponsor supplied drugs (TAK-951 vials), the investigator pharmacy/site must maintain records of drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee. The subject will return any unused vial/supplies.

Upon receipt of sponsor-supplied drug, the designated blinded pharmacist must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, designated site pharmacist should acknowledge the receipt of the shipment by signing bottom half of the packing list. If there are any discrepancies between the packing list versus the actual product received,

Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

Proper drug accountability includes, but is not limited to:

- Monitoring expiration dates.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the drug accountability log is completed for each prepared dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

9.0 STUDY PROCEDURES

The following sections describe the study procedures to be performed and data to be collected as indicated in the schedule of study procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters into the study and before any protocol-directed procedures are performed. The requirements of informed consent are described in Appendix B.

9.1.1.1 Assignment of Screening and Randomization Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur before randomization or allocation. Each subject will be assigned only 1 screening number. Screening numbers must not be reused for different subjects. Any subject who is screened multiple times will be assigned a new screening number for each screening event. Sponsor or their delegate's approval is required for rescreening subjects.

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be reassigned to another subject. A single subject cannot be assigned more than 1 randomization number.

9.1.1.2 Study Drug Assignment

Subjects will be randomized to study treatment after the screening visit is complete and before prodrome initiation. Subjects who meet screening criteria will be assigned a randomization

number in even allocation amongst randomized sequence groups. The randomization number encodes the subject assignment to either TAK-951 or placebo, according to the randomization schedule generated before the study. Each subject will be dispensed blinded study drug, labeled with his/her unique randomization number, throughout the study.

9.1.2 Inclusion and Exclusion

Each subject will be assessed through randomization, according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History/Demography

Qualified study personnel will collect subject significant medical history (past and concurrent medical conditions), per the clinical site's standard of care and appropriate clinical judgment, and subject demographics at the screening visit.

Qualified study personnel will review subject prior and concomitant medication use at screening and immediately before dosing. Medications are defined as prescription and over-the-counter drugs, vaccines, supplements, nutraceuticals, and oral herbal preparations.

9.1.4 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

Any concomitant medication use must first be discussed with the sponsor, unless the investigator or designee considers immediate administration is necessary. The occasional use of acetaminophen (approximately <1g/day) is allowed. Explicitly excluded medications are detailed in Section 7.3.

There should be no change to these regimens during the study without discussion with the principal investigator.

9.1.5 Medication Storage/Procedure Review

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and must remain in the original container until dispensed. The subject will store the blinded study drug/placebo dispensed from the site in the study-provided research freezer within 4 hours of receipt. Each subject's study freezer will be equipped with a temperature monitoring device and temperature excursions will be alerted to the site staff. Specific information and instructions will be provided in the pharmacy manual.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

A baseline physical examination conducted at the screening visit will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; and (10) lymph nodes. Any subsequent physical examinations should assess clinically significant changes from the assessment before the screening examination. Qualified site personnel will conduct physical examinations.

9.2.2 Height and Weight

Body weight and height will be obtained with the subject's shoes off, and jacket or coat removed at the screening visit and as clinically indicated.

9.2.3 BMI

BMI equals a subject's weight in kilograms divided by height in meters squared (BMI = kg/m^2). The values should be reported to 1 decimal place by rounding. For example, a BMI of 25.63 kg/m2 would be reported as 25.6 kg/m^2.

9.2.4 Vital Signs

Subjects should rest in a semirecumbent position for at least 3 minutes before vital signs are measured. Vital signs will include HR (bpm), respiratory rate, and systolic blood pressure and diastolic blood pressure in all parts of the study. All BP and HR assessments should be made in duplicate, and the average of both assessments should be used to calculate the final result. The HCP can take a third measurement within 10 minutes if there is inconsistency between assessments, or, if at screening or before dosing, the physician believes that these are artificially high due to subject's anxiety. Vital signs will be recorded in the eCRF.

For standing BP and pulse assessment, a BP and pulse assessment will be performed after the duplicate semirecumbent assessment has been completed. The subject should stand still for approximately 3 minutes before this assessment. Standing assessments must not be performed if semirecumbent systolic BP is <85 mm Hg, or if the subject presents with signs or symptoms suggestive of postural hypotension after standing (eg, lightheadedness or dizziness, nausea, blurry vision). Immediately before TAK-951 or matching TAK-951 placebo dosing, subjects who meet any cardiovascular criteria will be excluded from dosing during that episode as follows: subjects who have a SBP of ≤90 or ≥150 or DBP ≤60 or ≥95 mm Hg, or HR ≤50 or ≥110 bpm.

Subjects are instructed and reminded to remain supine/semirecumbent for 2 hours following study drug/placebo administration, however the subject may be mobilized after 2 hours if desired if orthostatic vital signs are normal and no additional symptoms are present. As detailed in Section 6.1, earlier mobilization and orthostatic vital sign checks will be considered pending ongoing safety data review.

When vital signs are scheduled at the same time as blood draws, they will be obtained before the scheduled blood draw.

Within 30 minutes before the discontinuation of the HCP monitoring at the end of each study episode (~8 hours postdose), a final set of vital signs will be obtained between bouts of emesis (if ongoing) to determine the subject's disposition at the end of the HCP monitoring period. Preliminary data from Study TAK-951-0001 observational CVS natural history study suggest that subjects with CVS may experience significant intermittent tachycardia (≥150 bpm) during emetic episodes in the absence of TAK-951 pharmacologic effect therefore it is possible that subjects may have elevated HR due to the disease itself at close of HCP monitoring if emesis is ongoing. To maintain subject safety, vital sign criteria to guide disposition decision making are defined below.

- If predose HR, supine and standing BP criteria are met and the subject is cardiovascularly stable (asymptomatic), then the HCP will discontinue the wearable patch, audio recording device, and event marker, complete the final study assessments and depart as scheduled.
- If HR and/or BP criteria are outside the defined predose parameters (as described above in Section 9.2.4), then the investigator must be contacted to determine safe disposition of the subject and identify if a transfer of care is necessary. The medical monitor should be informed if transfer of care is deemed necessary.

Transfer of Care

- If at any time during a dosed study episode (during HCP monitoring or within 5 half-lives of TAK-951 [~30 hours]), the HCP or investigator have concern regarding the subject's safety in the home setting, the investigator should determine safe disposition of the subject and identify if transfer of care (eg, emergency medical service EMS transport to local health care facility) is necessary. The investigator may elect to use telemedicine assessment of the subject to facilitate this decision. The medical monitor should be informed as to the final decision. If present, the HCP will remain with the subject until transfer of care occurs if one is deemed necessary. Subjects who require transfer of care will be withdrawn from the study.

9.2.5 12-Lead ECG

9.2.5.1 Screening and Safety ECG

A 12-lead ECG will be collected at the time points specified in the Schedule of Study Procedures (see Section 3.0).

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

The following parameters will be recorded on the eCRF from the subject's ECG trace: HR, respiratory rate interval, QRS interval, PR interval, QT interval, and QTcF.

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

Ad hoc 12-lead ECGs will also be required, if:

- the subject's resting HR is greater than 120 bpm,
- if the subject complains of palpitations, dizziness, breathlessness, chest tightness or any other symptoms suggestive of arrhythmia for >2 minutes OR
- if the subject's resting HR is ≥140 bpm without symptoms for >2 minutes.

The ECG, BP and pulse measurements will be reviewed by the investigator, who will use clinical judgment regarding further monitoring and management.

9.2.5.2 Telemetry

Cardiac monitoring (HR and single-lead ECG) will be assessed via a wearable patch and will be performed before dosing through to approximately 8 hours postdose. The HCP, investigator and medical monitor will have access to real-time tracings from the single lead ECG to monitor subject.

9.2.5.3 [redacted] *Audio Data, Event Marker,* [redacted]

The wearable patch will provide real-time remote [redacted] for ~8 hours after application. [redacted] In addition, the HCP will activate a passive recording device for audio data collection of retching and emesis for the duration of the HCP's stay in the subject's home (~8 hours). The audio data collected will not be used to inform any treatment recommendations or decisions. The subject will don a wrist-worn event marker as soon as possible after the identification of the onset of the prodrome to capture the number of vomiting/retching events and will wear through the duration of the HCP's stay in the home (~8 hours) for exploratory data collection. [redacted]

9.2.6 Study Drug Administration

Study Drug (TAK-951) will be administered SC as shown in the Schedule of Study Procedures in Section 3.0.

9.2.7 AE Monitoring

AE monitoring begins after signing of the informed consent form. Changes in subject health status from the baseline assessment until study drug administration should be captured in the subject's medical history. These will be recorded as pretreatment AEs. Of note, during episodes, the HCP and study staff will be exclusively responsible for recording and managing identified AEs. The audio data recording is not intended to be used for AE capture and will be analyzed after study completion however any identified AEs during annotation will be noted and cross checked with HCP/eCRF documentation. A complete description of AE collections and procedures is provided in Section 10.0.

9.2.8 Efficacy/COA Measurement

COA measurements in this study consist of PRO, ObsRO, and digital markers; 1) PRO measures include CVS related symptoms/signs, HRQOL and other outcomes on patients; 2) ObsRO measures include what HCP may observe on subjects such as emetic events, patient's ability to communicate/respond, general impression, and so on; 3) Digital markers may include audio information and event marking from patients to record vomiting/retching.

As several symptoms and signs (nausea, emesis, abdominal pain, and headache) may be collected from more than 1 source, a validation analysis of all endpoints (with data collected via ePRO, eObsRO, or audio recording device) will be conducted to determine the future COA measurement strategy. The analysis will examine the correlations among each measure as well as concordance of outcomes (eg, emesis counts), to identify and determine outcome(s) reliable for the future use. The full text of the scales and questionnaires can be found in the TAK-951-1501 Clinical Outcome Assessment Scales and Questionnaires.

9.2.8.1 Assessment of Nausea

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.

9.2.8.2 Assessment of Emetic Events

Emesis is defined as vomiting (the forceful discharge of even the smallest amount of stomach contents) or retching (the same muscular movements as vomiting but without expulsion of stomach contents). The occurrence and timing of emetic events will be monitored and documented by the subject (ePRO, event monitor), HCP (eObsRO) and audio recording. The HCP documentation of frequency and timing of emetic events will serve as the primary source for this

data during the ~8 hours of HCP monitoring and the ePRO is anticipated to be the primary source for this data collection after the departure of the HCP. The correlation between ePRO versus eObsRO versus audio recorder tracked emesis events versus event marker will be assessed, in addition to the primary analysis on eObsRO versus audio recorder vs event marker. As a sensitivity analysis, ePRO (instead of eObsRO) will be tested as the primary outcome.

9.2.8.3 Assessment of Abdominal Pain

Abdominal pain (defined as subjective discomfort localized to the abdominal region) will be scored using a self-reported, 4-point VRS ”none”, ”mild”, “moderate”, or “severe” abdominal pain. The presence and severity of subject-reported abdominal pain will be recorded in the ePRO.

9.2.8.4 Assessment of Headache

Headache (defined as subjective head discomfort) will be scored using a self-reported, 4-point VRS “none”, ”mild”, “moderate”, or “severe” headache. The presence and severity of subject-reported headache will be recorded in the ePRO.

Given the exploratory nature of this study and the CVS COA measurements are in the process of development, interviews with subjects and HCPs are planned to reflect their experience and insights: 1) study embedded interviews after the 1st episode are for the first 5 subjects and their HCPs, in order to fill potential gaps in outcomes or other design aspects; 2) study exit interviews after study completion for study subjects, to learn their experience on meaningful change on treatment effect, study experience, and any gaps. Participation to interviews is all on voluntary basis.

9.3 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures as detailed in the laboratory manual. Samples will be collected at the time points/windows stipulated in the schedule of study procedures (Section 3.0).

9.3.1 Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cells)	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells) with absolute differential	

9.3.2 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)	Estimated Creatinine Clearance

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

If subjects experience ALT or AST >3 times the ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase, and international normalized ratio) should be performed 24 hours after the abnormality was noted, (either at the study site or at an appropriate remote location) and the medical monitor should be contacted.

If ALT or AST remains elevated >3 times the ULN at the 24 hour recheck, the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE.

Please refer to Section 7.5 for subject discontinuation criteria regarding abnormal liver test results and Section 10.2.8.4 for guidance on reporting abnormal liver test results.

9.3.3 Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrate

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of red blood cell/high-power field, white blood cell/high-power field, and casts.

A urine pregnancy test (beta human chorionic gonadotropin) will be obtained predose in all females of childbearing capacity.

9.3.4 Glucose

Blood glucose will be monitored using finger-stick blood samples and will also be monitored using safety laboratory testing.

9.3.5 Diagnostic Screening

Diagnostic Test
HIV
FSH [a]
Beta-hCG (pregnancy) test
Hepatitis screen (hepatitis B surface antigen and core antibody, hepatitis C virus antibody)

Beta-hCG: beta human chorionic gonadotropin; FSH: follicle stimulating hormone for post menopausal women.

Urine

The urine drug screening assessment will include the following tests:

Amphetamines	3,4-methylenedioxy-methamphetamine
Barbiturates	Methadone/metabolite
Benzodiazepines	Opiates
Buprenorphine/metabolite	Oxycodone/oxymorphone
Cannabinoids	Phencyclidine
Cocaine/metabolites	

Subjects with positive results for cannabinoids and/or *prescribed* benzodiazepines or amphetamines will not be excluded from the study based on these results.

9.4 PK, Immunogenicity, and DNA Samples

Samples for PK, ADA and DNA (both buccal epithelial cells and whole blood) samples (see table below) will be collected as specified in the Schedule of Study Procedures (Section 3.0). Please refer to the laboratory manual for information on the collection, processing, and shipment of samples to the central laboratory.

#	Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
1	Plasma sample for TAK-951 PK	Plasma	NA	Pharmacokinetic measurements	Mandatory
2	Buccal epithelial cells sample for DNA	Epithelial cells	DNA	DNA measurements	Optional
3	Whole blood sample for DNA	Whole blood	DNA	DNA measurements	Optional
4	Serum sample for immunogenicity	Serum	NA	Immunogenicity assessments	Mandatory

NA: not applicable.

9.4.1 PK Measurements

Blood samples for plasma PK analysis will be collected as specified in the Schedule of Study Procedures (Section 3.0). Blood (venipuncture) samples for PK analysis of TAK-951 will be collected into chilled blood collection tubes (vacutainer). Please refer to the laboratory manual for information on the collection, processing, and shipment of samples to the central laboratory. Plasma PK samples may also be used for future pharmacokinetic exploration including metabolite characterization and/or further CVS related research evaluations. These data will be used for internal exploratory purposes and will not be included in the clinical study report.

It is important that the date and time of administration of the study drug dose before collection of the PK sample be recorded accurately in the source documents and the eCRF. Similarly, it is important that the date and time that each blood sample is drawn is accurately recorded in the eCRF. Blood samples collected outside the exact nominal time windows will not be captured as protocol deviations as long as the date and exact time of the sample collection is noted on the source document and eCRF.

9.4.2 Immunogenicity (ADA) Measurements

Protein products have the potential to induce antidrug immune response which may affect the safety and efficacy of the compound under study. Detection and analysis of ADA formation is a helpful tool in understanding drug immunogenicity, efficacy, and safety. To understand drug immunogenicity, blood samples will be collected at screening and at the End of Study visit. Samples for ADA will be taken as described in the Schedule of Procedures (Section 3.0).

A 3-tiered ADA testing strategy will be applied to this study. A sample will initially be screened for ADA by the ADA screening assay. Any positive sample in the screening assay is considered a potential positive, which will be confirmed for true positivity by the confirmatory assay. If a sample is confirmed as an ADA true positive, ADA titer will be assessed. The extra immunogenicity samples will be stored for future potential further ADA characterization which will be dependent on the initial assessment of the effect of ADA status on the observed PK, pharmacodynamic, safety, and efficacy profile of TAK-951 in this study as well as the regulatory request if it is applied.

9.4.3 DNA Measurements

9.4.3.1 Sample for DNA

Sampling of buccal epithelial cells and whole blood for DNA analysis is optional in this study and will only be performed for subjects who provide consent to participate in this assessment. A DNA sample may be analyzed [redacted] from each consented subject in the study.

[redacted]

[redacted]

As DNA research is an evolving science, further assessments may be performed based on newly available data and samples will be stored for future analysis. [redacted].
Detailed instructions for collection, storing, handling, and shipping samples will be provided in the laboratory manual.

9.4.4 Confinement

Not applicable.

9.5 Childbearing Status and Methods of Contraception

9.5.1 Women of Childbearing Potential

A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal, unless permanently sterile.

9.5.2 Women of Nonchildbearing Potential

A female subject of nonchildbearing potential is defined as satisfying at least 1 of the following criteria:

- Postmenopausal: At least 12 months of spontaneous amenorrhea and a follicle-stimulating hormone (FSH) concentration >40 mIU/mL.
- Surgically sterile by hysterectomy and/or bilateral salpingectomy, tubal ligation, or oophorectomy with appropriate documentation of surgical procedure.
- Has no uterus as a result of a congenital condition.

9.5.2.1 Contraception for Women of Nonchildbearing Potential

No contraception is required for women of nonchildbearing potential.

9.5.3 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 5 half-lives or 30 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.5.4 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral salpingotomy or bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those aged <45 years) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are as follows:
    - Non-Hormonal Methods:
    - Intrauterine device.
    - Bilateral tubal occlusion.
    - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success.
    - Same-sex partners not utilizing assisted reproductive technology.
    - Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method.
        – Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
            - Oral.
            - Intravaginal (eg, ring).
            - Transdermal.

– Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter until she has been on contraceptive for 3 months;

- Oral.
- Injectable.
- Implantable.

2. Unacceptable methods of contraception are:
    - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
    - Spermicides only.
    - Withdrawal.
    - No method at all.
    - Use of female and male condoms together.
    - Cap/diaphragm/sponge without spermicide and without condom.
    - Sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for female subjects, and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
    a. contraceptive requirements of the study
    b. reasons for use of barrier methods (ie, condom) in males with pregnant partners
    c. assessment of subject compliance through questions such as
        i. Have you used the contraception consistently and correctly since the last visit?
        ii. Have you forgotten to use contraception since the last visit?
        iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)?
        iv. Is there a chance you could be pregnant?

5. In addition to a negative serum hCG pregnancy test at screening, female subjects of childbearing potential must also have a negative urine hCG pregnancy test before receiving any dose of study medication.

9.5.5 Pregnancy

If any subject is found to be pregnant during the study she must be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 30 days after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs following study drug administration, defined as within 30 days of the last dose of active study drug, the pregnancy must be reported immediately, using a pregnancy notification form, to the contact listed in Section 15.0.

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

If the female subject or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject or female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

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

9.6 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is withdrawn at the screening visit, the investigator should complete the eCRF. The Interdisciplinary Review Team should be contacted as a notification of screen failure. The primary reason for screen failure is recorded in the eCRF using the following categories:

- Pretreatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other.

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

9.6.1 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment into the study and randomization into the treatment phase. If the subject is found to be not eligible for randomization to treatment, the investigator should record the primary reason for failure on the applicable eCRF.

9.6.2 Monitoring Subject Treatment Compliance

The HCP will administer study drug and record in the eCRF.

9.6.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Section 3.0. Assessments should be completed at the designated visit/time point(s).

9.6.4 Screening

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.6 for procedures for documenting screening failures. The sponsor or their delegate is required to approve all re-screening requests.

Procedures to be completed at screening include:

- Informed consent.
- Inclusion/exclusion criteria.
- Demographics, medical history, and medication history.
- Concomitant medications/therapies.
- Physical examination.
- Height, weight, BMI, and vital signs (BP, HR, and respiratory rate).
- Serum pregnancy test (hCG) for females of childbearing potential.
- FSH, if applicable.
- Hepatitis B Surface Antigen (HBsAg) and hepatitis C virus.
- Screening clinical laboratory tests.
- Alcohol breath test.
- 12-lead ECG.
- Pretreatment event/AE assessment.
- Home assessment.

9.6.5 End of Treatment/End of Study Visit

There will be 1 end-of-treatment/end-of-study visit within 7-10 days after the subject's final study dose or when the subject is terminated from the study, during which the following procedures will be performed and documented:

- Concomitant medications/therapies.
- AE assessment.
- Serum sample for immunogenicity.
- Buccal epithelial cells and whole blood DNA sample (optional).

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

9.6.6 Poststudy Care

Upon completion of the study, the subject should be returned to the care of a physician and standard therapies as required.

9.7 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 3.0. Details are provided in the study laboratory manual.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment. In this study, AEs related to the underlying disease (CVS), will not be reported as AEs unless they are deemed to be treatment-related SAEs as described in 10.1.1.

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease, like those in CVS, should not be considered AEs).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.

- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, CVS, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

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

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the sponsor.
- All cases of overdose (with or without associated AEs) will be documented. Adverse event(s) associated with an overdose will be documented on AE case report forms (CRFs) according to Section 10.0.
- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

10.1.2 Special Interest AEs

AEs of special interest for TAK-951 include injection site reactions, immunogenicity, hypotension, orthostatic hypotension, and tachycardia. These AEs will be monitored by the investigator and sponsor.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to NCI CTCAE Version 5.0. AEs not listed by the NCI CTCAE will be graded as displayed in Table 10.a.

Table 10.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.

AE: adverse event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

10.2.2 Assigning Causality of AEs

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

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as

underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of AE (Frequency)

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

10.2.6 Action Taken with Study Treatment

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

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).

- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

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

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until 5 half-lives of TAK-951 have elapsed, approximately 30 hours after the last dose of investigational product. For subjects who discontinue before the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE before the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin before the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol. All hospitalizations, including those deemed to be related to CVS but not TAK951/placebo as well as reasons for admission (ie, intractable nausea/vomiting due to CVS, tachycardia, hypotension etc), should be reported to the sponsor however AEs related to the underlying study disease (CVS) will not be reported as AEs unless they are deemed to be treatment-related SAEs.

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

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

- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

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

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

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

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Appendix 15.1.1.

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

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

10.2.8.3.1 SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.8.4 Management of Specific AEs

Tachycardia

If a subject experiences sustained (≥3 minutes) HR ≥120, the wearable patch will alert the HCP to evaluate the single lead ECG tracing to determine heart rhythm. If the HCP is unable to determine rhythm based on the single lead ECG tracing, the investigator will be contacted for review and a 12-lead ECG may be obtained.

CTCAE Grade	Management
CTCAE Grade 2 sinus tachycardia (ie, Symptomatic [a]; nonurgent medical intervention indicated) with HR 120 and above at rest for at least 5 minutes with no physical exertion.	1)CTCAE Grade 2 sinus tachycardia (ie, Symptomatic a; nonurgent medical intervention indicated) with HR 120 and above at rest for at least 5 minutes with no physical exertion) If the HCP is unable to determine based on the single lead ECG tracing, the investigator will be contacted for review and a 12-lead ECG may be obtained.
Any CTCAE Grade 3 sinus tachycardia (ie, urgent medical intervention indicated) or Grade 4 (life-threatening).	2) CTCAE grade 3 and grade 4 (life-threatening): Evaluate 12-lead ECG for abnormalities and contact the investigator and call 911 for immediate transfer.

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

Suspected Hypotension

If a subject develops symptoms suggestive of hypotension or postural hypotension, BP should be assessed for evidence of hypotension, which should be managed as per local guidelines, and the investigator and medical monitor should be contacted. If clinically significant hypotension (SBP <90 or DBP<60 with symptoms) develops, the subject should be repositioned in a supine position and HR/BP rechecked within 5 minutes. If the BP remains <90/60 with symptoms then the HCP will provide immediate treatment (eg, obtaining peripheral intravenous access and administering 1 liter normal saline (0.9%) by gravity and further immediate care as necessary) and contact the investigator. The medical monitor should be informed once immediate care for subject has been provided and investigator has been contacted. The subject should be discontinued from the study.

Injection Site Reaction

If a subject develops a NCI CTCAE Grade 3 (ulceration or necrosis; severe tissue damage, operative intervention need) or 4 (life-threatening consequences; urgent intervention indicated) discontinue administration of TAK-951, contact the investigator and medical monitor and call 911 for immediate transfer.

Hypersensitivity

If anaphylaxis or other serious allergic reactions occur, TAK-951 administration will be discontinued immediately and appropriate management initiated (eg, epinephrine, and antihistamines, and further immediate care as necessary) and call 911.

Abnormal LFTs

If a subject is noted to have ALT or AST >3× ULN and total bilirubin >2× ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.3 must also be performed.

10.2.9 Safety Reporting to Investigators, IRBs or Independent Ethics Committees, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities, investigators and IRBs or independent ethics committee (IECs), as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, suspected unexpected serious adverse reactions will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 External DMC

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.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

A SAP will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, or appropriateness of the planned statistical methods.

Separate documents will also be prepared, including psychometric SAP and study plan (including discussion guide) for embedded and exit interviews.

12.1.1 Analysis Sets

12.1.1.1 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.

12.1.1.2 Per Protocol Analysis Set

The per protocol analysis set 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.

12.1.1.3 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.

12.1.1.4 PK 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.

12.1.1.5 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.

12.1.2 Analysis of Demography and Other 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 BMI) for placebo group and TAK-951 using the FAS. 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.

12.1.3 Efficacy Analysis

The efficacy analyses will be conducted using the FAS. Sensitivity analyses based on the per protocol analysis set will be performed for selected secondary efficacy endpoints (eg, data collected via ePRO and eObsRO devices). Nominal p-values will be presented when appropriate. All efficacy data within the first 30 minutes immediately following TAK-951/placebo administration will be excluded from the efficacy analysis to allow for inclusion of those subjects who are dosed after the onset of the emetic phase, and 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 study protocol, a separate psychometric analysis plan will be developed to detail the COA evaluation methods of the COA endpoints.

Secondary Efficacy Endpoints

Binary secondary efficacy endpoints to be assessed at 2, 4, and 8 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).

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 (NLMEM) with repeated measures with treatment, sequence, period, 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 (ie, 2, 4, and 8 hours postdose), the associated 95% CI and nominal p-value obtained from the nonlinear mixed effects model will be presented. Binary efficacy endpoints may also be analyzed using generalized linear mixed effects model with fixed effects of sequence, treatment and period with random effect of subject modeled with a no diagonal factor analytic (FA0(2)) covariance structure with residual covariance matrix modeled by variance component grouped by treatment. Model based estimates comparing treatments along with corresponding CI in case the NLMEM model does not fit. Details will be provided in the SAP.

Longitudinal continuous secondary endpoints include:

- Peak nausea VRS score at 0, 1, 2, 4, and 8 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.
- Change in nausea VRS score at 1, 2 hours in all subjects and 4, and 8 hours postdose as compared to predose score in subjects who have not received 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 ADA assessment (ie, ADA-negative or ADA positive, and low or high ADA titer).

The longitudinal continuous secondary endpoints will be analyzed using mixed effects model with repeated measures (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. 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, and 8 hours postdose for peak nausea VRS score, and at 1, 2, 4, and 8 hours postdose for change in nausea VRS score. Missing VRS score will not be imputed. The analysis timepoints (0, 1, 2, 4, and 8 hours postdose) will be derived based on the actual time for the nausea VRS assessment taken relative to the time of dosing within each period. Missing data by subject and HCP may be examined at each time point as well as by treatment assignment.

Exploratory Endpoints

The exploratory endpoints include:

- 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) (event marker, audio recording).
- Absence of emesis within 8 hours postdose (Yes/No) (event marker, audio recording).
- Time from dose to first emetic event (vomiting or retching), if dosed during the prodromal period (ePRO, eObsRO, event marker, audio recording).
- Total duration (min) of CVS episode, defined as time from study dose to subject-determined resolution of recovery phase (ePRO).
- Abdominal pain (peak score) at 0, 1, 2 hours in all subjects and 4, and 8 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, and 8 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.
- HRQOL PROMIS-29 (ePRO) at baseline and every 4 weeks in inter-episodic phases.
- 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) (ePRO, eCRF).
- 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, eCRF).
- Rescue medication usage per CVS episode(Yes/No) (as defined by onset of prodrome in 1 study episode to subject's definition of resolution of that episode) (ePRO, eObsRO).
- Time from dosing to use of rescue medication (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 and exit interviews with patients and nurse practitioners).

- Subject activity as a proxy for functional disability [redacted]
- Change [redacted] from baseline (predose) to first emesis in those subjects who receive prodromal dosing (wearable event marker).

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. Kaplan-Meier (KM) estimates and KM plots for appropriate endpoints will be provided.

12.1.4 Safety Analysis

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

12.1.4.1 AEs

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.

12.1.4.2 Clinical Laboratory Evaluation

Absolute values including baseline and postdose assessments and change from baseline to postdose in clinical safety laboratory tests will be summarized descriptively by treatment groups. Individual results of laboratory tests from hematology, chemistry, and urinalysis that meet Takeda's markedly abnormal criteria will be flagged and tabulated. All clinical laboratory data will be provided in the data listings.

12.1.4.3 Vital Signs

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.

12.1.4.4 ECG

ECG data will be summarized descriptively for each treatment group. Values outside normal ranges and potentially clinically significant values will be tabulated.

12.1.4.5 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.

12.1.5 PK Analysis

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.

12.1.6 Immunogenicity Analysis

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

- ADA Negative – defined as subjects who do not have a confirmed positive ADA status in any postbaseline assessment.
- ADA positive – defined as subjects who have confirmed positive ADA status in any postbaseline assessment.
- High ADA titer – defined as subjects who have at least 1 postbaseline ADA titer >X (this value may change based the actual titer data).
- Low ADA titer – defined as subjects whose postbaseline ADA titer numbers are all ≤X (this value may change based the actual titer data).

Anti-drug antibody status and titer will be listed by subjects.

For effect of ADA on efficacy, subjects may be summarized within each ADA response status (negative, positive, high and low titer).

For effect of ADA on safety, subjects' incidence of AEs by ADA response status (negative, positive, high and low titer) may be provided. Injection-site reactions (preferred term) may also be summarized by ADA status. The same analysis may be repeated based on ADA titer.

The relationship between immunogenicity status (ADA and ADA titer) and PK may be explored.

12.2 Interim Analysis and Criteria for Early Termination

An interim analysis (IA) may be conducted during the study as specified in the SAP. Data for primary and 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 choose to perform such an IA, the details would be described in the SAP and/or data access management plan before unblinding.

12.3 Determination of Sample Size

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

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

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

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected,

where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 13.1.

14.0 ETHICAL ASPECTS OF THE STUDY

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

14.1 IRB and/or IEC Approval

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

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

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent

form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

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

14.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

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

Subjects who consented and provided a DNA sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. The sponsor should be notified of consent withdrawal.

14.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 14.2).

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

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study

information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

14.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

14.4.3 Clinical Trial Results Disclosure

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

14.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

15.0 ADMINISTRATIVE AND REFERENCE INFORMATION

15.1 Administrative Information

15.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. [redacted]

15.1.2 INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

15.1.3 Study-Related Responsibilities

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

15.1.4 List of Abbreviations

ADA	antidrug antibodies
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AE	adverse event(s)
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CHS	cannabinoid hyperemesis syndrome
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRF	case report form
CVS	cyclic vomiting syndrome
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
eObsRO	electronic observer-reported outcomes
ePRO	electronic patient-reported outcomes
EMS	emergency medical service
ER	emergency room
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCP	healthcare professional
HR	heart rate
HRQOL	health-related quality of life
IA	interim analysis

ICH	International Conference on Harmonisation
IRB	institutional review board
KM	Kaplan-Meier
LFT	liver function test
MMRM	mixed effects model with repeated measures
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NLMEM`	nonlinear mixed effects model
NRS	numeric rating scale
ObsRO	observer-reported outcomes
PK	pharmacokinetic(s)
PONV	postoperative nausea and vomiting
PRO	patient-reported outcomes
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
TB	total bilirubin
ULN	upper limit of normal

16.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. Adverse event(s), medical history, and concurrent conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

16.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

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

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

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

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

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

16.2 Record Retention

The investigator agrees to keep the records stipulated in Section 16.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source

documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

17.0 REFERENCES

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2. Bhandari S, Jha P, Thakur A, Kar A, Gerdes H, Venkatesan T. Cyclic vomiting syndrome: epidemiology, diagnosis, and treatment. Clin Auton Res 2018;28(2):203-9.
3. Hayes WJ, VanGilder D, Berendse J, Lemon MD, Kappes JA. Cyclic vomiting syndrome: diagnostic approach and current management strategies. Clin Exp Gastroenterol 2018;11:77-84.
4. Li BUK, Lefevre F, Chelimsky GG, Boles RG, Nelson SP, Lewis DW, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr 2008;47(3):379-93.
5. Venkatesan T, Levinthal DJ, Tarbell SE, Jaradeh SS, Hasler WL, Issenman RM, et al. Guidelines on management of cyclic vomiting syndrome in adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association. Neurogastroenterol Motil 2019;31(Suppl 2):e13604.

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adults: the illness, the patients, and problems of management. BMC Med 2005;3(20):1741-7015-3-20.

9. Venkatesan T, Sengupta J, Lodhi A, Schroeder A, Adams K, Hogan WJ, et al. An internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome (CVS). Exp Brain Res 2014;232(8):2563-70.

[redacted]

[redacted]

APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

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

Appendix B Elements of the Subject Informed Consent

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

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

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 30 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 30 days after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

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

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

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

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

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

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

Appendix D Overview of Study Design for TAK-951-1501 Trial Embedded and Exit Interviews

Two rounds of voluntary interviews with subjects and HCPs have been planned during and after the TAK-951-1501 trial.

- The first round is the **Embedded Interview**, which will take place following the first episode with up to the first 5 volunteering subjects and their paired HCPs. The purpose of embedded interview is to detect in a timely manner any potential issues or gaps in eCOA and other design aspects of TAK-951-1501 study. The findings of embedded interviews may inform protocol amendments.
- The second round is the **Exit Interview**, which will take place following the completion of subject's main trial activities, with up to all 20 subjects and their paired HCPs. The purpose of exit interview is to identify additional issues or gaps, obtain direct and in-depth input from patients on their treatment experience (eg, how they define a "meaningful change") and from HCPs on their trial experience to inform future trial design.

Participation of both interview rounds will be on voluntary basis. All interviews will be conducted as 1:1 via telephone. There will be 4 interview types: 1) embedded interview for subjects, 2) embedded interview for HCPs, 3) exit interview for subjects, and 4) exit interview for HCPs.

Separate semi-structured interview guides will be prepared for each of the 4 interview types, as described below:

1) **Subject embedded interview guide**: will be used to understand their trial experience from randomization to the completion of the first episode, assess subject's ability to use and complete the eCOA (particularly to detect difficulties or challenges with details), and collect their feedback on individual item level for the eCOA. Up to 5 subjects will be asked about the feasibility of the initial study visit (eg, with specifics about their recording of symptoms and other outcome changes during the first episode, their experience with the HCP's first at-home visit, their use of eCOA device and other monitoring devices).
2) **HCP embedded interview guide**: will be used to conduct interviews with the paired HCPs for the embedded subject interviewees. The discussion will cover the topics such as: their overall experience of the first home visit, feedback on study procedure and steps, and feedback on the use of eCOA (ie, observing patient use of ePRO, and self-use of eObsRO).
3) **Subject exit interview guide**: will contain questions about the subject's overall experience with the study process, interpretation on each eCOA item and their perception of "meaningful change" from treatment, experience of HCP visits, ease or difficulty with trial-involved devices, and other feedback on the clinical trial as a whole.
4) **HCP exit interview guide**: in addition to topics asked at the embedded interview, the exit one will reflect more questions about the HCP's overall experience with the study process, at-home visits, ease or difficulty with completion of study related data entries or forms, as well as overall suggestions about conducting interventional study with CVS patients.

A qualitative analysis plan (QAP) will be prepared to specify how the interview data will be handled and analyzed prior to initiation of the interviews.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	22-Nov-2021 18:47 UTC
	Biostatistics Approval	22-Nov-2021 19:26 UTC
	Clinical Pharmacology Approval	22-Nov-2021 20:31 UTC
	Pharmacovigilance Approval	22-Nov-2021 20:55 UTC