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STATISTICAL ANALYSIS PLAN

Protocol ID: AMDC-010-201

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF STACCATO® GRANISETRON (AZ-010) FOR THE ACUTE TREATMENT OF MODERATE TO SEVERE CYCLIC VOMITING SYNDROME

March 3, 2022

ALEXZA PHARMACEUTICALS, INC.

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1 AMENDMENT HISTORY

Not applicable

2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic-Chemical
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CI	Confidence interval
Cl	Chloride
COVID	Coronavirus Disease 2019
CRF	Case report form
CS	Clinically significant
CSR	Clinical study report
CVS	Cyclic Vomiting Syndrome
ECG	Electrocardiography
ePD	Electronic Patient Diary
GI	Gastrointestinal
GGT	Gamma-glutamyl transferase
HbsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
hr	Hour
HR	Heart rate
IAS	Intensity of Attack Scale
LDH	Lactic dehydrogenase
LS	Least-squares
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
MMRM	Mixed model for repeated measures
N	Sample size
Na	Sodium
NCS	Not clinically significant
P	Inorganic phosphate
PES	Prior Episode Questionnaire
QTcF	Fridericia's QT correction
RBC	Red blood cell count
RINVR	Rhodes Index of Nausea, Vomiting, and Retching
RR	Respiratory rate
SAP	Statistical analysis plan

Abbreviation	Term
SAS	Statistical Analysis Software
SD	Standard deviation
SEM	Standard error of the mean
T	Temperature
TEAE	Treatment-emergent AEs
TFLs	Tables, Figures, and Listings
VAS	Visual Analog Scale
WBC	White blood cell count
WHO-DD	World Health Organization-Drug Dictionary

3 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analysis for the study entitled “A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Staccato® Granisetron (AZ- 010) for the Acute Treatment of Moderate to Severe Cyclic Vomiting Syndrome” (Amendment 2 dated 28 APR 2021). Mock shells will be produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to the SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the clinical study report (CSR).

4 STUDY OBJECTIVES

The primary objectives for this study are to:

- Assess the efficacy of AZ-010 as an acute treatment for moderate to severe cyclic vomiting syndrome (CVS) in adult patients
- Assess the safety of AZ-010 in adult patients with moderate to severe CVS.

5 STUDY DESIGN

5.1 DURATION OF STUDY

The total period of the study will be up to approximately 15 weeks, including up to 2 weeks for Screening, 12 weeks for the home treatment period, and a post-dose visit 3-5 days following the last dose of the home treatment period.

5.2 NUMBER OF PARTICIPANTS

Approximately 150 participants are planned to be randomized at approximately 15 study centers.

5.3 DESIGN

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, efficacy and safety study of adult outpatients diagnosed with CVS and experiencing recurring episodes of stereotypical vomiting. Participants meeting all inclusion criteria and none of the exclusion criteria will be randomized to treatment with either 1 mg AZ-010, 3 mg AZ-010, or placebo in a 1:1:1 ratio (active:active:placebo). Each randomized participant will receive training in the use of the Staccato device and detailed instructions for the use of the ePD in the clinic as well as undergo a pre-test self-administration of their randomized study medication. Each participant will be monitored during a 2 hr. observation period and have 12-lead ECG (triplicate) assessments at pre-dose and 2, 30, 60, 90, and 120 minutes post dose. If there are no clinically-significant observations or abnormalities on the ECG, including QT prolongation, the participant will be provided with their Patient Kit that contains the remaining 5 unused Staccato devices in addition to the 1 Staccato device that they

used in the clinic. Up to 5 administrations of study medication will be allowed in an At Home environment. CVS patients between 18 and 60 years of age who have experienced at least 3 episodes of recurrent vomiting in the last 12 months and 2 episodes in the last 6 months (with stereotypical episodes of acute onset vomiting lasting <1 week and absence of vomiting between episodes) are eligible for participation. Approximately 50 participants will be randomized to each of 3 treatment groups: 1 mg AZ-010, 3 mg AZ-010, or matching Staccato Placebo (Staccato device without drug coating). Randomization will be stratified by duration of the participant's typical CVS episode into one of the following two categories: 1) Typical episode of CVS lasts 24 hrs. or less from the first vomiting/retching event; 2) Typical episode of CVS lasts greater than 24 hrs. from the first vomiting/retching event.

There will be 3 Research Clinic visits and a home treatment period, as indicated in the Study Schema (5.4).

Participants will be screened at the Research Clinic to determine if they are eligible for study participation no more than 14 days prior to Visit 2. After the study is explained to the participant and the participant has signed an informed consent form (ICF), the investigator will establish the participant's eligibility according to the inclusion and exclusion criteria via the following assessments: Medical history (with particular reference to history of vomiting symptoms, CVS diagnosis, typical duration of CVS episode (hrs. vs days), average number of vomiting/retching events in typical CVS episode, frequency of CVS episodes per year, any triggers for CVS episode, other GI conditions that may cause similar symptoms, treatment history, and current medications); full physical examination (including height, weight); vital signs (heart rate, blood pressure while sitting, respiratory rate, temperature); 12-lead electrocardiogram (ECG); blood draw and urine sample for routine clinical labs (chemistry, hematology, urinalysis); and serum pregnancy test (in female participants of child-bearing potential). In light of the COVID-19 pandemic, participants will also be screened for COVID-19 infection and appropriate social distancing and contact procedures should be taken to ensure participant safety when in the clinic.

Participants who continue to be eligible for the study will be asked to return to the Research Clinic for Visit 2. Participants meeting all inclusion criteria and none of the exclusion criteria will be randomized to treatment with either 1mg AZ-010, 3 mg AZ-010, or placebo in a 1:1:1 ratio (active:active:placebo). Each randomized participant will be provided with a Patient Kit that contains 6 Staccato devices, other study materials, and an electronic Patient Diary (ePD) to be used for at-home treatment. They will also receive training in the use of the Staccato device and detailed instructions for the use of the ePD in the clinic as well as undergo a pre-test self-administration of their randomized study medication. Each participant will be monitored during a 2 hr. observation period and have 12-lead ECG (triplicate) assessments at pre-dose and 2, 30, 60, 90, and 120 minutes post dose. If there are no clinically-significant observations or abnormalities on the ECG, including QT prolongation, the participant will continue in the study.

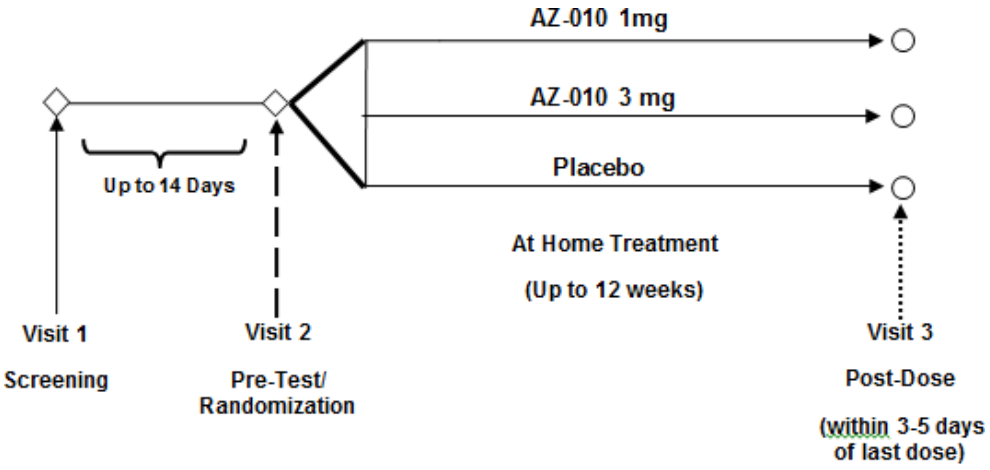
Randomized participants without clinical observations in the 2-hour observation period will be asked to treat a subsequent CVS episode (with single daily dosing up to 5 consecutive days) within 12 weeks after the randomization date. Enrolled participants will self-administer the study medication when they know their CVS episode is imminent or as soon as possible after a CVS-related vomiting episode has begun. Participants will interact with their ePD prior to initiation of treatment (if possible) and to capture the study data. The ePD will be used to record the date and time of study medication administration, the number of vomiting and retching events, and the participant reported outcome measures (including the intensity and duration of the CVS episode, severity of abdominal pain, nausea, and anxiety/panic, and characteristics of the nausea, vomiting and retching over defined time periods) (section 5.8). Participants will also record the number of vomiting and retching events in the 24 hours after dosing on a paper questionnaire.

Participants will be instructed to contact the Research Clinic at the earliest possible time after initiation of dosing and at any time should they require rescue medication, medical assistance or experience an intolerable AE at home during the treatment period. Participants will record rescue medications taken after administration of study medication in their ePD and on a paper concomitant medications form. Rescue medication may include any agent(s) from the list described in Section 9.8 of the protocol. Participants are encouraged to avoid rescue medication for the first 2 hrs. following treatment with the study medication.

Participants will be required to return to the Research Clinic (Visit 3) within 3-5 days from the last study medication administration for final in-clinic assessments, to return the Patient Kit containing the used and unused study medication, ePD, and any other unused supplies. Conversely, participants will be asked to return to the Research Clinic after 12 weeks with their unused Patient Kit if they did not treat a CVS episode within this time period.

Visit 3 will include the following assessments: Vital signs; full physical examination; assessment for treatment emergent adverse events; 12- lead ECG, concomitant medications (including rescue medication taken), and clinical labs.

5.4 STUDY SCHEMA



5.5 SCHEDULE OF EVENTS

Table 1 presents the schedule of study events.

Table 1: Schedule of Events

Event	Screening	Randomization[1]	Home Treatment Period[2] (Up to 12 Weeks Post Randomization)						Follow-Up /Termination
	Visit 1 (Up to Day -14)	Visit 2 (Day 1)	*Schedule of Assessments for each Dosing Day (Up to 5 days)*						Visit 3
			Pre-0	0	2 h post dose	6 h post dose	12 h post dose	24 h post dose	
Informed consent	X								
Eligibility assessment	X	X							
Demographics	X								
Medical history	X	X							
Urine Drug and alcohol breath screen	X								
Complete Physical Examination	X	X[3]							
Brief Physical Exam[4]		X							X
Height	X								
Weight	X	X							X
Pregnancy test[5]	X								X
Clinical laboratory testing[6]	X								X
Serology (HIV, HBV, HCV)	X								
COVID -19 test	X	X							
12-lead electrocardiogram	X	X[7]							X
Vital signs	X	X							X
Device Training		X							
ePD Instructions		X							
Randomization and assign Patient Kit		X							
Study Medication Administration[8]		X		X					
Patient activates ePD and study clock				X					
Patient records number of discrete vomiting/retching events (ePD)				X--------- X					
VAS Assessments (ePD)[9]					X	X	X	X	
RINVR Assessment (ePD)						X	X	X	
Intensity of Attack Scale (ePD)					X	X	X	X	

Event	Screening	Randomization[1]	Home Treatment Period[2] (Up to 12 Weeks Post Randomization)						Follow-Up /Termination
	Visit 1 (Up to Day -14)	Visit 2 (Day 1)	*Schedule of Assessments for each Dosing Day (Up to 5 days)*						Visit 3
			Pre-0	0	2 h post dose	6 h post dose	12 h post dose	24 h post dose	
Prior Episode Questionnaire ePD								X	
24 Hour Vomiting and Retching Questionnaire				X----------X					
Reconciliation of Patient Kit									X
Adverse events		X		X----------X					X
Rescue Med or HCP Visit				X----------X					
Concomitant medications	X	X	X----------X						X

HBV = hepatitis B virus; HCV = hepatitis C virus

[1] Randomization/Day 1 may occur any time after eligibility has been confirmed at Screening. The Home Treatment Period cannot begin until the triplicate ECG and adverse event assessments are evaluated from Visit 2.

[2] Participants will be asked to enter responses into the ePD daily during the Home Treatment Period to ensure the device is charged and working.

[3] Conducted upon return to clinic and prior to pre-test Study Medication administration only

[4] Brief Physical exam will be symptom directed prior to participant discharge from the clinic

[5] Serum pregnancy test only for females of childbearing potential

[6] Includes hematology, serum chemistry, and urinalysis performed by the central lab.

[7] ECG in triplicate at pre-dose and 2, 30, 60, 90, and 120 min post dosing with Study Medication

[8] Study medication should be administered as closely as possible to start of vomiting; once per day up to 5 consecutive daily doses can be administered as long as the participant is still experiencing the same CVS episode

[9] Includes separate scales for abdominal pain, nausea, and anxiety/panic

5.6 TREATMENT

Participants will be allocated to each treatment group according to the randomization scheme.

5.7 RANDOMIZATION

Participants will be randomized in a 1:1:1 ratio to 1 mg AZ-010, 3 mg AZ-010, or matching Staccato Placebo (Staccato device without drug coating). Randomization will be stratified by duration of the participant's typical CVS episode into one of the following two categories:

1. Typical episode of CVS lasts 24 hrs. or less from the first vomiting/retching event
2. Typical episode of CVS lasts greater than 24 hrs. from the first vomiting/retching event.

The randomization schedule will be generated prior to study start. All study participants, Investigators, and site study staff will be blinded to study medication assignment. Devices and packaging of AZ-010 and placebo are identical in appearance.

5.8 EFFICACY

5.8.1 *EFFICACY ASSESSMENTS*

5.8.1.1 NUMBER OF VOMITING AND RETCHING EVENTS IN THE FIRST 2 HOURS AFTER TREATMENT

The primary endpoint in the study is the number of vomiting and retching events in the first 2 hours following treatment based on patient-reported data entered into the ePD. Participants will record the number of vomiting and retching events that they experience within the first 30, 60, 90, and 120 minutes on the ePD. Each of these entries in the ePD are cumulative from the time of treatment, so the primary endpoint is the assessment at 120 minutes.

5.8.1.2 24 HOUR VOMITING AND RETCHING QUESTIONNAIRE

The 24 hour vomiting and retching questionnaire is a paper questionnaire on which participants will record the date of dosing with study medication and the total number vomiting and retching events that occurred within the first 24 hours after dosing. A vomiting or retching event is defined as one or more continuous episodes of vomiting (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents). If there is a break of at least 1 minute between vomiting and retching events, those should be considered two different events.

5.8.1.3 VISUAL ANALOG SCALE (VAS)

The visual analog scale is a scale of continuous measure initially developed for pain that has been used in a variety of clinical settings where the endpoint of interest is based on a subjective perception. The visual analog scale is a distinct 100-millimeter line anchored on the left end (0) at no degree of impairment and on the right end (100) at full degree of impairment, where indication of the degree of impairment perceived at the time of assessment is captured by marking the appropriate position on the line

between the anchor points. The measured distance of the mark from the left anchor is recorded in millimeters and this scale is adapted for the ePD.

There are 3 different VAS scales assessed in the study. In each case the participant is asked to rate the appropriate variable in relation to their last vomiting/retching episode:

- The assessment of abdominal pain whereby 0 = no pain and 100 = worst possible pain;
- The assessment of nausea whereby 0 = no nausea and 100 = worst possible nausea;
- The assessment of anxiety/panic whereby 0 = no anxiety/panic and 100 = worst possible anxiety/panic.

5.8.1.4 RHODES INDEX OF NAUSEA, VOMITING, AND RETCHING (RINVR)

The RINVR is designed to assess the degree of nausea distress and vomiting distress in patients. It is composed of 8 questions and each question has 5 choices (see protocol Appendix, Section 17.4). Questions 1, 4, 6, 7, and 8 deal with symptom occurrence and Questions 2, 3, 5 deal with degree of discomfort of the individual symptoms. Individual questions can be tracked over time, or a composite score can be formed by adding the total of the symptom occurrence and degree of discomfort questions together. This scale is adapted for the ePD and participants are prompted to answer the questions according to the Schedule of Events.

5.8.1.5 INTENSITY OF ATTACK SCALE

The Intensity of Attack scale is designed to assess the severity of the last vomiting/retching episode at the time of assessment. Severity ranges from Mild to Excruciating on a 4 point scale. This scale is administered on the ePD and participants are prompted to answer the questions according to the Schedule of Events.

5.8.1.6 PRIOR EPISODE QUESTIONNAIRE

The Prior Episode Questionnaire is designed to compare the overall intensity and duration of the current CVS episode with CVS episodes that the participant has typically experienced in the past. For both Intensity and Duration, the participant responds whether the current episode overall was Less than, the Same as, or Greater than their typical previous CVS episodes. The questions are prompted approximately 24 hours after each dose of study medication is administered.

5.8.2 *PRIMARY ENDPOINT*

Number of vomiting/retching episodes within two hours following initial treatment, during the Home Treatment Period.

5.8.3 *SECONDARY ENDPOINTS*

All secondary endpoints will be evaluated based on the first vomiting/retching episode.

- The percentage of participants with no vomiting or retching events and no anti-emetic benzodiazepine, or triptan rescue medication use in the first 24 hours following treatment. This endpoint will use incorporate data as captured in the 24 hour vomiting and retching questionnaire and the ePD.
- The intensity of the vomiting/retching attack (Intensity of Attack Scale) at 2, 6, 12, and 24 hours following treatment.
- The Rhodes Index of nausea, vomiting, and retching (RINVR) at 6, 12, and 24 hours following treatment.
- The assessment of abdominal pain at 2, 6, 12, and 24 hours following treatment (VAS 1-100; 0 = no pain and 100 = worst possible pain)
- The assessment of nausea at 2, 6, 12, and 24 hours following treatment (VAS 1-100; 0 = no nausea and 100 = worst possible nausea)
- The assessment of anxiety/panic at 2, 6, 12, and 24 hours following treatment (VAS 1-100; 0 = no anxiety/panic and 100 = worst possible anxiety/panic)
- The duration of the CVS episode at 24 hours in relation to their typical CVS episodes (Prior Episode Questionnaire)
- The intensity of the CVS episode at 24 hours in relation to their typical CVS episodes (Prior Episode Questionnaire)
- Use of rescue medication within the 24 hours following treatment with the study medication
- Visit to urgent care, emergency department, or physician's office for care related to the treated episode of CVS within the 24 hours following treatment with the study medication

5.9 SAFETY

Safety and tolerability of AZ-010 will be assessed by evaluating adverse events, vital signs, clinical laboratories, ECG results, as well as physical examinations.

5.9.1 *ADVERSE EVENTS*

An adverse event is any untoward medical occurrence that may appear or worsen in a participant during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the participant's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an adverse event.

All participants will be monitored for adverse events during the study. Assessments may include monitoring of the following parameters: the participant's clinical symptoms, laboratory, physical examination findings, or findings from other tests and/or procedures.

5.9.2 *LABORATORY ASSESSMENTS*

The following laboratory parameters will be collected at timepoints specified in the Schedule of Events.

HEMATOLOGY	CLINICAL CHEMISTRY	URINALYSIS
Haemoglobin [including Mean Corpuscular volume (MCV); Mean corpuscular haemoglobin (MCH); Mean corpuscular haemoglobin concentration (MCHC)]; haematocrit; red cell count (RBC); total white cell count (WBC) and Differential blood count, including: basophils, eosinophils, neutrophils, lymphocytes, and monocytes; Platelet count	Alanine aminotransaminase (ALT; SGPT); Albumin (ALB); Alkaline phosphatase (ALK-P) Aspartate aminotransaminase (AST; SGOT); Total bilirubin Conjugated bilirubin; Blood urea nitrogen (BUN) Calcium (Ca); Chloride (Cl) Total cholesterol Creatinine; Gamma-glutamyl transferase (GGT) Lactic dehydrogenase (LDH); Total protein; Inorganic phosphate (P) Potassium (K); Sodium (Na); Uric Acid	Bilirubin, Glucose, Ketones, Nitrates, Occult, Blood Protein; Specific gravity, Urobilinogen, pH; Leukocytes; Microscopic urine analysis if dipstick is positive AND a physician classifies it as clinically significant
DRUG SCREEN	**SEROLOGY (SCREENING ONLY)**	
Amphetamines (Urine); Barbiturates (Urine); Cocaine metabolites (Urine); Opiates (Urine); Benzodiazepines (Urine); Ethyl alcohol (Breath)	Human immunodeficiency virus antibody (HIV1+2-Ab) and antigen; Hepatitis B surface; antigen (HBsAg); Hepatitis C virus antibody (HCV- Ab)	
PREGNANCY		
Serum Pregnancy testing		

The approximate total blood volume drawn in the trial is shown below.

Sample	# Samples Taken		Sample Volume (mL)		Blood Volume
Hematology	2	X	4 mL	=	8mL
Serology	1		5 mL		5 mL
Serum Pregnancy	2		5 mL		10 mL
Chemistry	2		8.5 mL		17 mL
Total					**40 mL**

5.9.3 *VITAL SIGNS*

Vital signs will include blood pressure, pulse rate, pulse oximetry, respiratory rate, and temperature.

5.9.4 *ELECTROCARDIOGRAM*

Twelve-lead electrocardiograms will be performed after the participant has rested in a supine or semi-supine position for at least 5 minutes. Individual parameters including heart rate, PR, QT, QTcF, QRS, and RR intervals will be collected. Repeat electrocardiograms (if deemed necessary) should be performed at least 5 minutes apart. ECGs performed on Day 1 for pre-test assessment will be collected in triplicate for the pre-dose and post-dose collection times.

5.9.5 *PHYSICAL EXAMINATION*

A complete physical examination will include an examination of all major organ systems to include, but not be limited to, chest auscultation, abdominal auscultation and palpation, head, eyes, ears, nose and throat, and will exclude urinary and reproductive systems. A brief physical examination will be symptom directed.

5.10 COVID TESTING AND IMPACT

COVID testing, including date and time of test, will be administered per participant, with results reported as positive or negative.

Information regarding the impact of COVID on visits, assessments, or participant participation will also be collected.

6 STATISTICAL ANALYSES

6.1 GENERAL CONSIDERATIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.4 or higher. No imputation will be performed for missing data unless stated otherwise.
Data will be summarized by dosing group (1 mg AZ-010, 3 mg AZ-010, placebo). All data for analysis will be listed by participant.

The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and standard deviation.

Continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). For categorical variables, frequencies and percentages will be presented by treatment. Baseline is defined as the last observation prior to initiation of Study Medication.

Listings for CSR Appendix 16.2 will include all the participant data points being collected or derived for analyses. Data listings will be provided for all participants up to the point of study completion or withdrawal.

All statistical tests will be 2-sided with a significance value of 0.05. Participants will generally be summarized by actual treatment received.

If the 12-week treatment period has expired and participants have not yet treated a CVS episode, they will be excluded from efficacy analyses since they did not receive any study medication specifically in anticipation of a CVS episode.

6.2 SAMPLE SIZE DETERMINATION

This is a proof-of-concept study. There are no studies in the literature to provide reliable estimates of active treatment or placebo response rates using vomiting/retching events, or the estimate of variances around these measures, in participants with CVS being treated acutely with an abortive therapy. Consequently, sample size was not based on power calculations.

Approximately 150 participants will be randomized to 1 of 3 treatment groups. An N of 50 per group should be sufficient to describe and compare across the efficacy parameters.

6.3 STUDY DATA

The study data to be analyzed include all clinical data captured by the case report form (eCRF) or otherwise centrally, including safety lab data and ECGs. The database will be locked for the final analyses.

6.4 ANALYSIS SETS

The following analysis populations are defined.

- Efficacy Population - All participants who receive study medication and treated at least 1 episode of vomiting/retching due to their CVS, analyzed according to randomized treatment
- Safety Population - All participants who receive study drug
- Per Protocol (PP) Population – A PP population (subset of the Efficacy Population) may be decided upon which will exclude participants with important protocol deviations thought to potentially impact conclusions, if a sufficient number of participants with such deviations exist. If so, this population will be defined prior to breaking the blind.

6.5 TREATMENT GROUPS

The analyses will be conducted by treatment group:

- 1 mg AZ-010
- 3 mg AZ-010
- matching Staccato Placebo (Staccato device without drug coating)

6.6 STATISTICAL HYPOTHESIS TESTS

H_0: There will be no difference between AZ-010 (1 mg or 3 mg) and placebo in the mean number of vomiting/retching events in the 2 hours following treatment.

H_1: Treatment with AZ-010 (1 mg or 3 mg) will result in a statistically significant different mean number of vomiting/retching events versus placebo in the 2 hours following treatment.

6.7 MULTIPLICITY ADJUSTMENT

No adjustments will be made for multiple comparisons for this proof-of-concept study.

6.8 DEFINITION OF SUBGROUPS

No subgroup analyses are planned.

6.9 ENDPOINTS AND ESTIMANDS

6.9.1 *PRIMARY ENDPOINT AND ESTIMAND*

The mean number of vomiting/retching events in the 2 hours following treatment among those treated for a CVS episode (imminent or otherwise).

6.9.1.1 TARGET POPULATION

The target populations are given by the Efficacy Population which include all participants treated during the Home Treatment Period for a CVS episode (imminent or otherwise). If a PP Population is defined, the primary analysis will be repeated for the PP Population.

6.9.1.2 PRIMARY ENDPOINT

Number of vomiting/retching episodes within two hours following initial treatment, during the Home Treatment Period as assessed at the designated planned two-hour timepoint.

6.9.1.3 HANDLING OF INTERCURRENT EVENTS

1. Clinically significant ECG abnormality during the pre-test self-administration which preclude further participation - Principal Stratum Strategy:

    - Participants who are excluded from further participation are not included in efficacy analyses, with the population for anticipated use consistent with this exclusion. An underlying assumption is that potential treatment benefit is independent of the likelihood of exclusion for this reason.

2. Participant experiences a CVS episode (imminent or otherwise) requiring treatment during the home treatment period - Principal Stratum Strategy:

    - The principal stratum of interest is restricted to those participants experiencing at least one episode of CVS (imminent or otherwise) requiring treatment. An underlying assumption is that likelihood of experiencing at least one episode during the Home Treatment Period and severity of CVS

episodes is independent of randomized treatment assignment (and subsequent qualification for the Home Treatment Period).

3. Use of rescue medication prior to 2 hours - Treatment Policy Strategy:

   - Participants are encouraged not to use rescue prior to 2 hours, however vomiting retching episodes prior to 2 hours will be counted, irrespective of the use of rescue.

6.9.1.4 POPULATION-LEVEL SUMMARY

Mean number of vomiting retching events in the first 2 hours following the initial treatment (during the Home Treatment Period) from an analysis of variance model, with treatment group and randomization strata in the model.

6.9.1.5 MISSING DATA

The necessity and approach to handling missing data for the primary endpoint is dependent upon the extent of missing data and potential reasons for missingness as well as imbalance which may be observed with respect to missing data across treatment groups. A such, post-hoc exploratory analyses may be conducted for this proof-of-concept study to address missing data, including the use of non-missing data from CVS episodes after the first episode to assess treatment benefit.

6.9.2 *SECONDARY ENDPOINTS AND ESTIMANDS*

Secondary endpoints and associated estimands target the Efficacy Population and PP Population (if defined) and handle intercurrent events 1 and 2 as for the primary estimand and intercurrent event number 3 as for primary (except as noted). Secondary endpoints are described in section 5.8, and population-level summaries are as noted below.

6.9.2.1 POPULATION-LEVEL SUMMARY

The population-level summary for secondary endpoints are defined as follows:

- The intensity of the vomiting/retching attack (Intensity of Attack Scale [IAS]) at 2, 6, 12, and 24 hours following treatment. Participants rate the intensity of their last vomiting/retching episode on a scale of 1 (mild) to 4 (excruciating).
- The Rhodes Index of nausea, vomiting, and retching (RINVR) total score at 6, 12, and 24 hours following treatment.
- The assessment of abdominal pain at 2, 6, 12, and 24 hours following treatment (visual analog scale [VAS] 1-100; 0 = no pain and 100 = worst possible pain).
- The assessment of nausea at 2, 6, 12, and 24 hours following treatment (VAS 1-100; 0 = no nausea and 100 = worst possible nausea).
- The assessment of anxiety/panic at 2, 6, 12, and 24 hours following treatment (VAS 1-100; 0 = no anxiety/panic and 100 = worst possible anxiety/panic).
- The duration of the CVS episode at 24 hours in relation to their typical CVS episodes (Prior Episode Questionnaire [PES]), on a scale where 1=shorter, 2=same duration, and 3=longer.

- The intensity of the CVS episode at 24 hours in relation to their typical CVS episodes (Prior Episode Questionnaire), on a scale where 1=less intense, 2=same intensity, and 3=more intense.
- The proportion of participants requiring rescue medication (anti-emetics, benzodiazapines and triptans) within the 24 hours following treatment with the study medication, as reported either in the ePD or as a concomitant medication.
- The proportion of participants requiring a visit to urgent care, emergency department, or physician's office for care related to the treated episode of CVS within the 24 hours following treatment with the study medication.

6.10 MAIN ANALYTICAL APPROACH

Data from the RINVR, IAS, VAS, and PES will be analyzed using a mixed model for repeated measures (MMRM). Fixed effects will include treatment group, timepoint, randomization strata, and a treatment-by-timepoint interaction. Timepoint will be fit as a repeated effect using the repeated statement in SAS. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used. In the event an unstructured covariance structure fails to converge, a Toeplitz structure will be used.

Least squares means will be presented for treatment*timepoint, with the significance level of the treatment-by-timepoint interaction presented in summary tables. Pair-wise comparisons of differences in LS means, two-sided 95% confidence intervals (CIs) on differences, and p-values will be provided for each active treatment versus placebo for each timepoint.

Proportion data (ie, rescue medication or visits to urgent care/ER/doctor will be analyzed using a Mantel-Haenszel test, stratifying on randomization strata, in a pairwise fashion of each dose versus placebo.

7 PLANNED INTERIM ANALYSIS

No interim analyses are planned for this study.

8 PARTICIPANT INFORMATION

In general, all participant-level parameters will be summarized for the Safety and the Efficacy populations by treatment group, unless stated otherwise.

8.1 DISPOSITION INFORMATION

Disposition will be summarized for the Safety Population. The number and percentage of participants, who are randomized, treated, who enter the At Home treatment phase, who are treated in the At Home treatment phase, who prematurely discontinue, and complete will be summarized. The reasons of discontinuations include following categories:

- Adverse Event
- Death
- Lost to Follow-up
- Non-Compliance

- Investigator Decision
- Pregnancy
- Study Terminated by Sponsor
- Withdrawal of Consent by Participant
- Other

8.2 PROTOCOL DEVIATIONS

All reported, important protocol deviations will be documented and included in the CSR.

8.3 DEMOGRAPHICS AND SCREENING CHARACTERISTICS

Descriptive statistics or frequency tabulation will be provided for the Safety Population for the following parameters.

8.3.1 *DEMOGRAPHIC PARAMETERS AT SCREENING*

- Age (years)
- Sex (Male, Female)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Weight at Screening (kg)
- Height at Screening (cm)
- Body Mass Index (BMI) = Weight (kg) / [Height (m)]^2 rounded to 1 decimal.

8.4 MEDICAL HISTORY

All reported medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA, version 23.1), and summarized by MedDRA system organ class and preferred term, in order of descending overall frequency for the Safety Population.

8.4.1 *CVS HISTORY*

CVS history, including history of vomiting symptoms, CVS diagnosis, typical duration of CVS episode (hrs. vs days), average number of vomiting/retching events in typical CVS episode, frequency of CVS episodes per year, any triggers for CVS episode, other GI conditions that may cause similar symptoms, treatment history, and current medications and co-morbidities, will be summarized as well as provided in a listing.

The summary tabulation for CVS episodes history will include frequencies and percentages based on the following two categories of usual duration:

1. Typical episode of CVS lasts 24 hrs. or less from the first vomiting/retching event;

2. Typical episode of CVS lasts greater than 24 hrs. from the first vomiting/retching event.

8.5 PRIOR AND CONCOMITANT MEDICATIONS

All reported medications will be coded using the World Health Organization-Drug Dictionary (WHODrug version B3, September 2020). A frequency tabulation will be shown by WHO-DD ATC class level 4 and preferred term for the Safety Population for each of following two categories:

1) Prior medication: medication received during the 4 weeks (30 days) prior to Screening but is no longer being taken, collected on the CRF page “Prior Medication” at Screening.
2) Concomitant medication: medication received during the study, collected on the CRF page “Concomitant Medication”.

Concomitant and prior medications will be included in the participant data listing.

8.6 STUDY DRUG ADMINISTRATION

Study drug administration, including dose, will be listed by participant for each treatment group.

9 SAFETY

All safety analyses will be conducted on the Safety Population. All safety parameters will be summarized based on the actual treatment group. All safety summaries will be descriptive.

9.1 ADVERSE EVENTS

An adverse event reported after informed consent, but before the first dose of study medication, will be considered a pre-treatment adverse event (or interim medical event). Treatment-emergent adverse events (TEAEs) will be defined as any adverse event that occurs after administration of the first dose of study medication until the Follow Up Visit or the Early Termination Visit. The number and percentage of participants who report TEAEs will be summarized by system organ class and preferred term.

Treatment emergent adverse events will also be summarized by intensity as well as relationship to study drug.

Participants who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to study medication when summarized by relationship. If a participant reports multiple preferred terms for a system organ class, the participant will be counted only once for that system organ class.

The number and percentage of participants who experience TEAEs will be summarized by dosing regimen for the following:

- By system organ class and preferred term
- By severity/intensity, system organ class, and preferred term
- By relationship to study drug, system organ class, and preferred term
- Serious adverse events by system organ class and preferred term

- Serious adverse events by relationship to study drug, system organ class, and preferred term
- Adverse events resulting in discontinuation of study medication by system organ class and preferred term
- Adverse events that result in study medication dose interruption by system organ class and preferred term

Clinically significant deteriorations in physical examination findings (in the opinion of the investigator) are captured and summarized as adverse events.

By-participant listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment.

9.1.1 *CODING OF ADVERSE EVENTS*

The verbatim terms of adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1 or newer). Events are summarized by system organ class and preferred term.

9.2 CLINICAL LABORATORY EVALUATIONS

Laboratory values will be converted to the project-defined unit of measurement, as applicable, before analysis. Abnormal, clinically significant laboratory values will be reported and summarized as adverse events. Clinical laboratory tests (including re-check values if present) will be listed chronologically. ‘H’ and ‘L’, denoting values above or below the reference range (when present), will flag out-of-range results. At each time point, absolute values and change from baseline of the hematology and chemistry variables will be summarized by treatment and time with n, mean, SD, SEM, median, Min, and Max values. The categorical data of the urinalysis will be summarized by treatment and time in frequency tables by variable. Note, in some cases, baseline (the last assessment prior to dosing with randomized treatment) is obtained at the Screening visit.

9.3 VITAL SIGNS

The mean change from baseline to each scheduled assessment will be summarized descriptively by dose group for each vital sign variable specified in the protocol. Baseline will be defined as the last vital sign value obtained on Visit 2 and prior to any study medication administration.

9.4 ELECTROCARDIOGRAM

The change from baseline in electrocardiogram intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by dose group. Baseline will be defined as the last ECG obtained on Visit 2 and prior to any study medication administration. The number and percentage of participants who have a clinically notable ECG interval abnormality or other clinically significant ECG finding will be summarized. In addition to descriptive statistics of change from baseline, the number and percentage of participants with QTcF intervals > 450, > 480 and > 500 msec. as well as those with changes from baseline > 30 msec. and >60 msec. will be provided for

each treatment group at each timepoint. A listing of abnormal ECG values will also be provided. For ECGs collected in triplicate, the average value will be used.

9.5 PHYSICAL EXAMINATIONS

The number (N and %) of participants with abnormal physical examinations will be tabulated at each timepoint for each treatment.

When calculating the percentage reporting each category, the “Not Done” category will not be included in the denominator.

9.6 DRUG, ALCOHOL, HIV, HEPATITIS B & C, AND PREGNANCY SCREEN

Drug, alcohol, HIV, Hepatitis B & C, and pregnancy screen data will be included in the participant data listing.

10 COVID TESTING AND IMPACT

By-participant results from COVID testing and impact on study procedures will be provided in a listing.

11 EXPLORATORY

Potential exploratory analyses to assess the impact of missing data are discussed in section 6.9.1.5.

12 CHANGES FROM PROTOCOL

Additions exist with respect to analysis populations and potential (post-hoc) exploratory analyses which may be conducted depending on the extent of missing data.

13 TABLES, LISTINGS, AND FIGURES

A separate document containing the list of tables, listings, and figures (TFLs) to be included in the post-text Appendix 14 of the CSR will be provided. TFLs may be modified with Sponsor’s approval and as deemed necessary without update to the SAP.

NCT04645953

Protocol ID: AMDC-010-201

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF STACCATO® GRANISETRON (AZ-010) FOR THE ACUTE TREATMENT OF MODERATE TO SEVERE CYCLIC VOMITING SYNDROME

April 28, 2021

ALEXZA PHARMACEUTICALS, INC.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF STACCATO® GRANISETRON (AZ-010) FOR THE ACUTE TREATMENT OF MODERATE TO SEVERE CYCLIC VOMITING SYNDROME

INVESTIGATIONAL PRODUCT:	Staccato® Granisetron (AZ-010)
PROTOCOL NUMBER:	AMDC 010-201
ORIGINAL PROTOCOL:	28 SEP 2020
AMENDMENT 1	21 DEC 2020
AMENDMENT 2	28 APR 2021
IND NUMBER:	145487
SPONSOR NAME / ADDRESS:	Alexza Pharmaceuticals, Inc. 2091 Stierlin Court Mountain View, CA 94043

STUDY MONITORS / EMERGENCY CONTACT INFORMATION

Medical Monitor name and contact information will be provided separately.

ALEXZA SIGNATURE PAGE

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Safety and Efficacy of Staccato Granisetron (AZ-010) for the Acute Treatment of Moderate to Severe Cyclic Vomiting Syndrome

Protocol Number AMDC 010-201

	29 Apr 2021
Sponsor Representative Signature	**dd mmm yyyy**
Lawrence Carter	
Printed Name of Sponsor Representative	

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

1 SYNOPSIS

Name of Sponsor/Company: Alexza Pharmaceuticals, Inc.	Name of Investigational Product: AZ-010 (Staccato® Granisetron)	Name of Active Ingredient: Granisetron
Protocol Number: AMDC-010-201		
Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Staccato Granisetron (AZ-010) for the Acute Treatment of Moderate to Severe Cyclic Vomiting Syndrome		
Study Center(s): Multicenter study; approximately 15 sites; US		
Study Period (years): Estimated Date of First Subject Enrollment: February 2021 Estimated Date of Last Subject Completed: December 2021		Phase of Development: 2

Objectives:

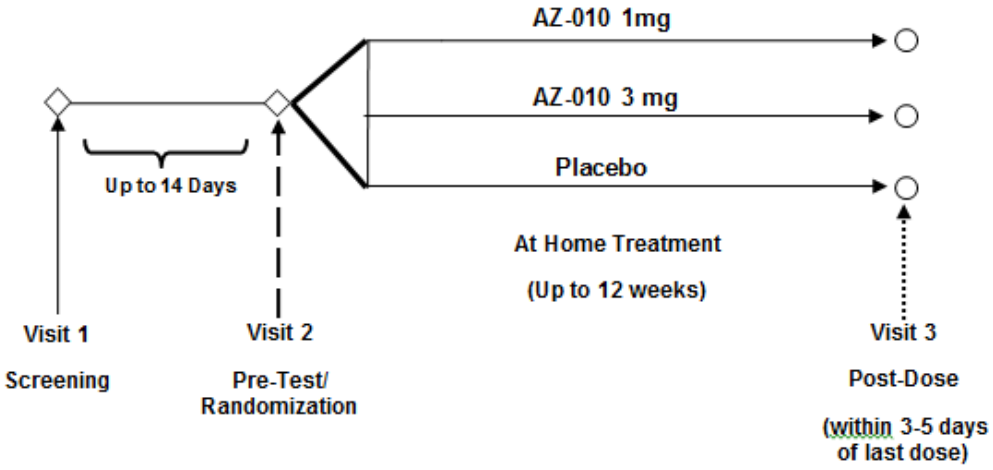
The primary objectives of the study are to assess:

- The efficacy of AZ-010 as an acute treatment for moderate to severe cyclic vomiting syndrome (CVS) in adult patients.
- The safety of AZ-010 in adult patients with moderate to severe CVS.

Methodology:

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, efficacy and safety study of adult outpatients diagnosed with CVS and experiencing recurring episodes of stereotypical vomiting. Up to 5 administrations of study medication will be studied in an At Home environment. CVS patients between 18 and 60 years of age who have experienced at least 3 episodes of recurrent vomiting in the last 12 months are eligible for participation. Approximately 50 patients will be randomized to each of 3 treatment groups: 1 mg AZ-010, 3 mg AZ-010, or matching *Staccato* Placebo (*Staccato* device without drug coating). Randomization will be stratified by duration of the patient's typical CVS episode into one of the following two categories: 1) Typical episode of CVS lasts 24 hrs or less from the first vomiting/retching event; 2) Typical episode of CVS lasts greater than 24 hrs from the first vomiting/retching event.

There will be 3 Research Clinic visits and a home treatment period:



Patients will be screened at the Research Clinic to determine if they are eligible for study participation no more than 14 days prior to Visit 2. After the study is explained to the patient and the patient has signed an informed consent form (ICF), the investigator will establish the patient's eligibility according to the inclusion and exclusion criteria via the following assessments: Medical history (with particular reference to history of vomiting symptoms, CVS diagnosis, typical duration of CVS episode (hrs, days, etc), average number of vomiting/retching events in typical CVS episode, frequency of CVS episodes per year, any triggers for CVS episode, other GI conditions that may cause similar symptoms, treatment history, and current medications); full physical examination (including height, weight); vital signs (heart rate, blood pressure while sitting, respiratory rate, temperature); 12-lead electrocardiogram (ECG); blood draw and urine sample for routine clinical labs (chemistry, hematology, urinalysis); and serum pregnancy test (in female participants of child-bearing potential). In light of the COVID-19 pandemic, patients will also be screened for COVID-19 infection and appropriate social distancing and contact procedures should be taken to ensure patient safety when in the clinic.

Patients who continue to be eligible to participate in the study will be asked to return to the Research Clinic for Visit 2. Patients meeting all inclusion criteria and none of the exclusion criteria will be randomized to treatment with either 1mg AZ-010, 3 mg AZ-010, or placebo in a 1:1:1 ratio (active:active:placebo). Each randomized patient will receive training in the use of the *Staccato* device and detailed instructions for the use of the ePD in the clinic as well as undergo a pre-test self-administration of their randomized study medication. Each patient will be monitored during a 2 hr observation period and have 12-lead ECG (triplicate) assessments at pre-dose and 2, 30, 60, 90, and 120 minutes post dose. If there are no clinically-significant observations or abnormalities on the ECG, including QT prolongation, the patient will be provided with their Patient Kit that contains the remaining 5 unused Staccato devices in addition to the 1 Staccato device that they used in the clinic.

Randomized patients will be asked to treat a subsequent CVS episode (with single daily dosing up to 5 consecutive days) within 12 weeks after the randomization date. Enrolled patients will self-administer the study medication when they know their CVS episode is imminent or as soon as possible after a CVS-related vomiting episode has begun. Patients will interact with their ePD prior to initiation of treatment (if possible) and to capture the study data. The ePD will be used to record the date and time of study medication administration, the number of vomiting and retching events, and the patient reported outcome measures (including the intensity and duration of the CVS episode, severity of abdominal pain, nausea, and anxiety/panic, and characteristics of the nausea, vomiting and retching over defined time periods). In addition, patients will complete a paper questionnaire to record the total number of vomiting and retching events within the first 24 hours after dosing. Patients will be instructed to contact the Research Clinic at the earliest possible time after initiation of dosing and any time should they require rescue medication, medical assistance or experience an intolerable AE at home during the treatment period. If the number of vomiting and retching events are not recorded on the ePD or the 24 hour vomiting and retching questionnaire and the patient has unused study medication, that patient may be allowed to continue participation in the 12-week Home Treatment Period in order to treat a second CVS episode during this time. Patients will also record in a paper diary the use of any medications taken during the Home Treatment period. Rescue medications may include any of the agent(s) from the list described in Section 9.8; however for the purpose of defining the responder endpoint, only anti-emetic medications, benzodiazepines, and triptans will be considered rescue medications. Patients are encouraged to avoid rescue medication use for the first 2 hrs following treatment with the study medication. Patients will be required to return to the Research Clinic (Visit 3) within 3–5 days from the last study medication administration for final in-clinic assessments, to return the Patient Kit containing the used and unused study medication, ePD, and any other unused supplies. Conversely, patients will be asked to return to the Research Clinic after 12 weeks with their unused Patient Kit if they did not treat a CVS episode within this time period. Visit 3 will include the following assessments: Vital signs; full physical examination; assessment for treatment emergent adverse events; 12-lead ECG, concomitant medications (including rescue medication taken), and clinical labs.
Number of Subjects (planned): Approximately 150 patients are planned to be randomized in the study. Patients will be randomized to treatment with either 1mg AZ-010, 3 mg AZ-010, or placebo in a 1:1:1 ratio (active:active:placebo).

Main Criteria for Inclusion:

Subjects eligible for enrollment in the study must meet all of the following inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

1. Adult males and females between 18 and 60 years of age, inclusive at the time of signing the informed consent document.
2. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted.
3. Diagnosis of cyclic vomiting syndrome (CVS) using the Rome IV diagnostic criteria and must have:
   - Stereotypical episodes of acute onset vomiting lasting < 1 week;
   - At least 3 discrete episodes of vomiting in the prior year and 2 episodes in the past 6 months, occurring at least 1 week apart;
   - Absence of vomiting between episodes (but milder symptoms may be present);
   - Symptoms must be present for the past 3 months with onset at least 6 months prior
4. Has a prodrome or pre-emetic symptoms associated with approximately half of their "typical" CVS episodes
5. If of reproductive age, female participants and female partners of male participants, willing and able to use a medically highly effective form of birth control from at least 4 weeks prior to Baseline until at least 30 days following last dose of study drug. Examples of medically highly effective forms of birth control are:
   - Surgical sterility (hysterectomy or bilateral ligation) or post-menopausal (cessation of menses for at least 12 months prior to screening)
   - Sexual partner is sterile, or of the same sex
   - Implants of levonorgestrel in females
   - Oral contraceptive (combined, patch, vaginal ring, injectable, implant) in females
   - Double-barrier method (any combination of physical and chemical methods)
   - Intrauterine device with a failure rate less than 1% per year
6. Male participants must:
   - Agree to use, with their partners, one of the highly effective contraceptive methods listed in Inclusion Criterion 5, from Baseline until at least 30 days following last dose of study drug.
   - Refrain from donating sperm during the study and for at least 30 days after the end of the study.
7. Otherwise healthy, as determined by the responsible physician, based on a medical evaluation including history, physical examination, vital signs, electrocardiograms (ECGs) and laboratory tests assessed at the screening visit.
8. Negative urine tests for selected drugs of abuse and alcohol breath test at Screening.
   Note: Patients with a positive urine drug screen for benzodiazepines or opioids may be allowed in the study provided the drug was prescribed by a physician.

9. Willing and able to adhere to overall study visit schedule, procedures and other protocol requirements.

Exclusion Criteria:

1. Any significant medical or psychiatric condition that could, in the Investigator's opinion, compromise the subject's safety or interfere with the completion of this protocol.
2. Any condition, including the presence of laboratory abnormalities or pulmonary condition, which according to the Investigator places the subject at unacceptable risk if he/she were to participate in the study.
3. A diagnosis of any gastrointestinal disorder other than CVS that in the judgement of the Investigator could compromise the subject's safety or interfere with the interpretation of safety or efficacy data.
4. Current history of clinically significant neurologic (e.g., seizures), cardiac, pulmonary (e.g., asthma, COPD), metabolic, renal, or hepatic conditions.
5. Use of drugs known to prolong the QTc interval with known risk of Torsade de Pointes. ECG findings of QTcF interval > 450 msec for men and > 470 msec for women obtained at screening visit or prior to the first dose of study drug.
6. Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), serum creatinine, or total bilirubin > 1.5 upper limit of normal (ULN) at screening or prior to the first dose of study drug. These laboratory tests may be repeated once, if they are abnormal on first screening, and if there is a medical reason to believe the results may be inaccurate. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not compromise the subject's safety and will not interfere with the interpretation of safety data.
7. Positive blood screen for human immunodeficiency virus (HIV antibody), hepatitis B virus surface antigen, or hepatitis C virus antibody at screening.
8. History of alcohol or illicit drug abuse within 1 year before the first dose of study drug.
9. Daily use of marijuana.
   Note: Occasional use of THC/cannabinoid products is allowed in the study
10. Participation in a clinical trial and receipt of an investigational medication or a new chemical entity within 90 days, 5 half-lives, if known, or twice the duration of the biological effect of any medication (whichever is longer) prior to the first dose of current study drug.
11. Donation of blood, plasma or other blood products or blood collection in excess of 470 mL within 8 weeks prior to dosing.
12. Known history of sensitivity to any of the study drugs or components thereof, or to other 5-HT3 receptor antagonists, or a history of medication allergy or other allergy that, in the opinion of the Investigator, contraindicates study participation.
13. Major surgery within 4 weeks of screening that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the Investigator.
14. Uncontrolled current illness (i.e., active infection).
15. Has a current or a history of cancer, with the exception of basal cell carcinoma.

Investigational Product, Dosage and Mode of Administration:

AZ-010 (*Staccato*® granisetron) is a hand-held, single dose, single-use drug-device combination product using the *Staccato* delivery system. Oral inhalation through the product is detected by the breath sensor, which in turn results in rapid heating of a thin film of granisetron causing the formation of a thermally generated drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

Each product is packaged inside a sealed foil pouch. Upon removing the product from the pouch, pulling the tab connected to the device renders it ready for use, as indicated by illumination of a green light on top of the device. Successful dosing is signaled by the extinguishing of the green light.

AZ-010 is administered as a single dose via inhalation, available as 1 mg or 3 mg per device.

Reference Therapy, Dosage and Mode of Administration:

Matching placebo which is the same Staccato inhalation device without coated granisetron film

Duration of Study Participation:

The Screening phase will last up to 14 days. Eligible subjects will be provided with a multipack of study medication and instructed to self-medicate upon occurrence of their next CVS episode within the next 12-week period. Up to 5 daily doses will be administered when a CVS episode occurs. Consequently, subject participation will range from approximately 1−4 months, depending on the timing of the Screening visit in relation to treatment.

Criteria for Evaluation:

Primary Efficacy Endpoint

- The number of vomiting/retching events in the 2 hours following treatment.

Secondary Endpoints

- The percentage of patients with no vomiting or retching events and no anti-emetic, benzodiazepine, or triptan rescue medication use in the first 24 hours following treatment.
- The intensity of the vomiting/retching attack (Intensity of Attack Scale) at 2, 6, 12, and 24 hours following treatment.
- The Rhodes Index of nausea, vomiting, and retching (RINVR) at 6, 12, and 24 hours following treatment.
- The assessment of abdominal pain at 2, 6, 12, and 24 hours following treatment (VAS 1−100; 0 = no pain and 100 = worst possible pain)
- The assessment of nausea at 2, 6, 12, and 24 hours following treatment (VAS 1–100; 0 = no nausea and 100 = worst possible nausea)
- The assessment of anxiety/panic at 2, 6, 12, and 24 hours following treatment (VAS 1−100; 0 = no anxiety/panic and 100 = worst possible anxiety/panic)

- The duration of the CVS episode at 24 hours in relation to their typical CVS episodes (Prior Episode Questionnaire)
- The intensity of the CVS episode at 24 hours in relation to their typical CVS episodes (Prior Episode Questionnaire)
- Use of rescue medication within the 24 hours following treatment with the study medication
- Visit to urgent care, emergency department, or physician's office for care related to the treated episode of CVS within the 24 hours following treatment with the study medication

All statistical tests will be 2-sided with a significance value of ≤ 0.05. There is no control for Type-1 error for the analyses.

Additional exploratory statistical analyses to further assess for treatment effect will be outlined in the Statistical Analysis Plan finalized prior to database lock.

Safety

Safety and tolerability of AZ-010 will be assessed by evaluating adverse events, vital signs, 12-lead ECG, clinical laboratory results, and physical examination.

2 TABLE OF CONTENTS

LIST OF TABLES

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Special Term	Explanation
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AR	Adverse Reaction
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve from time 0 to 24 hours post-dose
$AUC_{0\text{-}tlast}$	Area under the plasma concentration-time curve from time 0 to the last measurable concentration; calculated using linear trapezoid rule
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 to infinity
BMI	Body Mass Index
BP	Blood pressure
CBC	Complete Blood Count
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CL/F	Oral clearance
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EC	Ethics Committee
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator’s Brochure

Abbreviation or Special Term	Explanation
ICF	Informed Consent Form
ICH	International Council on Harmonization
IRB	Institutional Review Board
LC/MS/MS	Liquid Chromatography Tandem Mass Spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliters
PD	Pharmacodynamic
PK	Pharmacokinetic
PR	Pulse Rate
RR	Respiration Rate
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Apparent terminal half-life
T_{max}	Time to reach peak plasma concentration
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

4 INTRODUCTION AND RATIONALE

4.1 Background Information

Cyclic vomiting syndrome (CVS) is an idiopathic chronic disorder characterized by sudden episodes of nausea and rapid-fire vomiting lasting for 1–5 days followed by symptom-free periods (Hayes et al, 2018). This alternating pattern of disease and disease-free periods distinguishes CVS from other gastrointestinal disorders. There is no current drug therapy approved for treatment of CVS.

CVS is generally described as consisting of four phases. The *inter-episodic phase* occurs between attacks and patients remain relatively asymptomatic. This phase can last for several months. During the *prodromal phase*, some patients describe an 'aura' that lasts for minutes to hours. This phase usually consists of lethargy, anorexia, pallor or abdominal pain or autonomic symptoms such as sweating or salivation. The *hyperemesis phase* usually starts from the early hours of the morning to noon, and is characterized by intense persistent nausea and repeated vomiting. Typically, vomiting peaks in the first hour and then declines lasting at least 24 hours with episodes commonly occurring in the early morning or upon awakening. The vomiting frequency can be up to eight times every hour (Fleisher et al, 2005). This can last for 1–7 days. Finally, the *recovery phase* begins with the cessation of vomiting and ends when energy levels and appetite recover. Antiemetic agents have been reported to be a key component of support care for acute abortive treatment during the prodromal and emetic phases of CVS in adults (Abell et al, 2008). Abortive IV antiemetic agents such as the 5-HT_3 antagonist ondansetron at high doses and granisetron were reported for supportive treatment of acute vomiting episodes in CVS patients (Li and Misiewicz et al, 2003; Yang, 2010; Venkatasubramani, 2007).

Treatment of CVS remains largely based on real-world clinical experience. There is no current drug therapy approved for treatment of CVS. According to guidelines on management of cyclic vomiting syndrome in adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association (Venkatesan et al, 2019), treatment of CVS should be based on a biopsychosocial care model, integrating lifestyle modification, prophylactic and/or abortive medications, and evidenced-based psychotherapy to address psychiatric comorbidity. The guideline recommends using prophylactic medications in moderate-to-severe CVS and offering abortive medications to all patients to terminate an acute attack. For acute attacks, the committee conditionally recommends using serotonin antagonists, such as ondansetron, and/or triptans, such as sumatriptan or aprepitant to abort symptoms. Antiemetic intravenous therapy was reported to be effective for treatment of nausea and vomiting for CVS acute episodes (Jensen, 2015; Moses et al, 2014). Granisetron was reported to be an effective pharmacologic approach used for abortive and supportive care in CVS (Li and Balint, 2000; Li et al, 2008; Li and Misiewicz, 2003).

Granisetron is a highly selective and potent 5-hydroxyltryptamine type 3 (5-HT3) receptor antagonist widely used for over twenty years as an effective antiemetic treatment (Blower, 2003). The efficacy of granisetron in the prevention of nausea and vomiting has been extensively studied in clinical trials and is approved for chemotherapy-induced nausea and vomiting (CINV), radiation-induced nausea and vomiting (RINV), and for postoperative nausea and vomiting (PONV) (Kytril (granisetron hydrochloride) Prescribing Information 2011,

Aapro, 2004; Spartinou et al, 2017; Gilmore et al, 2018). Granisetron has also been shown to be effective and well tolerated in special populations, such as patients refractory to antiemetic treatment for gastroparesis (Simmons and Parkman, 2014), bulimia nervosa, cyclic vomiting syndrome, HIV (Evans, 2016) and patients with hepatic or renal impairment with minimal potential for drug-drug interactions (Aapro, 2004).

Antiemetic agents have been reported to be a key component of support care for acute abortive treatment during the prodromal and emetic phases of CVS in adults (Abell et al, 2008). Abortive IV antiemetic agents such as the 5-HT3 antagonist ondansetron at high doses (0.3–0.4 mg/kg up to 24 mg, q. 4–6 hours) and granisetron (10 µg/kg, q 4–6 hours) were reported for supportive treatment of acute vomiting episodes in CVS patients (Li and Misiewicz et al, 2003; Yang, 2010; Venkatasubramani, 2007). Despite the widespread use of 5-HT3 antagonists in the treatment of CVS, there have been no definitive clinical trials conducted to date.

Alexza Pharmaceuticals (Alexza) is currently developing *Staccato*® Granisetron for Inhalation (*Staccato* Granisetron; AZ-010) as an acute treatment of CVS. *Staccato* Granisetron represents a new dosage form of granisetron. It is a single-use, hand-held, drug-device combination product that delivers aerosolized granisetron. From a drug development perspective, one of the most compelling characteristics of *Staccato* Granisetron is that the drug can be delivered non-invasively with rapid IV-like pharmacokinetics to individuals. In previous clinical studies with *Staccato* Granisetron and a number of drugs using the *Staccato* technology, mean peak plasma concentration was achieved within minutes following inhalation. In a first-in-human, single ascending dose study with *Staccato* Granisetron (AMDC 010-101; refer to CSR: IND 145,487 SN 0009), the median time to maximum plasma concentration was approximately 2 minutes for doses ranging from 0.5–3 mg.

Staccato Granisetron may provide significant benefit for the treatment of CVS since it has rapid pharmacokinetics and bypasses GI absorption of the drug. Because of the simplicity of the delivery, the patient is only required to take a normal breath for delivery of the aerosolized drug. Consequently, inhalation via *Staccato* delivery could provide a non-invasive, rapid delivery of granisetron and lead to a more rapid and effective control of acute vomiting episodes, representing an improvement to existing patient care. Consequently, this study (AMDC 010-201) is designed to assess the effects of *Staccato* Granisetron as an acute treatment during an episode of CVS in patients with moderate to severe disease.

4.2 Study Medication Description

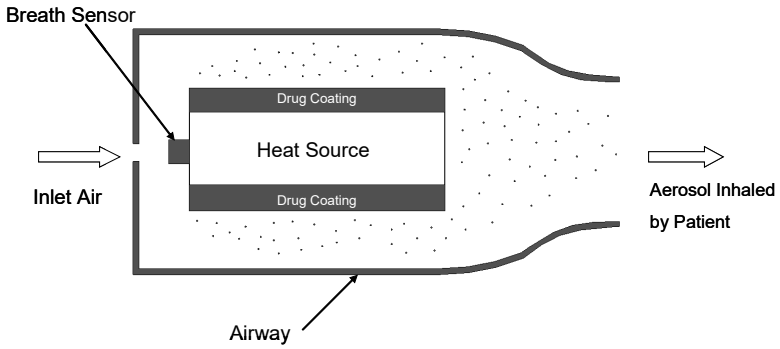
4.2.1 Staccato Granisetron for Inhalation

Staccato granisetron is a hand-held, single dose, single-use drug-device combination product using Alexza's proprietary *Staccato* delivery system. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free granisetron to form a thermally generated, highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

The principal components of *Staccato* Granisetron (shown schematically below) are as follows:

- Breath sensor: The breath-activation mechanism that initiates actuation of the heat source
- Heat source (i.e., heat package): The mechanism comprised of a reactant coating on the interior surface of a stainless-steel substrate that generates heat to vaporize the drug and produce the aerosol
- Drug coating: The thin film of excipient-free granisetron on the exterior surface of the stainless-steel substrate
- Airway: The medical-grade plastic housing surrounding the heat package; it controls and directs the airflow over the vaporizing drug.

Schematic Side-View of *Staccato* Granisetron



The interior surface of the stainless-steel substrate of the heat package is coated with a mixture of zirconium and molybdenum trioxide powder with a clay binder. When activated, this undergoes a controlled, gasless, oxidation-reduction (redox) reaction that liberates heat. The redox reaction is initiated by a battery-activated starter inserted into the heat package. Inhalation through the product is detected by the breath sensor, causing the starter to initiate the redox reaction and subsequent rapid heating of the substrate to approximately 400°C. Heat then transfers into the film of granisetron that is coated on the exterior surface of the substrate. The granisetron vaporizes in < 1 second, thereby limiting thermal decomposition. The vapor cools in the airflow and condenses to form aerosol particles that are characterized by a mass median aerodynamic diameter in the range of 1.0 to 3.5µm. The aerosolized granisetron is delivered to the lung within seconds of inhalation through the device.

Each product is packaged inside a sealed foil pouch. Removal of a pull tab from the product renders it ready for use, as indicated by illumination of a green light. Successful dosing is signaled by the extinguishing of the green light.

4.3 Preclinical Information for *Staccato* Granisetron

For a full discussion of the preclinical data generated to date with *Staccato* Granisetron, please see the Investigator Brochure (m1.14.4.1).

4.4 Clinical Information for *Staccato* Granisetron

While granisetron has been available worldwide in various formulations for many years, AZ-010 has been administered to healthy volunteers in a single ascending dose Phase 1 study (AMDC 010-101) and a multiple ascending dose study (AMDC 010-102). Study AMDC 010-101 was designed in 2 parts in separate cohorts of healthy volunteers. The primary objectives for each part are as follows. For Part A the purpose was to examine the tolerability, safety, and pharmacokinetics of single ascending doses of 0.5, 1, and 3 mg of AZ 010 in healthy volunteers. The purpose of Part B was to compare the pharmacokinetics and safety of a single dose of 1 mg of AZ-010 with that of 1 mg granisetron hydrochloride intravenous (IV) injection in healthy volunteers. The study was conducted in a total of 36 subjects at a single clinical research unit. Across the 3 doses of Part A, the drug was generally well tolerated with 3 of 8 subjects (6 AEs in total) in the 0.5 mg cohort, 3 of 8 subjects (6 AEs in total) in the 1 mg cohort, and 0 of 8 subjects in the 3 mg cohort reporting at least 1 adverse event. All adverse events were mild to moderate in severity and there were no serious adverse events (SAE).

Study AMDC 010-102 was designed to examine the tolerability, safety, and pharmacokinetics (PK) of AZ-010 following 7 days of dosing (up to 3 mg) in healthy volunteers. The data obtained from this study were intended to guide selection of safe and tolerable doses for the Phase 2 clinical trial. The study was conducted in a total of 30 subjects (8 for each of the AZ-010 dose groups and 6 for placebo) at a single clinical research unit. Across the 3 doses the drug was generally well tolerated with a total of 13 of 30 subjects (43%) experiencing an AE (7 of 8 subjects for 0.5 mg; 0 of 8 subjects for 1.0 mg; 4 of 8 subjects for 3.0 mg of AZ-010 and 2 of 6 subjects for placebo) There were a total of 30 AEs reported with the most reported for Gastrointestinal disorders (n = 9) and Nervous System disorders (n = 9). There were no clinical laboratory changes for serum chemistry or hematology or any changes in urinalysis between baseline and discharge that were notable. There were no serious adverse events (SAE).

For a full discussion of the clinical data generated to date with *Staccato* granisetron, please see the Investigator Brochure (m1.14.4.1).

5 ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the Sponsor and the Investigator abide by Good Clinical Practice (GCP), including but not limited to Title 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312, and the International Council on Harmonization (ICH) guidelines and directives. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki and applicable local regulatory requirements and law.

The Principal Investigator is responsible for protecting the rights, safety, and welfare of patients under his/her care, and for the control of the medications under investigation. All ethical, regulatory, and legal requirements must be met before the first patient is enrolled in the study.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drug, and their study-related duties and functions. The Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible from conducting or working on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Alexza Pharmaceuticals. The Investigator is required to immediately disclose to Alexza Pharmaceuticals in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by US FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator's knowledge) threatened.

5.1 Institutional Review Board (IRB)

The Institutional Review Board (IRB) will meet all FDA requirements governing IRBs according to CFR, Title 21, Part 56. The Investigator (or designee) must submit this study protocol and any amendments, the Sponsor's approved informed consent form(s) (ICF), patient information sheets, patient recruitment materials, and other appropriate documents to the IRB for review and approval. Following review of the submitted materials a copy of the written and dated approval/favorable opinion will be forwarded to the Sponsor (or designee).

Any advertisements used to recruit patients for the study will be reviewed by the Sponsor and the IRB prior to use.

5.2 Written Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the patient. Pre-screening for potential eligibility in person or by telephone may be conducted with an IRB-approved pre-screen script after a patient provides their consent.

The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50. The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is

voluntary must be explained to the patient. The patient must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must also be documented in the patient's source documentation prior to any testing under this protocol, including screening tests and assessments. The original signed consent form will be retained with the study records.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

6 STUDY OBJECTIVES

6.1 Primary Objectives

Objectives:

The primary objectives of the study are to assess:

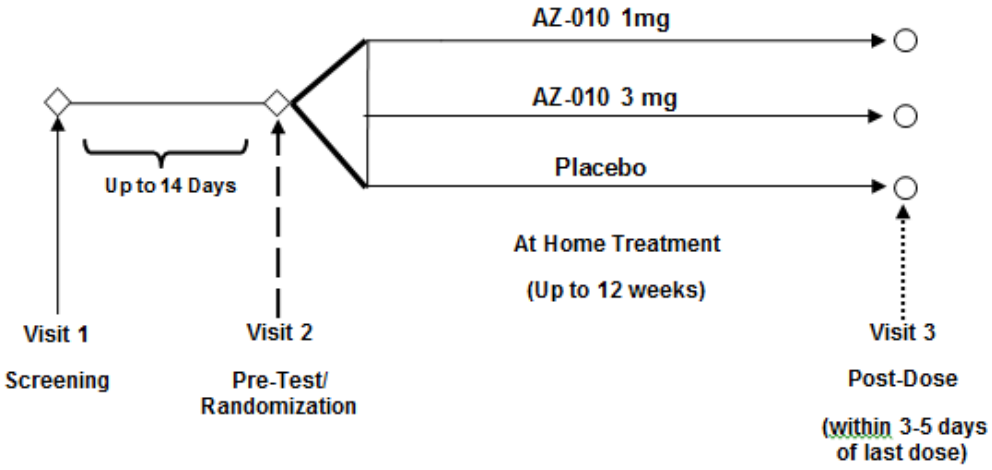
- The efficacy of AZ-010 as an acute treatment for cyclic vomiting syndrome (CVS) in adult patients.
- The safety of AZ-010 in adult patients with CVS.

7 OVERALL STUDY DESIGN

7.1 Study Design

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled, efficacy and safety study of adult outpatients diagnosed with CVS and experiencing recurring episodes of stereotypical vomiting. Up to 5 administrations of study medication will be allowed in an At Home environment. CVS patients between 18 and 60 years of age who have experienced at least 3 episodes of recurrent vomiting in the last 12 months and 2 episodes in the last 6 months are eligible for participation. Approximately 50 patients will be randomized to each of 3 treatment groups: 1 mg AZ-010, 3 mg AZ-010, or matching *Staccato* Placebo (*Staccato* device without drug coating). Randomization will be stratified by duration of the patient's typical CVS episode into one of the following two categories: 1) Typical episode of CVS lasts 24 hrs or less from the first vomiting/retching event; 2) Typical episode of CVS lasts greater than 24 hrs from the first vomiting/retching event.

There will be 3 Research Clinic visits and a home treatment period:



Patients will be screened at the Research Clinic to determine if they are eligible for study participation no more than 14 days prior to Visit 2. After the study is explained to the patient and the patient has signed an informed consent form (ICF), the investigator will establish the patient's eligibility according to the inclusion and exclusion criteria via the following assessments: Medical history (with particular reference to history of vomiting symptoms, CVS diagnosis, typical duration of CVS episode (hrs vs days), average number of vomiting/retching events in typical CVS episode, frequency of CVS episodes per year, any triggers for CVS episode, other GI conditions that may cause similar symptoms, treatment history, and current medications); full physical examination (including height, weight); vital signs (heart rate, blood pressure while sitting, respiratory rate, temperature); 12-lead electrocardiogram (ECG); blood draw and urine sample for routine clinical labs (chemistry, hematology, urinalysis); and serum pregnancy test (in female participants of child-bearing potential). In light of the COVID-19

pandemic, patients will also be screened for COVID-19 infection and appropriate social distancing and contact procedures should be taken to ensure patient safety when in the clinic.

Patients who continue to be eligible to participate in the study will be asked to return to the Research Clinic for Visit 2. Patients meeting all inclusion criteria and none of the exclusion criteria will be randomized to treatment with either 1 mg AZ-010, 3 mg AZ-010, or placebo in a 1:1:1 ratio (active:active:placebo). Each randomized patient will receive training in the use of the *Staccato* device and detailed instructions for the use of the ePD in the clinic as well as undergo a pre-test self-administration of their randomized study medication. Each patient will be monitored during a 2 hr observation period and have 12-lead ECG (triplicate) assessments at pre-dose and 2, 30, 60, 90, and 120 minutes post dose. If there are no clinically-significant observations or abnormalities on the ECG, including QT prolongation, the patient will be provided with their Patient Kit that contains the remaining 5 unused Staccato devices in addition to the 1 Staccato device that they used in the clinic.

Randomized patients will be asked to treat a subsequent CVS episode (with single daily dosing up to 5 consecutive days) within 12 weeks after the randomization date. Enrolled patients will self-administer the study medication when they know their CVS episode is imminent or as soon as possible after a CVS-related vomiting episode has begun. Patients will interact with their ePD prior to initiation of treatment (if possible) and to capture the study data. The ePD will be used to record the date and time of study medication administration, the number of vomiting and retching events, and the patient reported outcome measures (including the intensity and duration of the CVS episode, severity of abdominal pain, nausea, and anxiety/panic, and characteristics of the nausea, vomiting and retching over defined time periods). In addition, patients will complete a paper questionnaire to record the number of vomiting and retching events within the first 24 hours after dosing. Patients will be instructed to contact the Research Clinic at the earliest possible time after initiation of dosing and at any time should they require rescue medication, medical assistance, or experience an intolerable AE at home during the treatment period. If the number of vomiting and retching events are not recorded on the ePD or the 24 hour vomiting and retching questionnaire and the patient has unused study medication, that patient may be allowed to continue participation in the 12-week Home Treatment Period in order to treat a second CVS episode during this period. Patients will also record in their diary any medications taken during the Home Treatment period. Rescue medications may include any agent(s) from the list described in Section 9.8; however for the purpose of defining the responder endpoint, only anti-emetic medications, benzodiazepines, and triptans will be considered a rescue medication. Patients are encouraged to avoid rescue medication use for the first 2 hrs following treatment with the study medication. The patient will be required to return to the Research Clinic (Visit 3) within 3–5 days from the last study medication administration for final in-clinic assessments, to return the Patient Kit containing the used and unused study medication, ePD, and any other unused supplies. Conversely, patients will be asked to return to the Research Clinic after 12 weeks with their unused Patient Kit if they did not treat a CVS episode within this time period. Visit 3 will include the following assessments: Vital signs; full physical examination; assessment for treatment emergent adverse events; 12-lead ECG, concomitant medications (including rescue medication taken), and clinical labs.

Safety

Patient safety will be monitored throughout the trial by the Investigator and supported by regular review by the Medical Monitor. The subject will be tested to ensure they do not have the Hepatitis B or C virus, HIV, or COVID-19 during the screening period. Chemistry and hematology laboratory values will be assessed prior and subsequent to treatment of the CVS episode. Patients who experience intolerable symptoms during treatment may discontinue the study at the judgement of the Investigator. Patients may withdraw consent at any time.

All safety assessments will be carried out according to the study Schedules of Events (Table 1). Laboratory assessments are listed in the Appendix, Section 17.1 of the protocol. The approximate total blood volume drawn is the trial is shown below.

Sample	# Samples Taken		Sample Volume (mL)		Blood Volume
Hematology	2	X	4 mL	=	8mL
Serology	1		5 mL		5 mL
Serum Pregnancy	2		5 mL		10 mL
Chemistry	2		8.5 mL		17 mL
Total					**40 mL**

7.2 Number of Patients and Sites

Approximately 150 patients are planned to be randomized at approximately 15 study centers.

7.3 Method of Treatment Assignment and Blinding

Patients will be randomized in a 1:1:1 ratio to 1 mg AZ-010, 3 mg AZ-010, or matching Staccato Placebo (Staccato device without drug coating). Randomization will be stratified by duration of the patient's typical CVS episode into one of the following two categories:

1. Typical episode of CVS lasts 24 hrs or less from the first vomiting/retching event;
2. Typical episode of CVS lasts greater than 24 hrs from the first vomiting/retching event.

The randomization schedule will be generated prior to study start. All study patients, Investigators, and site study staff will be blinded to study medication assignment. Devices and packaging of AZ-010 and placebo be identical in appearance.

7.4 Rationale for Study Design, Doses, and Primary Endpoint

Double-blind, randomized, placebo-controlled studies are considered optimal for obtaining unbiased estimates of the efficacy and safety of investigational products. There have been no double-blind, randomized, placebo-controlled studies assessing the acute treatment of CVS in adults prior to this trial.

CVS is generally described as consisting of four phases. The *hyperemesis phase* usually starts from the early hours of the morning to noon, and is characterized by intense persistent nausea and repeated vomiting. The vomiting frequency can be up to eight times every hour (Fleisher et al, 2005). This can last for 1–7 days. Antiemetic agents have been reported to be a key component of support care for acute abortive treatment during the prodromal and emetic phases of CVS in adults (Abell et al, 2008). Abortive IV antiemetic agents such as the 5-HT_3 antagonists ondansetron at high doses and granisetron were reported for supportive treatment of acute vomiting episodes in CVS patients (Li and Misiewicz et al, 2003; Yang, 2010; Venkatasubramani, 2007).

Granisetron is a highly selective and potent 5-HT_3 receptor antagonist widely used for over twenty years as an effective antiemetic treatment (Blower, 2003). Because of its demonstrated effectiveness as an antiemetic treatment, granisetron was selected as the drug for development using the *Staccato* technology. One of the potential advantages of *Staccato* Granisetron (AZ-010) is rapid IV-like pharmacokinetics. In Phase 1 clinical trials with Staccato granisetron, mean peak plasma levels were achieved within minutes following inhalation. Because of this property, *Staccato* Granisetron offers flexibility compared to the IV route of administration since the patient can take the medication at home and achieve rapid drug exposure in a non-invasive way. In addition, as an abortive therapy, *Staccato* Granisetron offers an advantage to oral treatments that may be difficult to administer to an individual with uncontrolled vomiting.

IV administered granisetron at doses of 1 and 3 mg have been shown to be effective in treating nausea and vomiting. For example, a randomized, double-blind dose-ranging study for IV granisetron in the prevention of PONV found that a single dose of 1 mg or 3 mg resulted in a significant reduction in the numbers of patients experiencing postoperative nausea or vomiting during postoperative periods of 0–6 h and 0–24 h (78% and 77% of patients, respectively) (Wilson et al, 1996). Granisetron was well tolerated and the optimum dose was 1 mg. Consensus guidelines for the prevention of PONV in adults recommend treatment with 0.35–3 mg IV granisetron or 4 mg IV ondansetron at the end of surgery (Gan et al, 2014).

The selection of the 1 mg and 3 doses of AZ-010 for this study is supported by a Phase 1 study (AMDC 010-101) demonstrating the equivalence of PK exposure between 1 mg AZ-010 and 1 mg IV granisetron. In this crossover study conducted in healthy volunteers, mean peak and total granisetron exposure (C_{max} and AUC) were similar for both routes of administration with both treatments yielding peak exposure within 2 minutes. The half-life was the same with the IV and Staccato treatments at 10 hr. Consequently, given the importance of the 1 and 3 mg IV doses for granisetron in treating nausea and vomiting noted above and the PK equivalence of IV and *Staccato* granisetron, doses of 1 mg and 3 mg AZ-010 were selected for this study.

CVS is characterized by intense vomiting. The primary endpoint for this study is aimed at capturing the number of times the patient has vomited or retched (which will be considered the same as vomiting in the enumeration of events) in the time period specified post dosing. This endpoint is the most direct assessment of the primary symptom and will be recorded by the patient in the ePD.

7.5 Schedule of Events

The schedule of events is provided in Table 1.

Table 1: Schedule of Events

Event	Screening	Randomization[1]	Home Treatment Period[2] (Up to 12 Weeks Post Randomization)						Follow-Up /Termination
	Visit 1 (Up to Day -14)	Visit 2 (Day 1)	*Schedule of Assessments for each Dosing Day (Up to 5 days)*						Visit 3
			Pre-0	0	2 h post dose	6 h post dose	12 h post dose	24 h post dose	
Informed consent	X								
Eligibility assessment	X	X							
Demographics	X								
Medical history	X	X							
Urine Drug and alcohol breath screen	X								
Complete Physical Examination	X	X[3]							
Brief Physical Exam[4]		X							X
Height	X								
Weight	X	X							X
Pregnancy test[5]	X								X
Clinical laboratory testing[6]	X								X
Serology (HIV, HBV, HCV)	X								
COVID -19 test	X	X							
12-lead electrocardiogram	X	X[7]							X
Vital signs	X	X							X
Device Training		X							
ePD Instructions		X							
Randomization and assign Patient Kit		X							
Study Medication Administration[8]		X		X					
Patient activates ePD and study clock				X					
Patient records number of discrete vomiting/retching events (ePD)				X----------X					
VAS Assessments (ePD)[9]					X	X	X	X	
RINVR Assessment (ePD)						X	X	X	
Intensity of Attack Scale (ePD)					X	X	X	X	

Event	Screening	Randomization[1]	Home Treatment Period[2] (Up to 12 Weeks Post Randomization)						Follow-Up /Termination
	Visit 1 (Up to Day -14)	Visit 2 (Day 1)	*Schedule of Assessments for each Dosing Day (Up to 5 days)*						Visit 3
			Pre-0	0	2 h post dose	6 h post dose	12 h post dose	24 h post dose	
Prior Episode Questionnaire ePD								X	
24 Hour Vomiting and Retching Questionnaire				X----------X					
Reconciliation of Patient Kit									X
Adverse events		X		X----------X					X
Rescue Med or HCP Visit				X----------X					
Concomitant medications	X	X	X----------X						X

HBV = hepatitis B virus; HCV = hepatitis C virus

[1] Randomization/Day 1 may occur any time after eligibility has been confirmed at Screening. The Home Treatment Period cannot begin until the triplicate ECG and adverse event assessments are evaluated from Visit 2.

[2] Patients will be asked to enter responses into the ePD daily during the Home Treatment Period to ensure the device is charged and working.

[3] Conducted upon return to clinic and prior to pre-test Study Medication administration only

[4] Brief Physical exam will be symptom directed prior to patient discharge from the clinic

[5] Serum pregnancy test only for females of childbearing potential

[6] Includes hematology, serum chemistry, and urinalysis performed by the central lab.

[7] ECG in triplicate at pre-dose and 2, 30, 60, 90, and 120 min post dosing with Study Medication

[8] Study medication should be administered as closely as possible to start of vomiting; once per day up to 5 consecutive daily doses can be administered as long as the patient is still experiencing the same CVS episode

[9] Includes separate scales for abdominal pain, nausea, and anxiety/panic

7.6 Procedures for Protocol

The following sections provide details regarding the procedures to be performed at each study visit. All of the following assessments should be made according to the Schedule of Events (Table 1).

7.6.1 Visit 1: Screening Visit

Patients will report to the clinical site for a screening examination between Day -14 and Day -1 and the patient and clinical staff will follow all appropriate COVID-19 safety procedures.

Prior to performing any study-related activities or evaluations, the patient must be thoroughly informed about all aspects of the study and sign the Informed Consent Form (ICF). Patients will sign the study-specific consent form prior to any screening procedure. A signed copy of the ICF should be provided to each consenting patient and with the original to be retained in the patient's study records.

For all study procedures, see the Schedule of Events (Table 1). The following information and procedures will be performed and documented as part of the Screening assessment:

- COVID-19 testing.
- Assessment of eligibility according to inclusion/exclusion criteria.
- Demographics, including sex, ethnic origin, date of birth.
- Medical history (with emphasis on history of CVS noted above) including query for baseline signs/symptoms.
- Review of prior and ongoing concomitant medications (taken in previous 30 days).
- Complete physical examination plus height and weight.
- Vital signs measured with the subject in a seated position (for at least 2 minutes prior), including blood pressure, pulse rate, respiration rate, pulse oximetry, and temperature.
- Standard 12-lead ECG.
- Blood samples for routine clinical labs (clinical chemistry, hematology).
- Blood samples for serology (HIV, and hepatitis B and C evaluations).
- Urine samples for urinalysis and drugs of abuse screen.
- Alcohol breath test.
- Serum pregnancy test (females of childbearing potential only).

Compliance with inclusion criteria (listed in Section 8.1) and exclusion criteria (listed in Section 8.2) will be verified against information collected and documented in the case report form (eCRF).

Once all inclusion criteria are met, exclusion criteria ruled out, and laboratory measurements obtained and reviewed, consenting patients are eligible for randomization into the study.

7.6.2 Visit 2: Randomization and Pre-test Study Medication Administration

On arrival at the clinical site, all patients will follow the appropriate COVID-19 procedures and undergo the following assessments, which will be documented:

- COVID-19 testing.
- Confirmation of eligibility according to inclusion/exclusion criteria.
- Update of medical history including query for any pre-treatment adverse events.
- Concomitant medication use since the Screening visit.
- Physical examination plus weight.
- Vital signs measured with the subject in a seated position (for at least 2 minutes prior), including blood pressure, pulse rate, respiration rate, pulse oximetry, and temperature.
- Randomization and assignment of Patient Kit.
- *Staccato* device training.
- ePD instructions and training.

Upon determination of continued eligibility from above, the patient will undergo procedures to determine the safety and tolerability of their assigned (randomized) study medication. Patients will be instructed to take a pouch from their assigned Patient Kit, open it and self –administer the medication in the clinic. The patient should administer the dose while sitting or in a semi-supine position. They will be assessed and monitored pre-dose and following dosing for the next 2 hours as follows:

- 12-lead ECG in triplicate at pre-dose and 2, 30, 60, 90, and 120 min post dose
- Adverse Event assessment
- Brief Physical examination at 120 min post dose

Patients who meet all inclusion criteria and none of the exclusion criteria and have no clinically-significant observations or abnormalities on the ECG following administration of Study Medication (either 1 mg AZ-010, 3 mg AZ-010, or placebo) will be provided with their Patient Kit that contains 5 unused Staccato devices in addition to the 1 Staccato device that was used in the clinic.

7.6.3 Home Treatment Period

Randomized patients will be asked to treat a subsequent CVS episode within 12 weeks from the date that a patient receives their study medication for the Home Treatment Period. Enrolled patients will self-administer the study medication when they know their CVS episode is imminent or as soon as possible after a vomiting episode has begun. Patients will interact with their ePD CVS-related prior to initiation of treatment (if possible) and to capture the study data. The ePD will be used to record the date and time of study medication. Prior to dosing, the patient will engage the ePD to mark the dosing and onset of episode. If the patient has an episode that does not resolve within 1 day of dosing then they may administer another study medication for up to a total of 5 consecutive days. As soon as possible, they should contact the clinical site to inform them of the onset of the episode and treatment with study medication.

Patients will use the ePD and paper diaries to capture the study data. The ePD will be used to record the date and time of study medication administration, use of rescue medication, the number of vomiting and retching events at various time points, and the patient reported outcome measures (including the intensity and duration of the CVS episode, severity of abdominal pain, nausea, and anxiety/panic, and characteristics of the nausea, vomiting and retching over defined time periods). In order to keep the patient practiced in using the ePD over the possible 12-week period and to maintain charge of the device, the patient will be required to interact daily with the device. Full details will be provided with the ePD training. Patients will use paper diaries/logs to record additional details regarding the timing of vomiting/retching events, concomitant medication use, and adverse events.

Patients will be instructed to contact the Research Clinic at the earliest possible time after initiation of dosing and any time should they require rescue medication, medical assistance or experience an intolerable AE at home during the treatment period. Adverse events will be recorded separately by the patient in a paper diary. In the case of intolerable symptoms following study medication administration, the patient may take a rescue medication. Permitted rescue medications will not be provided to the patient, but it may include any agent(s) defined in the list in Section 9.8. Patients will record in their paper diary any medications taken during the Home Treatment period. Patients are encouraged to avoid rescue medication use for the first 2 hrs following treatment with the study medication. In the case of extreme distress, the patient should contact the clinical site and/or receive treatment from a health care facility.

Patients will be instructed to contact the study site when a CVS episode and dosing occurs (and study sites should try to contact a patient when they receive a notification that that patient has dosed) so that the study site may schedule the Follow up Visit to the clinic within 3–5 days after the last dose of study medication is taken (or if the 12-week treatment period has expired and the patient has not yet treated a CVS episode). These latter patients will be excluded from the efficacy analyses since they did not take any study medication to treat a CVS episode.

If the number of vomiting and retching events are not recorded on the ePD or the 24 hour vomiting and retching questionnaire and the patient has unused study medication, that patient may be allowed to continue participation in the 12-week Home Treatment Period in order to treat a second CVS episode during this period.

7.6.4 Visit 3: Follow up and Termination

The following assessments will be performed and documented for all patients completing the study. If a patient discontinues from the study prematurely during the Home Treatment Period, they should complete all assessments according to the Schedule of Events (Table 1) summarized below, if possible. The reason for discontinuation must be fully documented in the subject's source documentation and in the database:

- Symptom directed (brief) physical examination plus weight.
- Vital signs measured with the subject in a seated position (for at least 2 minutes prior), including blood pressure, pulse rate, respiration rate, pulse oximetry, and temperature.
- Blood samples for routine clinical labs.
- Adverse events: Subjects will be instructed to report AEs during the study.
- Concomitant medications: All concomitant medications, including rescue medications, will be documented in the database.
- Standard 12-lead ECG
- Urine samples for urinalysis
- Serum pregnancy test (females of childbearing potential only)

Subjects may be discharged from the clinic when all final procedures have been completed.

8 SELECTION AND WITHDRAWAL OF PATIENTS

Patients eligible for enrollment in the study must meet all of the following inclusion criteria and none of the exclusion criteria.

8.1 Inclusion Criteria

1. Adult males and females between 18 and 60 years of age, inclusive at the time of signing the informed consent document.
2. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted.
3. Diagnosis of cyclic vomiting syndrome (CVS) using the Rome IV diagnostic criteria and must have:
   - Stereotypical episodes of acute onset vomiting lasting < 1 week;
   - At least 3 discrete episodes of vomiting in the prior year and 2 episodes in the past 6 months, occurring at least 1 week apart;
   - Absence of vomiting between episodes (but milder symptoms may be present);
   - Symptoms must be present for the past 3 months with onset at least 6 months prior
4. Has a prodrome or pre-emetic symptoms associated with approximately half of their "typical" CVS episodes
5. If of reproductive age, female participants and female partners of male participants, willing and able to use a medically highly effective form of birth control from at least 4 weeks prior to Baseline until at least 30 days following last dose of study drug. Examples of medically highly effective forms of birth control are:
   - Surgical sterility (hysterectomy or bilateral ligation) or post-menopausal (cessation of menses for at least 12 months prior to screening)
   - Sexual partner is sterile, or of the same sex
   - Implants of levonorgestrel in females
   - Oral contraceptive (combined, patch, vaginal ring, injectable, implant) in females
   - Double-barrier method (any combination of physical and chemical methods)
   - Intrauterine device with a failure rate less than 1% per year
6. Male participants must:
   - Agree to use, with their partners, one of the highly effective contraceptive methods listed in Inclusion Criterion 5, from Baseline until at least 30 days following last dose of study drug.
   - Refrain from donating sperm during the study and for at least 30 days after the end of the study.

7. Otherwise healthy, as determined by the responsible physician, based on a medical evaluation including history, physical examination, vital signs, electrocardiograms (ECGs) and laboratory tests assessed at the screening visit.
8. Negative urine tests for selected drugs of abuse and alcohol breath test at Screening.

   Note: Patients with a positive urine drug screen for benzodiazepines or opioids may be allowed in the study provided the drug was prescribed by a physician.
9. Willing and able to adhere to overall study visit schedule, procedures and other protocol requirements.

8.2 Exclusion Criteria

1. Any significant medical or psychiatric condition that could, in the Investigator's opinion, compromise the subject's safety or interfere with the completion of this protocol.
2. Any condition, including the presence of laboratory abnormalities or pulmonary condition, which according to the Investigator places the subject at unacceptable risk if he/she were to participate in the study.
3. A diagnosis of any gastrointestinal disorder other than CVS that in the judgement of the Investigator could compromise the subject's safety or interfere with the interpretation of safety or efficacy data.
4. Current history of clinically significant central nervous system (e.g., seizures), cardiac, pulmonary (e.g., asthma, COPD), metabolic, renal, or hepatic conditions.
5. Use of drugs known to prolong the QTc interval with known risk of Torsade de Pointes. ECG findings of QTcF interval > 450 msec for men and > 470 msec for women obtained at screening visit or prior to the first dose of study drug.
6. Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), serum creatinine, or total bilirubin > 1.5 upper limit of normal (ULN) at screening or prior to the first dose of study drug. These laboratory tests may be repeated once, if they are abnormal on first screening, and if there is a medical reason to believe the results may be inaccurate. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not compromise the subject's safety and will not interfere with the interpretation of safety data.
7. Positive blood screen for human immunodeficiency virus (HIV antibody), hepatitis B virus surface antigen, or hepatitis C virus antibody at screening.
8. History of alcohol or illicit drug abuse within 1 year before the first dose of study drug.
9. Daily use of marijuana.

   Note: Occasional use of THC/cannabinoid products is allowed in the study
10. Participation in a clinical trial and receipt of an investigational medication or a new chemical entity within 90 days, 5 half-lives, if known, or twice the duration of the biological effect of any medication (whichever is longer) prior to the first dose of current study drug.

11. Donation of blood, plasma or other blood products or blood collection in excess of 470 mL within 8 weeks prior to dosing.
12. Known history of sensitivity to any of the study drugs or components thereof, or to other 5-HT3 receptor antagonists, or a history of medication allergy or other allergy that, in the opinion of the Investigator, contraindicates study participation.
13. Major surgery within 4 weeks of screening that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the Investigator.
14. Uncontrolled current illness (i.e., active infection).
15. Has a current or a history of cancer, with the exception of basal cell carcinoma.

8.3 Patient Withdrawal Criteria

All patients are free to withdraw from participation in the study at any time, for any reason, and without prejudice. The Investigator must withdraw any patient from the study if the patient requests to stop participating in the study. The Investigator, Sponsor, or its designee may remove a patient from the study at any time and for any reason.

Patients who withdraw or are withdrawn from the study will not be replaced.

8.3.1 Patient Withdrawal Procedures

A patient who prematurely discontinues study participation should have all Visit 3 assessments performed as an Early Termination Visit, (See Table 1).

If a patient terminates early from the study, the Investigator will record the reason(s) for early termination on the relevant electronic case report form (eCRF). The specific reason for the withdrawal should be carefully documented on the eCRF.

8.4 Emergency Unblinding of Treatment Assignment

In the case of a medical requirement to break the blind to determine appropriate treatment for an adverse event, unblinding of a patient's treatment assignment can be achieved through the study-specific Interactive Web Response System. If possible, the Investigator should discuss the circumstances with the Medical Monitor(s) prior to accessing unblinding information. In the event of a blind break, the Medical Monitor(s) will be notified through the electronic data capture system. The patient for whom the blind is broken should be subsequently withdrawn from the study. The details regarding the process of breaking the blind are outlined in the Medical Monitoring Plan.

8.5 Individual or Study Stopping Criteria

1. Individual Stopping Criteria

Patients experiencing a CTCAE Grade 3 or higher AE may be discontinued from the trial regardless of the assessment of attribution to the study drug (eg, potential relatedness) following review by the PI and Medical Monitor.

2. Study Stopping Criteria

The study should be stopped and the data reviewed if 2 or more patients develop the same CTCAE Grade 3 event or 1 patient develops a CTCAE Grade 4 or higher event.

Any termination required by the Sponsor must be implemented by the Investigator, if instructed to do so, in a time frame that is compatible with the patient's well-being.

9 DESCRIPTION OF STUDY TREATMENT

9.1 Description of Investigational Products (Study Medication)

Study Medication will be administered once per day for up to 5 days.

Study Medication

	Study Medication	
Product Name:	AZ-010	*Staccato* Placebo
Dose/Dosage Form:	1 mg and 3 mg *Staccato*	No active drug *Staccato*
Route of Administration:	Oral inhalation	Oral inhalation
Physical Description:	White plastic *Staccato* device	Matching white plastic *Staccato* device

9.2 Dose-Adjustment Criteria

No individualized dose adjustment is allowed during the study.

9.3 Packaging and Labeling

AZ-010 and *Staccato* placebo devices will be packaged inside a sealed foil pouch. Each patient will receive a kit containing 6 blinded study devices.

The label(s) for the study medication and placebo will include Sponsor name and address, the protocol number, investigational product name, dosage form, storage conditions, and required caution statements and/or regulatory statements, as applicable. Additional information may be included on the label as applicable per local regulations.

Adequate supplies of study medication will be provided to each site by the sponsor or designee. Study medication should be stored as stated on the product label, in a secure, temperature-monitored, locked area, under the responsibility of the Investigator or other authorized individual until dispensed to the patients.

Study medication dispensed to patients should be stored in the original sealed foil pouch at room temperature as stated on the package label. No special handling procedures are required.

9.4 Investigational Product Accountability and Disposal

To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. The clinical site must maintain accurate records of the receipt of all study drug, including date received, lot number, expiration date if applicable, amount received, condition of the package, and the disposition of all study drug.

Current dispensing records will also be maintained, including the date and amount of medication dispensed and the identity of the subject receiving the medication. Any device used by the

patient at home should be returned to the foil pouch from which it came and returned to the clinical site and held until the study monitor has completed product accountability.

9.5 Study Medication Preparation

Study Medication will be packaged and labeled by a vendor selected by the Sponsor and dispensed to the site for distribution to the patients. Patients will be instructed in the use of the Staccato device at the clinical research center. Instructions for use will be provided to the patient for home use.

9.6 Investigational Product Compliance

All investigational products used in this study will be monitored for compliant usage throughout the trial by Alexza or their designee. All *Staccato* devices not used in the study must be returned to the Sponsor facility after the study is completed.

9.7 Concomitant Medications and Procedures

Medications, including over the counter therapies (e.g., vitamins, herbal and nutritional supplements), taken during the At-Home Treatment Period dosing should be recorded.

Medications indicated for treatment of AEs will be permitted during the study if they are not interfering with study outcomes or subject safety in the opinion of the Investigator, and if they do not fall under the list of prohibited medications. Their use must be documented in the subject's eCRF. Any medication taken as a rescue medication following dosing with study medication must be recorded with time and dose in the ePD (patient's electronic diary).

9.8 Permitted Rescue Medications

The clinical site will discuss with the patient what they typically use to treat or abort their CVS episode. The site and the patient will agree in advance at Visit 2 what possible rescue medications will be used in the study. The PI will choose the rescue medication(s) consistent with the patient's preference and experience from the list below. Patients in distress and requiring the use of rescue medication should contact the clinical center prior to dosing if possible. Only anti-emetic medications, benzodiazepines, and triptans will be considered "rescue medications" for the purpose of characterizing participants who meet the responder endpoint.

Allowed rescue medications during emetic phase:

1. Anti-emetics: Prochlorperazine, Metoclopramide, or Aprepitant
2. Antihistamine: Diphenhydramine
3. Benzodiazepine: Lorazepam
4. Analgesics: Ibuprofen or Ketorolac
5. Gastric acid suppressants: Omeprazole or Ranitidine
6. Antimigraine: Sumatriptan, Zolmitriptan, and Frovatriptan

10 STUDY ASSESSMENTS AND PROCEDURES

All assessments and procedures will be performed according to the Schedule of Events (Table 1).

10.1 Demographic Characteristics and Medical History

Demographic characteristics [i.e., sex, ethnic origin, date of birth, and height and weight will be collected at the Screening Visit and detailed on the eCRF.

Prior to randomization. the patient's typical CVS episode will be classified by usual duration into one of the following two categories:

1. Typical episode of CVS lasts 24 hrs or less from the first vomiting/retching event;
2. Typical episode of CVS lasts greater than 24 hrs from the first vomiting/retching event.

A thorough medical history with particular reference to history of vomiting symptoms, CVS diagnosis, typical duration of CVS episode (hrs vs days), average number of vomiting/retching events in typical CVS episode, frequency of CVS episodes per year, any triggers for CVS episode, other GI conditions that may cause similar symptoms, treatment history, and current medications and co-morbidities will be collected at the Screening Visit and Randomization Visit for each dose group.

10.2 Vital Signs, Weight, and Height

Vital signs will be measured after the patient has been in a seated position for at least 2 minutes and will include blood pressure, pulse rate, respiratory rate, and temperature.

Patients should wear light clothing, empty pockets of heavy objects, and remove his/her shoes before weight is measured. Height will be measured after the patient has removed his/her shoes. Height will only be measured at the Screening Visit.

10.3 Physical Examination

A complete physical examination will include an examination of all major organ systems to include, but not be limited to, chest auscultation, abdominal auscultation and palpation, head, eyes, ears, nose and throat, and will exclude urinary and reproductive systems. A brief physical examination will be symptom directed.

10.4 Electrocardiogram

Twelve-lead electrocardiograms will be performed after the patient has rested in a supine or semi-supine position for at least 5 minutes. Individual parameters including heart rate, PR, QT, QTcF, QRS, and RR intervals will be collected. Repeat electrocardiograms (if deemed necessary) should be performed at least 5 minutes apart. The Investigator should indicate review of the electrocardiogram report by signing and dating the report. ECGs performed on Day 1 for pre-test assessment will be collected in triplicate for the pre-dose and post-dose collection times. The initial ECGs should be performed in a semi-supine position to accommodate appropriate dosing of the product.

10.5 Clinical Laboratory Assessments

The list of clinical laboratory assessments to be performed is included in the Appendix, Section 17.1. Specific days for clinical laboratory assessments can be found in the Schedule of Events (Table 1).

The results of clinical laboratory tests conducted at the Screening Visit must be assessed by the Investigator to determine each subject's eligibility for participation in the study. The Investigator should indicate review of the laboratory reports by adding their initials to the report.

Any significant abnormalities should be fully investigated. Whenever possible, the etiology of the abnormal findings will be documented. Laboratory results with significantly abnormal values should be investigated as such and checked for verification. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. In particular, if a clinically significant abnormal result is observed that is not resolved by the final study visit, repeat tests will be performed if possible and resolution or stability of the abnormality will be recorded in the source documentation.

Any significant laboratory abnormalities that are either serious or unexpected will be promptly reported to Alexza's Medical Monitor. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be reported to Alexza Pharmaceuticals or its representative.

10.6 24 Hour Vomiting and Retching Questionnaire

The 24 hour vomiting and retching questionnaire is a paper questionnaire on which patients will record the date of dosing with study medication and the total number vomiting and retching events that occurred within the first 24 hours after dosing. A vomiting or retching event is defined as one or more continuous episodes of vomiting (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents). If there is a break of at least 1 minute between vomiting and retching events, those should be considered two different events. In addition to the 24 hour vomiting and retching questionnaire, patients will record the number of vomiting and retching events that they experience within the first 30, 60, 90, and 120 minutes on the ePD.

10.7 Visual Analog Scale (VAS)

The visual analog scale is a scale of continuous measure initially developed for pain that has been used in a variety of clinical settings where the endpoint of interest is based on a subjective perception. The visual analog scale is a distinct 100-millimeter line anchored on the left end (0) at no degree of impairment and on the right end (100) at full degree of impairment, where indication of the degree of impairment perceived at the time of assessment is captured by marking the appropriate position on the line between the anchor points. The measured distance of the mark from the left anchor will be recorded in millimeters and this scale will be adapted for the ePD.

There will be 3 different VAS scales assessed in the study. In each case the patient will be asked to rate the appropriate variable in relation to their last vomiting/retching episode:

- The assessment of abdominal pain whereby 0 = no pain and 100 = worst possible pain;
- The assessment of nausea whereby 0 = no nausea and 100 = worst possible nausea;
- The assessment of anxiety/panic whereby 0 = no anxiety/panic and 100 = worst possible anxiety/panic.

10.8 Rhodes Index of Nausea, Vomiting, and Retching (RINVR)

The RINVR is designed to assess the degree of nausea distress and vomiting distress in patients. It is composed of 8 questions and each question has 5 choices (see Appendix, Section 17.4). Questions 1, 4, 6, 7, and 8 deal with symptom occurrence and Questions 2, 3, 5 deal with degree of discomfort of the individual symptoms. Individual questions can be tracked over time or a composite score can be formed by adding the total of the symptom occurrence and degree of discomfort questions together. This scale will be adapted for the ePD and patients will be prompted to answer the questions according to the Schedule of Events (Table 1).

10.9 Intensity of Attack Scale

The Intensity of Attack scale is designed to assess the severity of the last vomiting/retching episode at the time of assessment. Severity ranges from Mild to Excruciating on a 4 point scale. This scale will be adapted for the ePD and patients will be prompted to answer the questions according to the Schedule of Events (Table 1).

10.10 Prior Episode Questionnaire

The Prior Episode Questionnaire is designed to compare the overall intensity and duration of the current CVS episode with CVS episodes that the patient has typically experienced in the past. For both Intensity and Duration, the patient will respond whether the current episode overall was Less than, the Same as, or Greater than their typical previous CVS episodes. The questions will be prompted approximately 24 hours after each dose of study medication is administered.

11 ADVERSE EVENTS

11.1 Definition of Adverse Events

An adverse event is any untoward medical occurrence that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an adverse event. A diagnosis or syndrome should be recorded on the adverse event page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

All patients will be monitored for adverse events during the study. Assessments may include monitoring of the following parameters: the patient's clinical symptoms, laboratory, physical examination findings, or findings from other tests and/or procedures.

An adverse event reported after informed consent, but before the first dose of study medication, will be considered a pretreatment adverse event (or interim medical event) and will be captured on the eCRF. Adverse events will be considered treatment-emergent if the onset is after the first dose of study drug.

An abnormal laboratory value is considered to be an adverse event if the abnormality:

- Is considered clinically significant; OR
- results in discontinuation from the study; OR
- is judged by the Investigator to be of significant clinical importance requiring treatment, modification/interruption of investigational product dose, or any other therapeutic intervention.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the adverse event eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the adverse event. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

11.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to seriousness, severity/intensity, and relationship to Study Medication, duration, action taken, and outcome.

11.2.1 Serious Adverse Event (SAE)

A serious adverse event is an adverse event, as per Title 21 CFR 312.32 and ICH E2A.II.B that fulfills the following criteria:

- Is fatal (results in death);
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the patient's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect; or
- Constitutes an important medical event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Events **not considered** to be serious adverse events are hospitalizations for:

- A procedure for protocol/disease-related investigations (e.g., sampling for laboratory tests). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- A procedure that is planned (i.e., planned prior to the starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable serious adverse event.
- An elective treatment of or an elective procedure for a pre-existing medical condition that does not worsen.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an adverse event is considered serious, the adverse event eCRF must be completed.

For each serious adverse event, the Investigator will provide information on severity, start and stop dates, relationship to investigational product, action taken regarding investigational product, and outcome.

Queries pertaining to serious adverse events will be handled through the electronic data capture system or other appropriate means. Urgent queries (e.g., missing causality assessment) may be handled by telephone.

11.2.2 Severity/Intensity

For both adverse events and serious adverse events, the Investigator must assess the severity/intensity of the event.

The National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 should be used to grade the severity/intensity of all events. These criteria will be provided in a study manual. If a CTCAE criterion does not exist, the Investigator should grade the severity according to the following criteria:

- Grade 1 (mild): does not interfere with the patient's usual function
- Grade 2 (moderate): interferes to some extent with patient's usual function
- Grade 3 (severe): interferes significantly with patient's usual function
- Grade 4 (life-threatening): results in a threat to life or in an incapacitating disability
- Grade 5 (death): results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3 Relationship to Study Medication

Relationship should be assessed and provided for every adverse event/serious adverse event based on currently available information. Relationship is to be reassessed and provided as additional information becomes available. Adverse events will be classified by the Investigator as follows:

Related for Regulatory Reporting Assessment:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The event resolves or improves upon withdrawal of drug (de-challenge). The event would be considered as definitely related to the Study Medication upon results of a positive re-challenge procedure.

Probably Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors that may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events) is unlikely, and the event follows a clinically reasonable response upon withdrawal of drug (de-challenge).

Possibly Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the Study Medication). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events).

Unrelated for Regulatory Reporting Assessment:

Unlikely Related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or concurrent or underlying disease provide plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).

Not related: The adverse event is completely independent of Study Medication administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

11.2.4 Duration

For all adverse events whether or not considered serious, the Investigator will provide a record of the start and stop dates of the event. Every effort should be made to resolve all adverse events with continued follow-up with the patient until appropriate resolution can be achieved. If an event is unresolved at the end of the study it will be recorded as ongoing.

11.2.5 Action Taken

The Investigator will record the action taken with investigational product as a result of an adverse event or serious adverse event on the eCRF, as applicable (e.g., discontinuation, or interruption of investigational product, as appropriate) and record if concomitant and/or additional treatments were given for the event.

11.2.6 Outcome

The Investigator will record the outcome of adverse events on the eCRF, as applicable (e.g., recovered, recovered with sequelae, not recovered, or death (due to the adverse event)).

11.3 Follow-Up

Adverse events assessed as not related to Study Medication, including clinically significant laboratory tests, ECGs, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

Adverse events assessed as related to Study Medication and serious adverse events will be followed for as long as necessary to adequately evaluate the patient's safety, or until the event stabilizes, is otherwise explained, death occurs, or the patient is lost to follow-up. If resolved, a resolution date should be provided. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the adverse event. This may include additional clinical laboratory testing or investigations, examinations, or consultation with other health care professionals as is practical.

11.4 Pregnancy

The Sponsor must be informed within 24 hours upon learning that a patient, or male patient's partner, has become pregnant any time after the first dose of Study Medication until 4 weeks after the last dose of Study Medication. Patient pregnancies (or pregnancy of a male patient's partner) must be followed until termination of pregnancy or the birth of the child.

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking the investigational product should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

11.5 Recording Adverse Events

All adverse events (regardless of seriousness or relationship to Study Medication) including those from the time informed consent is obtained through to the final study visit are to be recorded in the eCRF. Each individual adverse event is to be listed as a separate entry. The Investigator will provide information about dates of onset and resolution, seriousness, severity, action(s) taken, outcome, and relationship to the Study Medication. All adverse events should be documented in the patient's source documents.

11.6 Reporting Adverse Events

The Investigator must report to Sponsor or its designee all adverse events that occur during the study from the time written informed consent is given until the final study visit or early termination, regardless of their relationship to the Study Medication. Serious adverse events and pregnancies will be reported from the time written informed consent is given through 30 days beyond the last dose of Study Medication.

11.6.1 Reporting Serious Adverse Events

The Investigator is required to notify the Sponsor, and the Sponsor's designated Drug Safety Unit within 24 hours after becoming aware of the occurrence of a serious adverse event. All serious adverse events will be reported through completion of the adverse event eCRF. The Investigator will be responsible for reporting serious adverse events to the IRB.

Medical Monitor and Emergency Contact Information:

Dr. Lawrence Blob, Medical Director, Cognitive Research Corporation
200 Central Avenue, Suite 1230, St. Petersburg, FL33701
Phone: 410-262-1908
Fax: 727-897-9009
e-mail: lblob@cogres.com

If an Investigator becomes aware of a serious adverse event within 30 days after the last dose of Study Medication and it is considered by him/her to be caused by the Study Medication with a reasonable possibility, the event must be documented and reported through completion of the adverse event eCRF.

11.6.2 Reporting Urgent Safety Issues

If the study site staff becomes aware of an actual or potential urgent safety issue, then the Sponsor and Medical Monitor must be immediately contacted so that appropriate urgent safety measures can be agreed upon. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of patients participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include: (1) issues with an investigational drug or comparators; (2) study procedures; (3) intercurrent illness (including pandemic infections); (4) concomitant medications; (5) concurrent medical conditions; or (6) any other issues related to the safe conduct of the study or that pose a risk to study patients.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, the Investigators may take urgent safety measures before informing the Sponsor, but the Sponsor must be informed immediately after the hazard has resolved.

12 STATISTICAL ANALYSES

12.1 Overview

Full details for statistical methods will be provided in the Statistical Analysis Plan.

12.2 Interim Analysis

No formal statistical interim analysis is planned.

12.3 Determination of Sample Size

This is a proof of concept study. There are no studies in the literature to provide reliable estimates of active treatment or placebo response rates using vomiting/retching events, or the estimate of variances around these measures, in patients with CVS being treated acutely with an abortive therapy. Consequently, sample size was not based on power calculations. Approximately 150 patients will be randomized to 1 of 3 treatment groups. An N of 50 per group should be sufficient to describe and compare across the efficacy parameters.

12.4 Endpoints

12.4.1 Efficacy

Primary Efficacy Endpoint

- The number of vomiting/retching events in the 2 hours following treatment.

Secondary Endpoints

- The percentage of patients with no vomiting or retching events and no anti-emetic benzodiazepine, or triptan rescue medication use in the first 24 hours following treatment.
- The intensity of the vomiting/retching attack (Intensity of Attack Scale) at 2, 6, 12, and 24 hours following treatment.
- The Rhodes Index of nausea, vomiting, and retching (RINVR) at 6, 12, and 24 hours following treatment.
- The assessment of abdominal pain at 2, 6, 12, and 24 hours following treatment (VAS 1–100; 0 = no pain and 100 = worst possible pain).
- The assessment of nausea at 2, 6, 12, and 24 hours following treatment (VAS 1–100; 0 = no nausea and 100 = worst possible nausea).
- The assessment of anxiety/panic at 2, 6, 12, and 24 hours following treatment (VAS 1–100; 0 = no anxiety/panic and 100 = worst possible anxiety/panic).
- The duration of the CVS episode at 24 hours in relation to their typical CVS episodes (Prior Episode Questionnaire).

- The intensity of the CVS episode at 24 hours in relation to their typical CVS episodes (Prior Episode Questionnaire).
- Use of anti-emetic, benzodiazepine, or triptan rescue medication within the 24 hours following treatment with the study medication.
- Visit to urgent care, emergency department, or physician's office for care related to the treated episode of CVS within the 24 hours following treatment with the study medication.

12.4.2 Safety

Safety and tolerability of AZ-010 will be assessed by evaluating adverse events, vital signs, clinical laboratories, ECG results, as well as physical examinations.

12.5 Analysis Populations

The Efficacy Population will include all patients who receive study medication and treated at least 1 episode of vomiting/retching due to their CVS. The Safety Population will include all patients who receive study drug. Patients will be summarized according to study medication dose received (i.e., as treated) should it differ from the randomized arm.

12.6 Analyses

For the study, data will be summarized by dosing group (1 mg AZ-010, 3 mg AZ-010, placebo). All data for analysis will be listed by patient.

Continuous measures will be summarized descriptively (mean, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

12.6.1 Disposition and Baseline Characteristics

Disposition will be summarized by randomized dose group. The number and percentage of patients, who are randomized, treated, prematurely discontinued, and completers will be summarized.

Baseline characteristics will be summarized by dose group for patients participating in the Treatment Period.

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred term.

Concomitant medications will be summarized by World Health Organization Drug Dictionary for Anatomical-Therapeutic-Chemical classification and preferred term.

12.6.2 Efficacy

All efficacy tests will be described in detail in the Statistical Analysis Plan (SAP) The SAP will be finalized prior to database lock.

12.6.3 Safety

All safety summaries will be descriptive with no statistical hypothesis testing and based on the Safety Population. All safety endpoints will be listed in by-patient data listings.

Adverse events will be coded using MedDRA and summarized by system organ class and preferred term. Clinically significant deteriorations in physical examination findings will be reported and summarized as adverse events.

Laboratory values will be converted to the project-defined unit of measurement, as applicable, before analysis. Abnormal, clinically significant laboratory values will be reported and summarized as adverse events.

Adverse Events

An adverse event reported after informed consent, but before the first dose of study medication, will be considered a pre-treatment adverse event (or interim medical event). Treatment-emergent adverse events (TEAEs) will be defined as any adverse event that occurs after administration of the first dose of study medication until the Follow Up Visit or the Early Termination Visit. The number and percentage of patients who report TEAEs will be summarized by system organ class and preferred term.

Treatment emergent adverse events will also be summarized by intensity as well as relationship to study drug.

Patients who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to study medication when summarized by relationship. If a patient reports multiple preferred terms for a system organ class, the patient will be counted only once for that system organ class.

The number and percentage of patients who experience TEAEs will be summarized by dosing regimen for the following:

- By system organ class and preferred term
- By severity/intensity, system organ class, and preferred term
- By relationship to study drug, system organ class, and preferred term
- Serious adverse events by system organ class and preferred term
- Serious adverse events by relationship to study drug, system organ class, and preferred term

- Adverse events resulting in discontinuation of study medication by system organ class and preferred term
- Adverse events that result in study medication dose interruption by system organ class and preferred term

By-patient listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment.

Clinical Laboratory

Clinical laboratory tests (including re-check values if present) will be listed chronologically. 'H' and 'L', denoting values above or below the reference range (when present), will flag out-of-range results. At each time point, absolute values and change from baseline of the hematology and chemistry variables will be summarized by treatment and time with n, mean, SD, SEM, median, Min, and Max values. The categorical data of the urinalysis will be summarized by treatment and time in frequency tables by variable.

Vital Signs

The mean change from Baseline to each scheduled assessment will be summarized descriptively by dose group for each vital sign variable specified in this protocol. Baseline will be defined as the last vital sign value obtained on Visit 2 and prior to any study medication administration.

Electrocardiogram

The change from Baseline in electrocardiogram intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by dose group. Baseline will be defined as the last ECG obtained on Visit 2 and prior to any study medication administration. The number and percentage of patients who have a clinically notable ECG interval abnormality or other clinically significant ECG finding will be summarized. A listing of abnormal ECG values will also be provided.

12.6.4 Concomitant Medications

All concomitant medications will be displayed in a listing.

13 REGULATORY CONSIDERATIONS

It is the responsibility of the clinical site and staff to notify the Sponsor and Sponsor's designee immediately upon becoming aware of a serious breach of GCP or of the study protocol. It is the responsibility of the Sponsor or its designee to notify appropriate regulatory authorities of any serious breach which is likely to effect, to a significant degree, the safety or mental integrity of the patients of the study or the scientific value of the study.

13.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from the IRB prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2 Sponsor's Responsibilities

The Sponsor or its designee is responsible for the following:

- Selecting qualified Investigators
- Providing Investigators with the information they need to properly conduct an investigation
- Ensuring proper monitoring of the investigation
- Ensuring that the applicable regulatory authorities, and all participating Investigators are properly informed of significant new information regarding adverse events or risks associated with the medication being studied

If required by standard operating procedures, a representative of the Sponsor may visit the investigational study site before entering a patient into the study to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from Alexza Pharmaceuticals or its representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations.
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to the Sponsor and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

As the Sponsor, Alexza Pharmaceuticals has delegated some responsibilities to a designee, or Contract Research Organization.

13.3 Investigator's Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Each Investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the Study Medication, and their study-related duties and functions. The Principal Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible from conducting or working on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Alexza Pharmaceuticals. The Investigator is required to immediately disclose to the Sponsor in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by the FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator's knowledge) threatened.

The Investigator is responsible for keeping a record of all patients who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient's source documents.

The Investigator should inform the IRB of any event likely to affect the safety of patients or the continued conduct of the study, in particular any change in safety. Additionally, all updates to the Investigator's Brochure will be sent to the IRB. A progress report will be sent to the IRB and the

protocol will be reviewed annually (e.g., re-approved) or more frequently, as required by the IRB or local regulations.

The Investigator will maintain a copy of all correspondence with the IRB, including copies of approved documents. The Investigator will also maintain a copy of the IRB membership list with occupation and qualification (or a statement confirming compliance with GCP requirements for committee composition).

The Investigator will notify the IRB of the conclusion of the clinical study within 1 month of completion or termination of the study. The final report sent to the IRB will also be sent to the Sponsor along with the completed electronic case report forms (eCRFs) and all necessary regulatory documents, thereby fulfilling the Investigator's regulatory responsibility.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to patient records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

13.4 Protocol Amendments

Any change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. All amendments to the protocol will be written by the Sponsor. Except for deviations that are necessary to protect the health or safety of the participants, Investigators must await IRB approval of protocol amendments before deviating from an IRB-approved protocol. A protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately, and the IRB notified within 5 days. The Sponsor will ensure submission of any protocol amendments to the appropriate regulatory agencies.

When the amendment to the protocol substantially alters the study design and/or increases the potential risk to the patient, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained from patients enrolled in the study before continued participation under the new amendment.

13.5 Audits and Inspections

The Sponsor's Quality Assurance Unit (or representative) may conduct audits at the study site(s). Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of eCRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by Sponsor, its representatives, or any appropriate regulatory agencies.

13.6 Quality Control and Quality Assurance

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

A quality control and quality assurance plan addressing aspects of the study that may impact data integrity or the protection of human subjects may be instituted for this study. All audit findings will be summarized and placed on file with appropriate

14 DATA HANDLING AND RECORDKEEPING

14.1 Confidentiality

All information disclosed or provided by the Sponsor (or designee), or generated or produced during the study including, but not limited to, the protocol, the eCRFs, the Investigator's Brochure, and the results obtained during the course of the study, are confidential. The Investigator or any person under his/her authority agrees to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

Submission of this protocol and any other necessary documentation to the IRB is expressly permitted, IRB members having the same obligation of confidentiality. Authorized regulatory officials and Sponsor personnel (or designee) will be allowed full access to inspect and copy the records. The copied and inspected records will remain at the site and will not be transmitted or removed from the site. Study Medication, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor and responsible ethics committee(s) or regulatory authorities.

Patients' names may, however, be made known to a regulatory agency or other authorized officials in the event of inspections. Documents containing the full name or other personally identifiable information of the patient are to remain at the site. This information will not be transferred to the Sponsor nor be contained in regulatory filings.

14.2 Patient Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., protected health information authorization).

Patients will be identified only by unique patient numbers in eCRFs and other datasets generated for this study. The patient will not be identified by name in the eCRF, in any study samples or study reports. All data generated in this study is for research purposes only. The Sponsor, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

The Sponsor will protect individual patient information to the fullest extent possible during this study. At no time will a patient become identified in any publication or presentation. However, the patient may have to become identified in the event of a regulatory authority audit or inspection in order to verify the accuracy of the data. Access to patient information is at the discretion of the Sponsor and cannot occur prior to database lock or other specified events as determined solely by the discretion of the Sponsor.

14.3 Data Collection

All data obtained for analysis in the clinical study described in this protocol will use an electronic data capture system. Data reported in the eCRFs should be consistent with and substantiated by the patient's medical record and original source documents. Any discrepancies must be explained.

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on eCRFs.

14.4 Case Report Form Completion

Data within the eCRF will be monitored by a Clinical Research Associate according to the Monitoring Plan. Queries will be generated based on discrepancies found while monitoring. Site personnel will review and respond to these queries appropriately. Additionally, the Sponsor's designee and the Sponsor may periodically perform aggregate data reviews, which could result in queries being generated for site personnel resolution. The completed eCRF for each patient must be signed and dated by the Principal Investigator to signify that the Principal Investigator has reviewed the eCRF and certifies it to be complete and accurate.

14.5 Database Management, Data Clarification, and Quality Assurance

The Sponsor's designee (i.e., a designated Contract Research Organization) will be responsible for data management. Data Management will develop a Data Management Plan (DMP) document, and provide it to the Sponsor for approval. The DMP document will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, data-flows, eCRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

The programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

Quality control procedures will be conducted prior to database lock according to the designated Contract Research Organization standard operating procedures.

When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time will only be made by joint written agreement between the Sponsor, Statistician, Data Manager, and Quality Assurance Auditor according to designated standard operating procedures of the Contract Research Organization.

14.6 Inspection of Records

According to the ICH guidelines for GCP, the Sponsor or designee must verify data entered in the eCRF entries against the source documents. The objective of source document verification is to comply with GCP and international regulatory requirements and to reduce the risks of fraud. Source document verification means ensuring that source documents are an accurate and confirmable reflection of the patient's evaluations during participation in the study and that all relevant information recorded in the source document is accurately entered into the eCRF. All source documents should be correctly labeled and filed and associated with a single, verifiable patient.

All data required for this study should be captured in source notes. No data obtained by the Investigator or other study personnel should be captured directly in the eCRF. All source

documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons. If electronic progress notes and other electronic source documents are not compliant with applicable regulatory guidance, they are not considered a valid source for this study. All patient progress notes must be dated and signed at the time of the visit. The Sponsor reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

The Investigator will note in a source independent from the eCRF the following information:

- Information to confirm that the patient exists (e.g., initials, date of birth, and sex);
- Confirmation that the patient satisfies the inclusion/exclusion criteria;
- Confirmation that the patient is taking part in the clinical study;
- Confirmation of the informed consent process;
- Visit dates and documentation of protocol assessments and procedures;
- Information concerning all adverse events;
- Details of concomitant and investigational medications.

Source document verification is not a substitute for clinical study monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the eCRF has been fully and accurately completed, source document verification has been carried out, and the study timelines and enrollment goals and requirements have been met.

14.7 Retention of Records

For investigational drug studies, clinical Investigators must retain study records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

The Investigator must maintain all study documentation as confidential, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must notify the Sponsor prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform the Sponsor. The relevant records shall be transferred to a mutually agreed upon designee.

15 PUBLICATION

All information concerning the product as well as any information such as clinical indications for the study drugs, their formula, their formulation, methods of manufacture and other scientific data relating to it, that have been provided by Alexza Pharmaceuticals or designee, and are unpublished, are confidential and must remain the sole property of Alexza Pharmaceuticals. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Alexza Pharmaceuticals is obtained. Alexza Pharmaceuticals has full ownership of the data collected as part of the study.

The results of this study will be published in a medical publication, journal, or another public dissemination, or may be presented at a medical conference or used for teaching purposes. Additionally, this study and its results will be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by Alexza Pharmaceuticals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

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17 APPENDICES

17.1 Laboratory Assessments

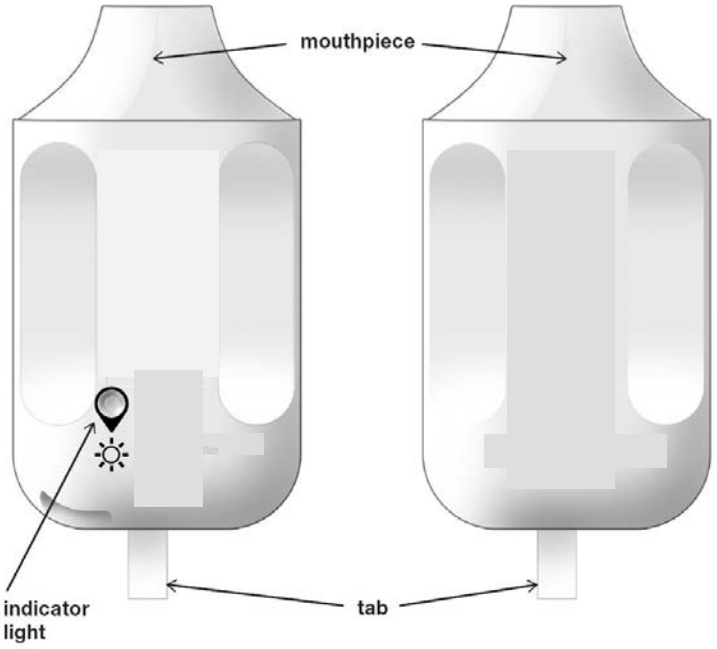
HEMATOLOGY	**CLINICAL CHEMISTRY**	**URINALYSIS**
Haemoglobin [including Mean Corpuscular volume (MCV), Mean corpuscular haemoglobin (MCH), Mean corpuscular haemoglobin concentration (MCHC)], haematocrit, red cell count (RBC), total white cell count (WBC) and Differential blood count, including: basophils, eosinophils, neutrophils, lymphocytes, and monocytes. Platelet count.	Alanine aminotransaminase (ALT; SGPT) Albumin (ALB) Alkaline phosphatase (ALK-P) Aspartate aminotransaminase (AST; SGOT) Total bilirubin Conjugated bilirubin Blood urea nitrogen (BUN) Calcium (Ca) Chloride (Cl) Total cholesterol Creatinine Gamma-glutamyl transferase (GGT) Lactic dehydrogenase (LDH) Total protein Inorganic phosphate (P) Potassium (K) Sodium (Na) Uric Acid	Bilirubin Glucose Ketones Nitrates Occult Blood Protein Specific gravity Urobilinogen pH Leukocytes Microscopic urine analysis if dipstick is positive AND a physician classifies it as clinically significant.
DRUG SCREEN	**SEROLOGY (SCREENING ONLY)**	
Amphetamines (Urine) Barbiturates (Urine) Cocaine metabolites (Urine) Opiates (Urine) Benzodiazepines (Urine) Ethyl alcohol (Breath)	Human immunodeficiency virus antibody (HIV1+2-Ab) and antigen, Hepatitis B surface antigen (HBsAg) Hepatitis C virus antibody (HCV-Ab)	
PREGNANCY		
Serum Pregnancy testing		

17.2 *Staccato* Instructions for Use

Becoming Familiar with *Staccato*® for Inhalation

Read all instructions before use.

Staccato for Inhalation is a single dose, single-use inhaler for oral inhalation only. The pictures below show the features of *Staccato* for Inhalation:



The indicator light conveys important information about dose delivery:

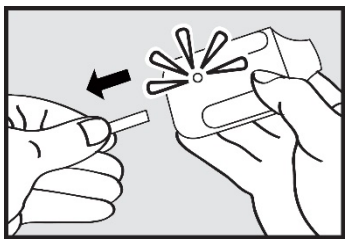
- The indicator light is off when *Staccato* for Inhalation is removed from the pouch.
- The indicator light turns on (green) when the tab is pulled out. The inhaler is then ready for use.
- The indicator light turns off after the patient inhales. This indicates the dose has been delivered.
- If the indicator light does NOT turn off, the dose has NOT been delivered. See Instructions for Use.

Staccato For Inhalation Instructions for Use

Read the following 6 steps before administering *Staccato* for Inhalation to a subject. Do not open the pouch until ready to use.

1. Open pouch

Tear open the foil pouch and remove the inhaler from the package.



2. Pull tab

Firmly pull the plastic tab from the rear of the inhaler.

IMPORTANT: Check that the green light turns on. This indicates that the inhaler is ready for use.

Use inhaler within 15 minutes after removing the tab or else the green light will turn off indicating the inhaler is not usable.

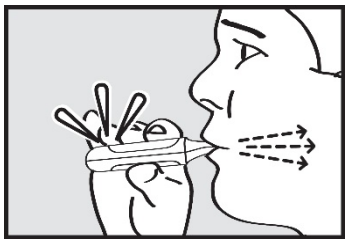
3. Explain Procedures to Subject

Explain the administration procedures to the subject prior to use and let patients know it is important to follow the instructions. Advise subjects that the inhaler may produce a flash of light or a clicking sound, or become warm during use. These are normal.

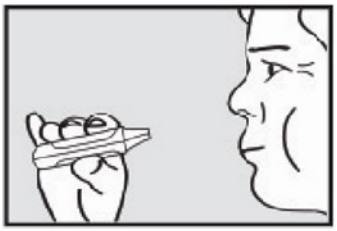
Instruct the Subject to:

4. Inhale

Inhale through the mouthpiece with a steady deep breath.



IMPORTANT: Check that the green light turns off after the patient inhales. The light will turn off indicating that the dose has been delivered.



5. Hold breath

Remove the mouthpiece from the mouth and hold breath for as long as possible, up to 10 seconds.

Important: If the green light stays on after the subject inhales, the dose has NOT been delivered. Instruct the subject to repeat steps 4, and 5 up to 2 additional times.

If the green light still does not turn off, discard the inhaler and use a new one.

17.3 Rhodes Index of Nausea, Vomiting and Retching

(Sample, NOT to be used in trial)

NOTE:

For 6 hr assessment the reference should be "in the last 4 hours…"; for 12 hr assessment the reference should be "in the last 6 hours…", for the 24 hr assessment the reference will be as shown below

Instructions:

Please mark the box for each question that most clearly corresponds to your experience. Please do not miss out a question and place only one **X** in a box for each question. *e.g.* ☒ The ____ in statements represents the selected phrase.

1. In the last 12 hours I threw up ____ times:

- 7 or more ☐
- 5-6 ☐
- 3-4 ☐
- 1-2 ☐
- I did not throw up ☐

2. In the last 12 hours, from retching and dry heaves, I have felt ____ distress:

- no ☐
- mild ☐
- moderate ☐
- great ☐
- severe ☐

3. In the last 12 hours, from vomiting or throwing up, I have felt ____ distress:

- severe ☐
- great ☐
- moderate ☐
- mild ☐
- no ☐

4. In the last 12 hours, I have felt nauseated or sick to my stomach:

- not at all ☐
- 1 hour or less ☐
- 2-3 hours ☐
- 4-6 hours ☐
- more than 6 hours ☐

5. In the last 12 hours, from nausea/sickness to my stomach, I have felt ____ distress:

- no ☐
- mild ☐
- moderate ☐
- great ☐
- severe ☐

6. In the last 12 hours, each time I threw up I produced a ____ amount:

- very large (3 cups or more) ☐
- large (2-3 cups) ☐
- moderate (1/2-2 cups) ☐
- small (up to 1/2 cup) ☐
- I did not throw up ☐

7. In the last 12 hours, I have felt nauseated or sick to my stomach ____ times:

- 7 or more ☐
- 5-6 ☐
- 3-4 ☐
- 1-2 ☐
- no ☐

8. In the last 12 hours, I have had periods of retching or dry heaves without bringing anything up ____ times:

- no ☐
- 1-2 ☐
- 3-4 ☐
- 5-6 ☐
- 7 or more ☐

17.4 Intensity of Attack Scale

Rate the Intensity of your last vomiting/retching episode:

1. Mild
2. Moderate
3. Severe
4. Excruciating

17.5 VAS Scales

17.5.1 Abdominal Pain VAS

Place a vertical line reflecting the *Abdominal Pain* associated with your last vomiting/retching episode

No Pain (0) ----------(100) Worst Possible Pain

17.5.2 Nausea VAS

Place a vertical line reflecting *the Nausea* associated with your last vomiting/retching episode

No Nausea (0) ----------(100) Worst Possible Nausea

17.5.3 Anxiety/Panic VAS

Place a vertical line reflecting *the Anxiety/Panic* associated with your last vomiting/retching episode

No Anxiety/Panic (0) ----------(100) Worst Possible Anxiety/Panic

17.6 Prior Episode Questionnaire

1. Compared to my "typical" CVS episode, the **Intensity** of this current CVS episode was:
    1. ***Less Intense*** than my "typical" CVS episode
    2. ***The Same Intensity*** as my "typical" CVS episode
    3. ***More Intense*** than my "typical" CVS episode

2. Compared to my "typical" CVS episode, the **Duration** of this current CVS episode was:
    1. ***Shorter*** than my "typical" CVS episode
    2. ***The Same Duration*** as my "typical" CVS episode
    3. ***Longer*** than my "typical" CVS episode

17.7 24 Hour Vomiting and Retching Questionnaire

AMDC-010-201
24 HOUR VOMITING AND RETCHING QUESTIONNAIRE

INVESTIGATOR:
SITE PHONE NUMBER:
SITE ADDRESS:
SUBJECT NUMBER:

INSTRUCTIONS: Please record the number of vomiting and retching events within 24 hours after you take a dose of study medication at home on this form. Record the date that you took a dose of study medication in the left column. Record the total number of vomiting or retching events in the 24 hours after taking that dose of study medication in the right column. If you take more than one dose of study medication on another day, record the date and number of events on the next row. If you have no vomiting or retching events in the 24 hours after dosing, write 0 in the right column.

Reminders:

- A vomiting or retching event is defined as one or more episodes of vomiting (expulsion of stomach contents through the mouth) or retching/dry heaves (an attempt to vomit that is not productive of stomach contents)
- If there is a break of at least 1 minute between vomiting and retching events, those should be considered two different events
- Please try to avoid taking any rescue medications (to treat nausea and vomiting) in the first 2 hours after dosing with study medication

Date I took a dose of study medication	Number of vomiting or retching events in the 24 hours after dosing
1.	
2.	
3.	
4.	
5.	