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A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis

Protocol: GAS-001

STATISTICAL ANALYSIS PLAN

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical/Therapeutic/Chemical
AUC	Area Under the Curve
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
bpm	Beats per minute
CI	Confidence Interval
CFB	Change from Baseline
CSR	Clinical Study Report
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EOT	End of treatment
GCSI	Gastroparesis Cardinal Symptom Index
GEBT	Gastric Emptying Breath Test
GM	Geometric Mean
ICH	International Council for Harmonisation
ICF	Informed Consent Form
kg	Kilograms
kg/m^2	Kilograms per meter squared
LSM	Least Squares Mean
MedDRA	Medical Dictionary For Regulatory Activities
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity
PRO	Patient reported outcomes
PT	Preferred term
QTcF	QT with Fredericia's correction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the framework for the summarization and analysis of the clinical data from the study, "A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis." Changes made to the SAP after it has been signed but prior to the unblinding of the study following database lock will be documented in a SAP amendment and/or the clinical study report (CSR).

2.0 STUDY DESIGN

Study GAS-001 is a Phase 2, randomized, double-blind, placebo-controlled pilot study of CNSA-001 (sepiapterin) powder for suspension administered 10 mg/kg twice a day orally in women with moderate to severe diabetic gastroparesis. This is an outpatient study in which up to 20 subjects will be enrolled at multiple centers. The study is comprised of five phases:

Screening Period (Day -28 Through Day 1 Predose)

An informed consent form (ICF) must be signed before any study-related procedures are performed. After providing consent, subjects will undergo Screening procedures to determine study eligibility, as indicated in the schedule of events (Appendix A). Subjects who are eligible based on Screening evaluations will undergo baseline evaluations before initiation of study drug (CNSA-001 or placebo), be randomized, and proceed to the Treatment Period.

Treatment Period (Day 1 Through Day 14)

Following the Screening Period and completion of baseline evaluations, all randomized subjects will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Subjects will undergo procedures during the Treatment Period as indicated in Appendix A.

Study drug may be prematurely discontinued for safety reasons. Subjects may also withdraw from the study for any reason. If a patient discontinues study drug early, the patient should return to the study site within 24 hours of withdrawal and complete all of the procedures outlined for the End of Treatment (EOT) (Appendix A). If a patient withdraws early from the study before undergoing EOT evaluations, the patient will be asked to return to the study site within 24 hours of withdrawal and complete all of the procedures outlined for the EOT (Appendix A). If a patient withdraws from the study before undergoing End of Study (EOS) evaluations, the patient will be asked to return to the study site within 24 hours of withdrawal and complete all of the procedures outlined for the EOS (Appendix A).

End of Treatment Period (Day 14 Through Day 15 Evaluations)

Subjects will undergo EOT evaluations on Day 14 and Day 15 as indicated in Appendix A. Preliminary efficacy will be assessed by the changes from baseline (Day 1) in the nutrient satiety on Day 14. The GCSI and the PAGI-SYM will also be administered on Day 14 (+1 day), and the GEBT will be conducted on Day 15.

End of Study Period (Day 15 After Evaluations Through Day 28 [±1 Day] Evaluations)

Subjects will undergo EOS evaluations on Day 28 (±1 day) as indicated in Appendix A. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 28. The GCSI and PAGI-SYM will also be administered on Day 28 ±1, and the GEBT will be conducted on Day 27 or Day 29.

Follow-up Period (Day 28 [±1 Day] After Evaluations Through Day 44 [±3 Days])

Subjects will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix A.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

Primary objectives:

The primary objective of this study is to assess the impact of CNSA-001 on gastric accommodation, as measured by nutrient satiety testing, in women with moderate to severe diabetic gastroparesis.

Secondary objectives:

The secondary objectives of this study are, in women with moderate to severe diabetic gastroparesis:

- To evaluate the effect of CNSA-001 on improvement of gastroparesis symptoms measured by the change from baseline in the global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]).
- To evaluate the effect of CNSA-001 on patient-reported outcomes (PROs) as measured by the change from baseline in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM)
- To evaluate the effect of CNSA-001 on emptying of the stomach, as measured by the change from baseline in the Gastric Emptying Breath Test (GEBT)
- To assess the safety and tolerability of CNSA-001 20 mg/kg/day

3.2 Study Endpoints

Primary Efficacy Endpoint:

- Changes in maximal tolerated volume consumed during the nutrient satiety test from Day 1 to Day 14 and Day 1 to Day 28.

Secondary Efficacy Endpoints include

- Observed maximal tolerated volume consumed during the nutrient satiety test
- Observed and changes from baseline through Day 14 (±1 day) and through Day 28 (±1 day) in the PAGI-SYM subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores
- Observed and changes from baseline through Day 14 (±1 day) and through Day 28 (±1 day) in the gastroparesis symptoms measured by global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI])
- Observed and changes from baseline through Day 14 (±1 day) and through Day 28 (±1 day) in the patient-reported outcomes (PROs) as measured by the quality of life questionnaire Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM)
- Observed and changes from baseline through Day 14 (±1 day) and through Day 28 (±1 day) in Gastric emptying, as measured by the Gastric Emptying Breath Test (GEBT)

The safety endpoints will be as follows:

- Observed and changes in hematology, chemistry, HbA1c, and urinalysis
- Observed and changes in vital signs
- Observed ECGs
- Observed and changes in Physical examination
- Severity and number of AEs and SAEs

3.3 Study Duration and Dates

The study duration for each patient will be up to 75 days, extending from Screening (Day -28 through Day -1) through the final assessments on Day 44 (±3 days). Duration of treatment will be 14 days.

4.0 ANALYSIS POPULATIONS

4.1 Randomized Population

The Randomized Population will include all randomized subjects. Subjects in the randomized population will be summarized based on the randomized study drug.

4.2 Safety Population

The Safety Population will consist of all subjects who received any amount of study drug (CNSA-001 or placebo).

visit.

5.0 STATISTICAL METHODS AND GENERAL CONSIDERATIONS

5.1 Sample Size

The primary objective of this study is to assess the impact of CNSA-001 on gastric accommodation, as measured by nutrient satiety testing, in women with moderate to severe diabetic gastroparesis. A total of 10 subjects will be enrolled in each treatment group. If it is assumed that the standard deviation for the change from baseline in nutrient meal volume ingested is approximately 235 mL (data on file) and using a one-sided t-test at the 0.025 significance level, this trial has 80% power to detect a treatment difference greater than 288 mL (i.e., an effect size of 1.23) in the CNSA-001group. The study also has 90% power to detect a treatment difference greater than 330 mL (i.e., an effect size of 1.41) in the CNSA-001 group.

5.2 Randomization and Masking

Subjects who fulfill the eligibility criteria and provide informed consent will be randomized in a ratio of 1:1 to the CNSA-001 or placebo group via the randomization scheme generated for the study. Subjects who are randomized will be considered enrolled.

As this is a double-blind study, blinding of the drug contents from the subjects, Investigator, and other study personnel at each site is necessary. The subject will be assigned with an identification number at Day 1 which will remain with the subject throughout the study.

5.3 Interim Analysis

No interim analyses are planned for this study.

5.4 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Baseline - A baseline value, unless specified otherwise, is the last non-missing value recorded prior to the first dose of study drug. If an assessment has both a date and time that exactly match the date and time of first dose of study drug, the assessment will be counted as baseline.
- Change from Baseline - Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus the baseline value.
- Study day – For a given date, study day is calculated as days since the date of first dose of study drug within the dosing cohort:
    - Study day = date – first dose date + 1, where date ≥ first dose date
    - Study day = date – first dose date, where date < first dose date
- Days – Durations, expressed in days, between one date (date1) and another later date (date2) are calculated using the following formula: duration in days = (date2 - date1 + 1).
- Body Mass Index (BMI) - BMI (kg/m^2) = weight (kg) / [[height (cm)/100]^2]
- Age will be computed from the informed consent date and birth date.
- Unless otherwise stated, when summation is based on the Safety Population, N = Number of subjects in the Safety population, n = Number of subjects in the specific category. Percentages are calculated as 100 x (n/N).

5.5 General Comments on the Statistical Analyses

- In general, the summary tables will be presented by treatment and Visit, as appropriate.
- Continuous variables will be summarized using number (n), mean, standard deviation (SD), median, minimum, and maximum.
- Frequency counts and percentages will be reported for all categorical data.

- All listings will be sorted by subject number and study day in ascending order. All relevant data captured on the electronic case report forms (eCRFs), including specific descriptions of 'other' and comments fields will be included on the listings.
- If a laboratory result is reported relative to a lower/upper range of detection for an assay, for example, "<10", the numeric portion of the result (10) will be used for statistical analyses and the full result, including any symbols, will be provided in the subject listings.
- Version 9.4 (or higher) of the SAS statistical software package will be used to provide all summaries, listings, figures and statistical analyses.
- The analyses described in this plan are considered a priori, in that they have been defined prior to unblinding of the study following database lock. Any analyses performed subsequent to unblinding will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

5.6 Handling of Missing Data

Missing data are handled as follows:

- Missing values for individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- Where individual data points are missing, categorical data will be summarized based on reduced denominators (i.e., only subjects with available data will be included in the denominators).
- All AEs with partial or missing dates and times will be considered treatment emergent unless a partial start date and/or time indicates the AE began prior to the start of study medication or a stop date indicates the AE ended prior to the start of study medication.
- All medications with partial or missing dates and times recorded on the concomitant medication eCRF will be considered concomitant unless a partial stop date and time clearly indicates it was stopped before the first dose of study treatment.

6.0 STATISTICAL ANALYSES

6.1 Subject Disposition

Subject disposition information will be summarized for all subjects by treatment using the Randomized Population. Summaries will include: the number of subjects in each population,

the number of subjects completing the study and the primary reason for premature discontinuation of study drug and the study.

A listing of all subjects who prematurely discontinued from study drug or study will be presented, and the primary reason for discontinuation provided.

6.2 Protocol Deviations

In accordance with International Council for Harmonisation (ICH) E3, Sponsor-defined eligibility violations and important post-randomization protocol deviations will be identified and listed.

6.3 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be presented for the Safety Population. A summary table will present the subject demographics (e.g., gender, age, ethnicity, race and diabetes mellitus type) and baseline characteristics of height (cm), weight (kg) and BMI (kg/m^2), collected prior to the administration of study drug.

A demographic listing will also be provided.

6.4 Medical History

Medical and surgical history collected at screening will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. Medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT) for the Safety Population. Subjects who report 2 or more medical and surgical history items that are coded to the same SOC and/or PT will be counted only once by the unique coded term in the summary.

A listing of disease-specific medical and surgical history will be provided.

6.5 Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and generic drug name using the World Health Organization (WHO) drug dictionary, enhanced March 2018.

Prior medications are those medications started prior to the start of study drug. Concomitant medications are those medications taken after the start of study drug. As such, medications

started before first dose of study drug and continued after the first dose of study drug are also considered concomitant medications.

Prior medications and concomitant medications will be summarized WHO ATC level 1 term, ATC level 3 term and generic drug name with the number and percentage of subjects. At each level of subject summarization, a subject is counted once if he/she reported one or more medications at that level. Each summary will be ordered alphabetically by each level of ATC class and generic drug name within each level of ATC class. The summaries of prior and concomitant medications will be provided for the Safety Population.

Prior and concomitant medications will also be listed.

6.6 Extent of Exposure and Study Drug Treatment Compliance

Compliance for each subject will be determined by the number of doses received, divided by the number of expected dosing relative to the subject's time on treatment. Descriptive statistics for the level of compliance (n, mean, SD, median, minimum, and maximum) with the number and percentage of subjects belonging to compliance categories (<80%, ≥ 80% and <120%, and ≥120%) will be provided by treatment group for the Safety Population.

Extent of exposure to study drug will be evaluated by summarizing each subject's total time of exposure in days.

A listing of the study drug administration dosing diary will be provided.

6.7 Nutrient Satiety Test

For the nutrient satiety test, subjects consume 150 mL of Ensure™ every 5 minutes. At 5-minute intervals, subjects score their fullness using a rating scale that combines verbal descriptors on a scale graded 0 to 5 (0: no symptoms, 1: first sensation of fullness [threshold], 2: mild, 3: moderate, 4: severe and 5: maximum or unbearable fullness). Subjects are told to stop when a score of 5 is obtained. The actual volume of Ensure™ consumed at this point is the maximum tolerated volume. Symptoms are measured 30 minutes after completing the test with subjects scoring each symptom of bloating, fullness, nausea and pain on a visual analogue scale with 100-mm lines and the words "unnoticeable" and "unbearable" as anchors.

Results from the visual analogue scale will be evaluated as percentages where the percentages will be calculated as the (VAS score)/(Scale length) *100.

The sum of the four percentages provides an aggregate symptom

score.

The nutrient satiety test will be administered in the clinic at Screening, on Day 1 (pre-dose), and on Day 14 and Day 28.

Using the Safety Population, the changes from baseline (Day 1) to Day 14 in maximal tolerated volume consumed during the nutrient satiety test will be compared between treatment groups using analysis of covariance (ANCOVA) with baseline tolerated volume as a covariate and treatment group as a factor. Other covariates such as site will be considered for inclusion. A similar analysis will be performed for the change from baseline to Day 28.

Summary statistics for the values at each visit and changes from baseline will be presented for the maximal tolerated volume, the aggregate symptom score, and the scores for each symptom (bloating, fullness, nausea, and pain).
All nutrient satiety scores will be listed.

6.8 Gastroparesis Cardinal Symptom Index

The GCSI consists of 9 items which are a subset of items from the PAGI-SYM instrument. The GCSI consists of 4 subscales: nausea/vomiting (Questions 1 to 3), Post-prandial fullness/early satiety (Questions 4 to 7) and bloating (Questions 8 and 9).
Each question is rated on a 5-point Likert scale (0 = None, 1 = Very Mild, 2 = Mild, 3 = Moderate, 4 = Severe and 5 = Very Severe). To obtain a patient-specific score on each subscale the scores on each question within the subscale will be summed for each subject and divided by the number of questions in the subscale. A GCSI total score will be similarly derived. The GCSI will be administered in the clinic on Day 1 (predose) and on Day 14 (+1 day), and Day 28 (±1 day). Using the Safety Population, summary statistics will be provided for each subscale and each time point. The change from baseline will be summarized for each of the subscales using summary statistics.

Using the Safety Population and for each subscale, the changes from baseline to Day 14 will be evaluated between treatment groups using ANCOVA with baseline as a covariate. Other covariates such as site will be considered for inclusion. A similar analysis will be performed for the change from baseline to Day 28. All GCSI subscale scores and total scores will be listed.

6.9 Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity

The PAGI-SYM is a 20-item upper GI symptom severity instrument with 6 subscales: nausea/vomiting (Questions 1 to 3), Post-prandial fullness/early satiety (Questions 4 to 7),

bloating (Questions 8 and 9), upper abdominal pain (Questions 10 and 11) and lower abdominal pain (Questions 12 and 13), heartburn/regurgitation (Questions 14 to 20). Each question is rated on a 5-point Likert scale (0 = None, 1 = Very Mild, 2 = Mild, 3 = Moderate, 4 = Severe and 5 = Very Severe). To obtain a patient-specific score on each subscale and the Total PAGI-SYM, the scores on each question within the subscale will be summed for each subject and divided by the number of questions in the subscale. The PAGI-SYM will be administered in the clinic on Day 1 (pre-dose) and on Day 14 (+1 day), and Day 28 (±1 day). Using the Safety Population, summary statistics will be provided for each subscale, Total PAGI-SYM and each time point. The change from baseline will be summarized using summary statistics.

Using the Safety Population and for each subscale and Total PAGI-SYM, the changes from baseline to Day 14 will be evaluated between treatment groups using ANCOVA with baseline as a covariate. Other covariates such as site will be considered for inclusion. A similar analysis will be performed for the change from baseline to Day 28 (±1 day).

All PAGI-SYM scores will be listed.

6.10 Gastric Emptying Breath Test (GEBT)

The GEBT is a nonradioactive non-invasive test, conducted over a four-hour evaluation period and is designed to show how rapidly the stomach empties solids by measuring carbon dioxide in a subject's breath.

The Cairn Gastric Emptying Breath Test (GEBT) measures the rate of CO^2 excretion after consumption of a C-enriched test meal. The subject's CO^2 excretion rate at any measurement time "t" is calculated and reported using the GEBT metric "kPCD." The acronym kPCD stands for "1000 X Percent Carbon-13 Dose (PCD) excreted per minute." A kPCD value is calculated at each measurement time and the calculations incorporate the subject's gender, age, height and weight.

The GEBT will be administered in the clinic on Day -1, Day 15, and Day 27 or Day 29 after the subject has fasted overnight (a minimum of 8 hours before test administration with the exception of 4 ounces of water up to 1 hour before the test). At the clinic, the subject provides baseline (premeal) breath samples and then consumes a standardized 230 kCal meal, Single post-meal breath samples are collected in capped glass tubes at 45, 90, 120, 150, 180, and 240 minutes after the meal is consumed. The GEBT kPCD value ($^{13}CO_2$ excretion rate) is proportional to the rate of gastric emptying. Increasing GEBT values represent

increasing rates of gastric emptying. Some subjects may have a GEBT in Screening as evidence of delayed gastric emptying.

Using the Safety Population, summary statistics of the GEBT kPCD values at each breath sample time will be provided along with the time matched change from baseline. In addition to individual plots, mean (SD) plots will also be provided. For each visit and timepoint the number and percentage of subjects with delayed gastric emptying will be determined.

All GEBT values will be listed.

GEBT area under the curve (AUC), maximum GEBT, time of maximum GEBT, and time to first normal gastric emptying will be derived, summarized and listed using the Safety Population. The GEBT AUC will be calculated for each visit using a linear up, linear down trapezoidal method. Maximum GEBT will be the maximum value within the 240 minute profile and will also be calculated for each visit. Change from baseline for each parameter will also be calculated, summarized and listed. For the parameters to be calculated, the subject must have a complete 240-minute profile.

Using the GEBT Parameter Population and for the parameters AUC and the maximum, the changes from baseline to Day 14 will be compared between treatment groups using ANCOVA with baseline GEBT as a covariate. Other covariates such as site will be considered for inclusion. The difference in least squares means and the associated 95% confidence interval will be provided A similar analysis will be performed for the change from baseline to Day 28 (±1 day).

6.11 Adverse Events

Adverse events will be coded to system organ class (SOC) and preferred term (PT) using MedDRA, version 21.0. The coding process will be described in the Data Management Plan.

Summaries will be provided for AEs, with the number and percentage of subjects reporting each type of event presented. If a subject reports the same preferred term more than once, it is counted only once within that category. Similarly, if a subject has AEs of two or more preferred terms under the same SOC, then that subject only counts once for that SOC.

Furthermore, for a given summary, the preferred term will only be counted once at its worst severity and strongest relationship to study drug.

Pre-treatment adverse events are defined as adverse events that have an onset on or after the date the informed consent was signed but prior to the time of the first dose of study drug.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened after the first dose of study drug.

The following summaries for TEAEs will be provided:

- An overall summary table of TEAEs summarizing the number and percent of subjects, in the following categories: any AE, any TEAE, TEAEs by highest severity, TEAEs by relationship to study drug, serious TEAE, TEAEs leading to premature discontinuation of study drug, TEAEs leading to premature discontinuation from the study, and TEAEs with a fatal outcome.
- Incidence of TEAEs by MedDRA SOC and PT.
- Incidence of TEAEs by MedDRA SOC, PT, and worst severity.
- Incidence of TEAEs by MedDRA SOC, PT, and strongest relationship to study drug.
- Incidence of serious TEAEs (SAEs) by MedDRA SOC and PT.
- Incidence of TEAEs (SAEs) Leading to Study Discontinuation by MedDRA SOC and PT.
- Listing of all AEs (with treatment-emergent events flagged)
- Listing of subjects with SAEs.

  Listing of all AEs for subjects who prematurely discontinued study drug due to an AE or discontinued from study due to an AE.

6.12 Clinical Laboratory Evaluations

Descriptive statistics for chemistry, hematology and (quantitative) urinalysis parameter values, as specified in Appendix B, and the change from baseline will be summarized for the Safety Population at each scheduled time points:

- End of Treatment visit (if there is early termination) or Day 14/Day 15 if subjects stay enrolled in the study.
- End of Study (Day 28 ±1 Day).

HbA1c values will be summarized similarly.

Change from baseline will be calculated for each subject at the specified visit as the value at the specified visit minus the baseline value.

Additionally, shifts from baseline at each post-baseline visit will be presented for hematology, chemistry, and HbA1c values based on the lab reference ranges for high, normal and low. Shifts are summarized by visit and maximum and minimum post baseline values.

A listing of hematology, chemistry, urinalysis, and HbA1c labs measurements will be provided. Baseline pregnancy test results (serum and urine) will also be listed.

6.13 ECG Parameters

ECGs will be recorded in triplicate at the Screening Visit, where each reading will be taken 1 minute apart. The mean of available triplicate values will be calculated and reported.

ECG parameters of RR interval, PR interval, QRS interval, QT interval, and QTcF interval will be summarized using descriptive statistics.

A listing of electrocardiogram data will also be provided and will include the tracing results of normal, abnormal and clinically significant status for these measurements.

6.14 Vital Signs

Systolic and diastolic blood pressures (mmHg), pulse rate (bpm), respiratory rate (breaths/minute), and temperature (^{o}C), will be summarized using descriptive statistics at all scheduled time points:

- Screening
- Baseline
- Day 1 two hours post-dose
- Day 14 (or Day 15)
- End of Study (Day 28 ±1 Day).

Descriptive statistics and changes from baseline to each post baseline time point will also be provided.

Vital signs results will also be presented in by-subject listings.

6.15 Physical Examinations

The number and percentage of subjects with normal, abnormal (not clinically significant) and abnormal (clinically significant) observations in physical examinations will be

summarized for the Safety Population separately for each body system at Baseline and each scheduled post-baseine visit.

Body systems to be included are: General appearance, Dermatologic, HEENT, Lymphatic, Cardiovascular, Respiratory, Gastrointestinal, Musculoskeletal, Neurological, and Other. Physical examination results will also be presented in by-subject listings.

7.0 CHANGES FROM PROTOCOL PLANNED ANALYSES

- Participants are referred to as ‘Subjects’ instead of ‘Patients’
- The Randomized Population was added.
- The definition of Safety Population removed the requirement of randomization.
- The Efficacy Population is removed and the Safety Population will be used for all efficacy analyses.
- The 95% confidence intervals are provided on the least squares treatment differences of the change from baseline instead of the change from baseline within a treatment group.
- VAS scores will be transformed into a percentage prior to analysis.

Appendix A: Schedule of Assessments and Procedures

Evaluation	Screening Period		Treatment Period		Follow-up Period			
					EOT		EOS	Telephone Follow-up
	-28 to -1	Day 1 (Predose)	Day 1 Through Day 13	Day 14[a]	Day 1 4[a]	Day 15	Day 28 (±1 Day)	Day 44 (±3 Days)
Informed consent	X							
Confirm inclusion/exclusion criteria eligibility	X							
Randomization	X[b]							
Demographics	X							
Medical history[c]	X	X						
Vital signs, weight, and height[d]	X	X	X		X		X	
Physical examination[e]	X	X			X		X	
Clinical laboratory tests[f]	X	X			X		X	
HbA1c[g]	X				X		X	
Serum/urine pregnancy test[h]	X	X			X		X	
ECG[i]	X							
Prior/concomitant medications[j]	X	X	X	X	X		X	
AEs[k]	X	X	X	X	X		X	X[l]
Nutrient satiety test[m]	X[n]	X			X		X	
GCSI[o]	X[p]	X			X		X	
PAGI-SYM[q]		X			X		X	
GEBT[r]	X[w]					X	X	
GES	X[w]							
Dispense study drug			X					
Dispense dosing diary			X[s]					
Study drug dosing[t]			X[u]	X				
Collect study drug, dosing diary, assess compliance					X[v]	X[v]	X[v]	

[a] Study Day 14 is included both in the Treatment Period and EOT.

[b] Randomize subject on Day -1.

[c] Includes specific information related to any prior or existing medical conditions or surgical procedures involving the following systems: dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological.

[d] Includes blood pressure, pulse, respiratory rate, and temperature. Obtain vital signs before collection of any laboratory samples and after subjects have rested for 5 minutes in a supine position. Obtain vital signs both predose and 2 hours postdose on Day 1; for all other timepoints, obtain at any time during the indicated visits. Obtain height only at Screening. Obtain weight at Screening to determine response to Exclusion Criterion #5 (Section 4.3) and on Day -1 (Section 6.3).

[e] Conduct a complete physical examination of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters.

[f] Includes clinical chemistry panel (ALB, AP, ALT, AST, BUN, Ca, CO_2, Cl, creatinine, GGT, glucose, LDH, phosphorus, K, Na, total bilirubin, direct bilirubin, total cholesterol, total protein, uric acid); hematology panel (HCT, HGB, platelet count, RBC count, WBC count, and WBC differential); and urinalysis (bilirubin, glucose, ketones, occult blood, pH, protein, specific gravity, urobilinogen and microscopic examination of WBC, RBC, and epithelial cells). Subjectss will fast overnight before blood sample collections.

[g] Subjects will fast overnight before blood sample collections.

[h] Serum and urine pregnancy tests required for all women of childbearing potential; serum testing is to occur during the Screening Period, and urine testing is to occur before dosing on Day 1 and at an EOT visit on Day 28 (±1 day). Any positive urine pregnancy test should be confirmed by a serum pregnancy test.

[i] Obtain 12-lead ECG recordings in triplicate with 1 minute separating the first and second and second and third recordings.

[j] Record all treatments and over-the-counter medications (including herbal medications) received from 30 days prior to Screening (to determine responses to Inclusion Criterion #9 [Section 4.2] and Exclusion Criteria #11 through #14 and #21 [Section 4.3] concerning medications) and through Day 28 ±1 day before the subject leaves the clinic after completion of all EOS evaluations.

[k] Collect AEs from the time of informed consent through Day 28 ±1 day before the subject leaves the clinic after completion of all EOS evaluations and SAEs from the time of informed consent through telephone Follow-up.

[l] Telephone Follow-up is to assess SAEs only.

[m] Administer the nutrient satiety test (Section 6.7) at Screening, on Day 1 (predose), and on Day 14 and Day 28 after overnight fasts and after any medications that can alter GI sensation or accommodation or gastric emptying have been held overnight.

[n] Administer the nutrient satiety test at Screening to determine the response to Inclusion Criterion #6 (Section 4.2)

[o] Administer the GCSI (Section 6.8, Appendix 2) at Screening, on Day 1 (predose), on Day 14 (+1 day) and on Day 28 (±1 day).

[p] Administer the GCSI (Section 6.8, Appendix 2) to determine response to Inclusion Criterion #5 (Section 4.2).

[q] Administer the PAGI-SYM (Section 6.9, Appendix 2) in the clinic on Day 1 (predose), on Day 14 (+1 day), and on Day 28 (±1 day).

[r] Administer the GEBT on Day -1, on Day 15, and on Day 27 or Day 29. For the GEBT (Section 6.10), subjects will fast overnight before the GEBT (a minimum of 8 hours before test administration with the exception of 4 ounces of water up to 1 hour before the test). Collect a premeal breath sample and then provide a standardized 230 kCal meal, consisting of a proprietary standardized ^{13}C-labeled egg component (which is rehydrated and then microwaved for 1.5 minutes) and 6 saltine crackers, accompanied by 6 ounces of water. Encourage the subject to consume the meal within 10 minutes. Collect single postmeal breath samples in capped glass tubes at 45, 90, 120, 150, 180, and 240 minutes after the meal is consumed and send the samples to the specified local laboratory for analysis.

[s] Dispense a dosing diary with instructions to record times all doses of study drug are taken.

[t] If a subject vomits after taking a dose of study drug, the subject should wait until the next scheduled timepoint to take another dose. A missed dose should be taken as soon as possible, but >2 doses should not be taken on the same day.

[u] Subjects will take their first doses of study drug (CNSA-001 or placebo) on Day 1 while in the clinic.

[v] Collect study drug, dosing diary, assess compliance on Day 14 if the subject takes the last dose of study drug on Day 14 while in the clinic or, if the subject takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day).

[w] GES or GEBT may be performed at Screening is historical confirmation of gastric emptying is >2 years prior to enrollment into the study.

Abbreviations: AE = adverse event; ALB = albumin; ALT = alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT]); AP = alkaline phosphatase; AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT]); BUN = blood urea nitrogen; ^{13}C = carbon-13; Ca = calcium; CO_2 = carbon dioxide; Cl = chloride; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; GCSI = Gastroparesis Cardinal Symptom Index; GES = Gastric Emptying Scintigraphy; GEBT = Gastric Emptying Breath Test; GI = gastrointestinal; GGT = gamma glutamyl transferase; HCT = hematocrit; HGB = hemoglobin; HEENT = head, eyes, ears, nose, and throat; HbA1c = glycosylated hemoglobin A1c; K = potassium; LDH = lactate dehydrogenase; Na = sodium; PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity; RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell.

Appendix B: Laboratory Testing Parameters

Hematology:

Hematocrit (HCT)
Hemoglobin (HGB)
Platelet count
Red blood cell (RBC) count
White blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)

Urinalysis:

Bilirubin
Glucose
Ketones
Occult blood
pH
Protein
Specific gravity
Urobilinogen
Microscopy:
- WBCs
- RBCs
- Epithelial cells

Serum Chemistry:

Albumin (ALB)
Alkaline phosphatase (AP)
Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT])
Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT])
Blood urea nitrogen (BUN)
Calcium (Ca)
Carbon dioxide (CO_2)
Chloride (Cl)
Creatinine
Gamma glutamyl transferase (GGT)
Glucose
Lactate dehydrogenase (LDH)
Phosphorus
Potassium (K)
Sodium (Na)
Total bilirubin
Direct bilirubin
Total cholesterol
Total protein
Uric acid

Other:

Glycosylated hemoglobin A1(HbA1c)