CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Study Phase:	2 Pilot
Product Name:	CNSA-001 (sepiapterin)
Dosage Form:	Oral powder for suspension
Indication:	Treatment of women with moderate to severe diabetic gastroparesis
Investigators:	Multicenter study
Sponsor:	Censa Pharmaceuticals 65 William Street Wellesley, MA 02481
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	06 September 2018

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

SPONSOR SIGNATURES

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Final Date:	06 September 2018

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed [redacted] Date: 6 SEP 2018

[redacted]
Censa Pharmaceuticals, Inc.

Signed [redacted] Date: September 5th 2018

Censa Pharmaceuticals

INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Final Date:	06 September 2018

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signature

Date (DD Month YYYY)

Printed Name, Credentials

Affiliation

Address

Phone Number

SYNOPSIS

Sponsor:
Censa Pharmaceuticals

Name of Finished Product:
CNSA-001

Name of Active Ingredient:
Sepiapterin

Name of Inactive Ingredients:
Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid

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

Study Number:
GAS-001

Study Phase: Phase 2 pilot

Primary Objective:

- 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:

In women with moderate to severe diabetic gastroparesis:

- To evaluate improvement of gastroparesis symptoms measured by global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]) (Section 6.8, Appendix 2)
- To evaluate patient-reported outcomes (PROs) as measured by the quality of life questionnaire Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) (Section 6.9, Appendix 2)
- To evaluate the emptying of the stomach as measured by the Gastric Emptying Breath Test (GEBT)
- To assess the safety and tolerability of CNSA-001 20 mg/kg/day

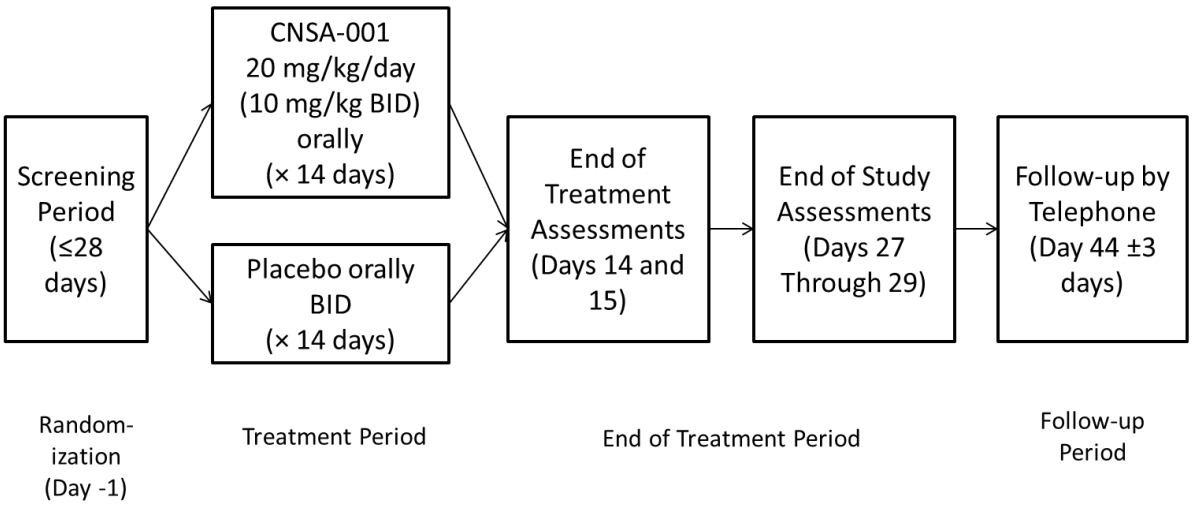
Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled pilot study of multiple doses of CNSA-001 (sepiapterin) powder for suspension administered orally in women with moderate to severe diabetic gastroparesis. Patients will be randomized in a ratio of 1:1 to receive CNSA-001 20 mg/kg/day or placebo, each dosed twice a day (BID); each group will consist of 10 patients. All patients will receive the standard of care for diabetic gastroparesis. Approximately 4 centers will participate in this study. The study design is summarized in the study schema below. A schedule of study events is provided in Appendix 1.

All study clinic visits will be outpatient visits.

Patients will continue their usual diet without modification throughout the study. Patients are required to have been fasting overnight for the following assessments:

- Clinical laboratory, including glycosylated hemoglobin A1c (HbA1c), tests
- The nutrient satiety test
- The GEBT



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, patients will undergo Screening procedures to determine study eligibility, as indicated in Appendix 1. Patients 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 patients will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Patients will undergo procedures during the Treatment Period as indicated in Appendix 1.

End of Treatment Period (Day 14 Through Day 15 Evaluations)
Patients will undergo End of Treatment (EOT) evaluations on Day 14 and Day 15 as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 14. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) 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)
Patients will undergo End of Study evaluations on Day 28 (±1 day) as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 28. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) 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])
Patients will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix 1.

Number of Patients:
Up to 20 women ≥18 and ≤65 years of age will be enrolled in this study and randomized in a ratio of 1:1 to receive CNSA-001 or placebo.

Main Criteria for Inclusion and Exclusion:
Patients are eligible to participate if they meet all the following inclusion criteria:

1. Informed consent
2. Females ≥18 and ≤65 years of age
3. Diagnosis of diabetes mellitus
4. Documentation of delayed gastric emptying on gastric emptying scintigraphy (within 1 year of enrollment)
5. Symptoms of gastroparesis for at least 6 months with GCSI (Section 6.8, Appendix 2) score >21 indicating moderate to severe symptoms
6. Gastric accommodation, as measured by nutrient satiety testing, of ≤600 mL
7. Negative upper endoscopy or upper gastrointestinal (GI) series within 3 years of enrollment (no evidence of mechanical obstruction or peptic ulcer disease)
8. Either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following:
   - Hormonal contraception (stable dose for 3 months)
   - Intrauterine device/Intrauterine Hormone-releasing System
   - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

   Patients who are abstinent will not be required to use a contraceptive method unless they become sexually active.
9. If on analgesics, including narcotics; promotility agents, including metoclopramide, or neuromodulators, including tricyclic antidepressants, gabapentin, and pregabalin, doses are stable for >30 days before randomization and the patient is not expected to require dose changes during the study through the EOT
10. Have not used tobacco (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks prior to Day 1 and willingness to abstain from these products during the study through the EOT

Patients are not eligible to participate if they meet any of the following exclusion criteria:

1. Male gender
2. Normal gastric emptying
3. Gastroparesis from postsurgical etiologies
4. Another active disorder that could, in the opinion of the Investigator, explain symptoms
5. Weight >100 kg
6. Alanine aminotransferase > 2× upper limit of normal (ULN)
7. Pregnant, breastfeeding, or considering pregnancy
8. Clinically significant cardiac arrhythmia at Screening
9. QT interval corrected for heart rate (QTc) ≥480 msec (based on triplicate measurements taken at Screening)
10. Recent clinically GI significant bleeding
11. Taking levodopa or domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT
12. Taking erythromycin within 30 days before randomization or expected to require erythromycin within 30 days before randomization or expected to require erythromycin during the study

through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization

13. Taking any fundic-relaxing agents including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT
14. Taking any systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)
15. Pulmonary dysfunction (e.g., chronic obstructive pulmonary disease)
16. Surgery for placement of a gastric stimulator within the past 6 months (patients postoperative >6 months with persistent symptoms and delayed gastric emptying are eligible)
17. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, small bowel malabsorption) that could affect the absorption of study drug or contraindicate undergoing the GEBT
18. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
19. History of allergies or adverse reactions to tetrahydrobiopterin or related compounds, to any excipients in the study drug formulation, or to egg, wheat, or algae (Spirulina)
20. Inability to tolerate oral medication
21. Current participation in any other investigational drug study or use of any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening
22. Any clinically significant laboratory abnormality; in general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range unless deemed not clinically significant by the Investigator
23. Major surgery within the previous 90 days
24. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study
25. History of alcohol or drug abuse within 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
26. Episodes of ketoacidosis or hypoglycemia that are frequent as defined by the Investigator
27. Any other conditions, including diabetic comorbidities, that, in the opinion of the Investigator or Sponsor, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

Test Product, Dose, and Mode of Administration:
The test product is CNSA-001 (sepiapterin) oral powder for suspension. CNSA-001 will be suspended in Medisca® Oral Mix prior to dispensing to the patient. Patients randomized to receive CNSA-001 will receive CNSA-001 20 mg/kg/day (i.e., 10 mg/kg BID) for 14 days.

Reference Therapy; Dose; and Mode of Administration:
The reference product is placebo. The placebo is a ready-made suspension containing microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, ascorbic acid, and colorant (Yellow No. 6) that is suspended in Medisca® Oral Mix.

Duration of Treatment:
Patients will be treated for a total of 14 days.

Criteria for Evaluation:

Safety:

Safety and tolerability of CNSA-001 as measured by severity and number of treatment-emergent adverse events (TEAEs), including assessment of severity of TEAEs, and changes in clinical laboratory and HbA1c tests, vital signs, and physical examinations

Efficacy:

The primary efficacy measure will be the change in maximal tolerated volume consumed during the nutrient satiety test from Day 1 to Day 14 and Day 1 to Day 28.

Secondary efficacy measures will consist of changes in the following from baseline to Day 14 and baseline to Day 28 (±1 day):

- GCSI (Section 6.8, Appendix 2) PAGI-SYM (Section 6.9, Appendix 2) subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores
- Gastric emptying as measured by the GEBT

Statistical Methods:

The following study populations will be analyzed:

- Safety population: all patients who were randomized and received any amount of study drug (CNSA-001 or placebo)
- Efficacy population: all patients who were randomized, received any amount of study drug (CNSA-001 or placebo), and had available Day 1 and Day 14 nutrient satiety test maximum tolerated volume results

Safety will be assessed in the Safety population. Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and treatment group. Severity of AEs and serious adverse events (SAEs) will be summarized similarly. Those AEs leading to premature discontinuation from the study drug and the serious TEAEs will be presented in a table or a listing. Clinical laboratory and HbA1c test results and vital signs will be summarized at each visit as will changes from baseline for each treatment group. A frequency distribution of abnormal physical examination results will be provided.

Efficacy will be assessed in the Efficacy population. The changes from Day 1 to Day 14 and from Day 1 to Day 28 in maximal tolerated volume consumed during the nutrient satiety test will be compared between treatment groups using a student's t-test. Results from the nutrient satiety test through Day 14 and Day 28, the GEBT through Day 15 and Day 27 or Day 29, and the GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) through Day 14 (+1) and through Day 28 (±1) will be summarized using summary statistics (number of patients, mean, standard deviation, median, and range) at each visit as well as changes from baseline within each treatment group. The 95% confidence intervals for the changes from baseline will be provided. Additional analyses may be conducted, and details will be provided in the statistical analysis plan.

Date of Original Protocol: 06 September 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALB	Albumin
ALT	Alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT])
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
$AUC_{0\text{-last}}$	Area under the concentration time curve from 0 to the last measurement
BH4	Tetrahydrobiopterin
BID	Twice a day
BUN	Blood urea nitrogen
^{13}C	Carbon-13
Ca	Calcium
CFR	Code of Federal Regulations
Cl	Chloride
C_{max}	Maximum concentration
CO_2	Carbon dioxide
$^{12}CO_2$	Carbon-12 dioxide
$^{13}CO_2$	Carbon-13 dioxide
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GCSI	Gastroparesis Cardinal Symptom Index
GEBT	Gastric Emptying Breath Test
GGT	Gamma glutamyl transferase
GI	Gastrointestinal

GLP	Good Laboratory Practice
HbA1c	Glycosylated hemoglobin A1c
HCG	Human chorionic gonadotropin
HCT	Hematocrit
HEENT	Head, eyes, ears, nose, and throat
HGB	Hemoglobin
ICF	Informed consent form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
K	Potassium
kPCD	the Gastric Emptying Breath Test metric; "k" is a multiplier of 1000, and "PCD" is an acronym for percent carbon-13 dose excreted (as carbon-13 dioxide)
LAR	legally authorized representative
LDH	Lactate dehydrogenase
MedDRA®	Medical Dictionary for Regulatory Activities
Na	Sodium
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
PAGI-QOL	Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity
PRO	Patient-reported outcome
QTc	QT interval corrected for heart rate
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction

TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell

1 INTRODUCTION

1.1 Diabetic Gastroparesis

Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction; symptoms are chronic with episodic symptom exacerbation (Parkman et al, 2004). Gastroparesis affects women 4 times more than men (Soykan, et al, 1998). Idiopathic gastroparesis accounts for most cases, but gastroparesis is frequently associated with diabetes (diabetic gastroparesis) (Soykan, et al, 1998; Karamanolis et al, 2007). Several cross-sectional studies have found delayed gastric emptying of solids and/or liquids in 30% to 50% of patients with Type 1 or Type 2 diabetes (Horowitz et al, 2002). Patients with diabetes mellitus commonly experience gastric and intestinal dysfunction (Feldman and Schiller, 1983).

The actual mechanism of diabetic gastroparesis is not well known. Vagal nerve dysfunction and/or damage, interstitial cells of Cajal loss, and smooth muscle and enteric neuron dysfunction have all been implicated in the pathogenesis of diabetic gastroparesis (Stacher, 2001; Parkman et al, 2004). In addition, acute hyperglycemia has the potential to slow gastric emptying (Camilleri et al, 2013).

At a molecular level, attention has been devoted to the potential role of altered nitrergic signaling in the enteric nervous system. Gastric motility is regulated in large part by neurons of the enteric nervous system located in the muscle wall (Wood et al, 1999). These neurons are either excitatory (releasing acetylcholine) or inhibitory (releasing nitric oxide [NO] and vasoactive intestinal peptide). Nerves throughout the luminal gastrointestinal (GI) tract express neuronal nitric oxide synthase (nNOS), which generates NO, a key neurotransmitter in the regulation of GI motility (Takahashi, 2003); it is the principal nonadrenergic noncholinergic inhibitory neurotransmitter in the GI tract. In diabetic rats, which serve as a model for type 1 diabetes, nNOS expression was found to be impaired. This impairment in nNOS messenger RNA expression was associated with impaired smooth muscle relaxation in response to electrical stimulation of circular muscle fibers obtained from the proximal stomach of these rats (Takahashi et al, 1997). It has been demonstrated that female diabetic rats had slower gastric emptying than age matched diabetic male rats, female control rats had greater nitrergic relaxation of circular antral muscle strips compared to male controls, and nitrergic relaxation was impaired in diabetic female rats but not matched diabetic male rats (Gangula et al, 2007).

The core signs and symptoms of gastroparesis by incidence are nausea (92% to 96%), vomiting (68% to 88%), postprandial fullness (54% to 77%), early satiety (42% to 60%), and upper abdominal pain (36% to 85%) (Soykan et al, 1998; Hoogerwerf et al, 1999; Anaparthy et al, 2009). Patients may experience any combination of signs and symptoms with varying degrees of severity. Pain is less prevalent in diabetic gastroparesis than idiopathic gastroparesis. Patients with diabetic gastroparesis may experience further derangement of glucose control because of unpredictable gastric emptying and altered absorption of orally administered hypoglycemic drugs, which may, in turn, affect measurement of core signs and symptoms. Severe signs and symptoms may cause complications such as malnutrition,

esophagitis, and Mallory-Weiss tears. Gastroparesis adversely affects the lives of patients with the disease, resulting in decreased social interaction, poor work functionality, and development of anxiety or depression (Soykan et al, 1998; Parkman et al, 2004).

1.2 Impaired Gastric Accommodation in Gastroparesis

Patients with diabetic gastroparesis have also been shown to have gastric hypersensitivity, especially in the postprandial state, and impairment of the postprandial accommodation response. (Kumar et al, 2008). The stomach functions as 2 separate regions: the fundus acts as a reservoir accommodating a meal without a significant increase in intragastric pressure, and the distal stomach/antrum triturates gastric contents. Receptive relaxation or accommodation is vagally mediated resulting in the release of NO and activation of nitrergic myenteric neurons. Nitrergic signaling is responsible for gastric accommodation and pyloric relaxation in response to a meal (Ishiguchi et al, 2001).

Impaired accommodation has been associated with symptoms of early satiety and weight loss in patients with idiopathic gastroparesis (Karamanolis et al, 2007). A study of patients with diabetic gastroparesis found that 90% of patients had impaired gastric accommodation to a nutrient meal (Kumar et al, 2008). In the distal stomach, NO is required for the propulsive contractions that triturate gastric contents and control of pyloric closure; lack of NO can lead to delayed gastric emptying and impaired gastric accommodation (Gangula et al, 2007).

Several co-factors are known to be important for nNOS activity, including nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), calcium, and tetrahydrobiopterin (BH4) (Werner et al, 2003). The homodimeric conformation of all 3 isoforms of nitric oxide synthase (NOS) is regulated by BH4 (Werner et al, 2003). In the absence of BH4, uncoupling of NO production occurs and leads to super oxide production, resulting in further impaired nNOS bioactivity.

1.3 Current Treatment of Diabetic Gastroparesis

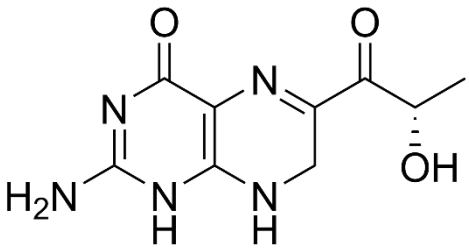
Therapies for gastroparesis have been targeted at accelerating gastric emptying or controlling symptoms. Available therapies for accelerating gastric emptying are limited in number and efficacy. These include metoclopramide (Snape et al, 1982), erythromycin (Arts et al, 2005), and domperidone (not available in the United States [US]) (Prakash and Wagstaff, 1998). There is also poor correlation between gastric emptying and baseline symptom severity (Karamanolis et al, 2007; Talley et al, 2001) and in response to therapeutic intervention. In part, as a result of lack of understanding of the underlying pathogenesis that leads to alterations in GI motility and sensation, medical therapies have not been targeted at the underlying pathophysiology of gastroparesis.

The first-line medical therapy for patients with diabetic gastroparesis is generally a combination of an antiemetic agent in addition to the promotility drug. Unfortunately, many patients with diabetic gastroparesis will not experience adequate symptom relief despite first-line therapy. For patients with refractory disease, options include combination prokinetic therapy, psychotropic medications, pyloric botulinum toxin injection, and gastric electric stimulation (Fass, 2010; Camilleri et al, 2013).

1.4 CNSA-001 (Sepiapterin)

Sepiapterin is 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$.

The chemical structure of sepiapterin is:



Sepiapterin serves as a substrate for BH4 synthesis via the pterin salvage pathway (Mayer and Werner, 1995). Oral administration of sepiapterin was shown to be more potent (>2 fold) than oral administration of BH4 in increasing intracellular BH4 in normal mice (Sawabe et al, 2002). Translation of this finding to humans has been confirmed in a Phase 1 study, PKU-001, conducted by Censa Pharmaceuticals.

1.5 Rationale for Study

BH4 biosynthesis is impaired in chronic diabetes. The mechanism of impairment is not well understood but is thought to be a result of hyperglycemia-induced proteasome-mediated degradation of GTP-cyclohydrolase, the rate-limiting enzyme in the synthesis pathway for BH4 (Xu et al, 2007).

CNSA-001 is the first viable formulation of sepiapterin, shown to increase intracellular BH4 (Section 1.4), intended for the treatment of female patients with diabetic gastroparesis. CNSA-001 was studied in a single and multiple ascending-dose study in healthy volunteers, the Phase 1 study, Study PKU-001. Part A of this study assessed the safety and pharmacokinetics of CNSA-001 at 6 dose levels inclusive of an assessment of food effect (i.e., 2.5 mg/kg, 7.5 mg/kg, 20 mg/kg, 40 mg/kg, 80 mg/kg, and 10 mg/kg [to assess food effect]). Additionally, Kuvan® (sapropterin dihydrochloride), a synthetic BH4 commercially available product, was administered at equivalent doses for the first 3 dose levels (2.5 mg/kg, 7.5 mg/kg, and 20 mg/kg). Dose-dependent correlations between CNSA-001 and plasma BH4 concentrations were observed with each successive dose level. Dose proportionality was observed between the top 2 dose levels (40 mg/kg and 80 mg/kg) and resultant BH4 concentrations. Administration with a standard high-fat (approximately 50 percent of total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) meal resulted in approximately 80% higher plasma BH4 concentrations (area under the concentration time curve from 0 to the last measurement [$AUC_{0\text{-last}}$] and maximum concentration [C_{max}]) than in subjects who had fasted before receipt of CNSA-001. Treatment-emergent adverse events (TEAEs) in Part A of Study PKU-001 were reported in 26 subjects (44.1%, 26/59). The TEAEs for CNSA-001 were generally mild and consistent with reported adverse events (AEs) for Kuvan® and placebo. The frequency of TEAEs did

not appear to increase with increasing dose. The TEAEs that were judged to be related to study treatment were reported in 17 subjects: 11 subjects (26.2%, 11/42) who received CNSA-001, 4 subjects (44.4%, 4/9) who received Kuvan®, and 2 subjects (25.0%, 2/8) who received placebo. No TEAEs were severe or serious or led to discontinuation of study drug. Headache and dizziness were the most common TEAEs , but these TEAEs occurred at a similar frequency as with placebo.

Part B of Study PKU-001 assessed multiple ascending doses CNSA-001 in healthy volunteers. Data indicate CNSA-001 was well tolerated following daily doses of 5, 20, and 60 mg/kg/day for 7 days and that TEAEs were reported in 14 subjects (58.3%, 14/24). The TEAEs in subjects who received CNSA 001 were mild or moderate and consistent with the TEAEs in subjects who received placebo: TEAEs were experienced by 10 subjects (55.6%, 10/18) who received CNSA-001 at doses from 5 mg/kg to 60 mg/kg daily for 7 days and by 4 subjects (66.7%, 4/6) who received placebo. No TEAEs were severe, serious, or led to discontinuation. Of the 10 TEAEs reported in subjects who received CNSA-001, only 4 were judged to be related to study drug, and, of the 4 TEAEs reported in subjects who received placebo, only 1 was judged to be related to study drug. Somnolence, fatigue, headache, and procedural pain (secondary to performance of 2 sequential lumbar punctures 7 days apart) were the most common TEAEs reported, and they occurred at a similar frequency when compared with placebo with the exception of fatigue and headache, which were each reported in 2 subjects who received CNSA-001 (11.1%, 2/18).

This Phase 2 pilot study will assess CNSA-001 doses of 20 mg/kg/day administered as 10 mg/kg twice a day (BID) in comparison to placebo administered BID in female patients with diabetic gastroparesis. This study will help support the design of future Phase 2/3 studies in patients with diabetic gastroparesis.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the impact of CNSA-001 on gastric accommodation, as measured by nutrient satiety testing (Section 6.7), in women with moderate to severe diabetic gastroparesis.

2.2 Secondary Objectives

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

- To evaluate improvement of gastroparesis symptoms measured by global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]) (Section 6.8, Appendix 2)
- To evaluate patient-reported outcomes (PROs) as measured by the quality of life questionnaire Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) (Section 6.9, Appendix 2)
- To evaluate the emptying of the stomach, as measured by the Gastric Emptying Breath Test (GEBT) (Section 6.10)
- To assess the safety and tolerability of CNSA-001 20 mg/kg/day

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Study GAS-001 is a Phase 2, randomized, double-blind, placebo-controlled pilot study of multiple doses of CNSA-001 (sepiapterin) powder for suspension administered orally in women with moderate to severe diabetic gastroparesis. This is an outpatient study in which up to 20 patients will be enrolled at approximately 4 centers.

The Schedule of Events is provided in Appendix 1. The study schema is displayed in Figure 1.

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, patients will undergo Screening procedures to determine study eligibility, as indicated in Appendix 1. Patients 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 patients will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Patients will undergo procedures during the Treatment Period as indicated in Appendix 1.

Study drug may be prematurely discontinued for safety reasons, as described in Section 6.14.1. Patients may also withdraw from the study for any reason, as described in Section 6.14.2. 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) (Section 7.5, Appendix 1). 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 (Section 7.5, Appendix 1). 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 (Section 7.6, Appendix 1).

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

Patients will undergo EOT evaluations on Day 14 and Day 15 as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test (Section 6.7) on Day 14. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) will also be administered on Day 14 (+1 day), and the GEBT (Section 6.10) will be conducted on Day 15.

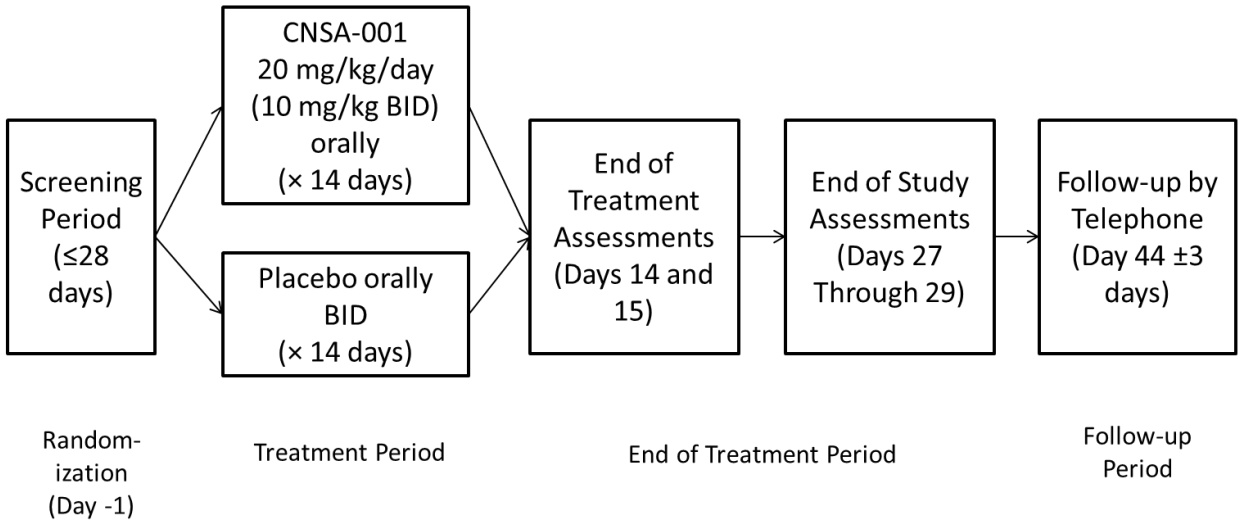
End of Study Period (Day 15 After Evaluations Through Day 28 [±1 Day] Evaluations)

Patients will undergo EOS evaluations on Day 28 (±1 day) as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test (Section 6.7) on Day 28. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) will also be administered on Day 28 ±1, and the GEBT (Section 6.10) will be conducted on Day 27 or Day 29.

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

Patients will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix 1.

Figure 1: Study Schema



Abbreviations: BID = twice a day.

3.2 Rationale for Study Design and Control Group

CNSA-001 (sepiapterin) is a new chemical entity that is an endogenous, naturally occurring precursor of BH4 via the pterin salvage pathway. Animal studies and data from a Phase 1 single and multiple ascending-dose study in healthy volunteers conducted by Censa Pharmaceuticals indicate rapid intracellular conversion of sepiapterin to BH4. It is expected that oral administration of CNSA-001 to women with diabetic gastroparesis will result in increases in both intracellular and circulating BH4 concentrations. In chronic diabetes, BH4 biosynthesis is impaired (Xu et al, 2007).

CNSA-001 was studied in two 14-day Good Laboratory Practice (GLP) toxicity studies, as described in Section 5.3, and in a single and multiple ascending-dose study in healthy volunteers, Study PKU-001, as described in Section 1.5.

Because all patients will receive the standard of care for diabetic gastroparesis in addition to their assigned study drug, the study design of a randomized study of CNSA-001 versus

placebo in female patients with diabetic gastroparesis will not expose patients to the risk of no treatment.

This study has a double-blind design intended to reduce bias.

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).

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 4 study centers will enroll up to 20 women with moderate to severe diabetic gastroparesis this study.

4.2 Inclusion Criteria

Patients are eligible to participate in this study if they meet all the following inclusion criteria:

1. Informed consent
2. Females ≥18 and ≤65 years of age
3. Diagnosis of diabetes mellitus
4. Documentation of delayed gastric emptying on gastric emptying scintigraphy (within 1 year of enrollment)
5. Symptoms of gastroparesis for at least 6 months with GCSI (Section 6.8, Appendix 2) score >21 indicating moderate to severe symptoms
6. Gastric accommodation, as measured by nutrient satiety testing, of ≤600 mL
7. Negative upper endoscopy or upper GI series within 3 years of enrollment (no evidence of mechanical obstruction or peptic ulcer disease)
8. Either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following:
   - Hormonal contraception (stable dose for 3 months)
   - Intrauterine device/Intrauterine Hormone-releasing System
   - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

   Patients who are abstinent will not be required to use a contraceptive method unless they become sexually active
9. If on analgesics (including narcotics), promotility agents (including metoclopramide), or neuromodulators (including tricyclic antidepressants, gabapentin, and pregabalin), doses are stable for >30 days before randomization and the patient is not expected to require dose changes during the study through the EOT
10. Have not used tobacco (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks prior to Day 1 and willingness to abstain from these products during the study through the EOT

4.3 Exclusion Criteria

Patients are not eligible to participate in this study if they meet any of the following exclusion criteria:

1. Male gender
2. Normal gastric emptying
3. Gastroparesis from postsurgical etiologies
4. Another active disorder that could, in the opinion of the Investigator, explain symptoms
5. Weight >100 kg
6. Alanine aminotransferase > 2× upper limit of normal (ULN)
7. Pregnant, breastfeeding, or considering pregnancy
8. Clinically significant cardiac arrhythmia at Screening
9. QT interval corrected for heart rate (QTc) ≥480 msec (based on triplicate measurements taken at Screening)
10. Recent clinically significant GI bleeding
11. Taking levodopa or domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT
12. Taking erythromycin within 30 days before randomization or expected to require erythromycin within 30 days before randomization or expected to require erythromycin during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization
13. Taking any fundic-relaxing agents including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT
14. Taking any systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)
15. Pulmonary dysfunction (e.g., chronic obstructive pulmonary disease)
16. Surgery for placement of a gastric stimulator within the past 6 months (patients postoperative >6 months with persistent symptoms and delayed gastric emptying are eligible)
17. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, small bowel malabsorption) that could affect the absorption of study drug or contraindicate undergoing the GEBT (Section 6.10)

18. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
19. History of allergies or adverse reactions to BH4 or related compounds, to any excipients in the study drug formulation, or to egg, wheat, or algae (Spirulina)
20. Inability to tolerate oral medication
21. Current participation in any other investigational drug study or use of any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening
22. Any clinically significant laboratory abnormality; in general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range unless deemed not clinically significant by the Investigator
23. Major surgery within the previous 90 days
24. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study
25. History of alcohol or drug abuse within 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
26. Episodes of ketoacidosis or hypoglycemia that are frequent as defined by the Investigator
27. Any other conditions, including diabetic comorbidities, that, in the opinion of the Investigator or Sponsor, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Test Product

The test product is CNSA-001 (sepiapterin) oral powder for suspension. CNSA-001 contains the new chemical entity, sepiapterin. Sepiapterin is 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$. Inactive ingredients in CNSA-001 include microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid. CNSA-001 will be suspended in Medisca® Oral Mix prior to dispensing it to the patient.

5.1.2 Placebo Control

The placebo is a ready-made suspension containing microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, ascorbic acid, and colorant (Yellow No. 6) that is suspended in Medisca® Oral Mix.

5.2 Treatments Administered

Patients will be randomized in a ratio of 1:1 to the following treatment groups:

- CNSA-001 20 mg/kg/day (10 mg/kg BID) for 14 days
- Placebo BID for 14 days

Dosing of CNSA-001 is based on the patient's weight. The weight obtained on Day -1 will be used to calculate the exact amount (mg) of CNSA-001 active ingredient (sepiapterin) required for each patient's daily dose.

The placebo is formulated as ready-made suspension. The placebo will be administered in the same manner (volume) as CNSA-001.

Details on preparation of study drug and dosing guidelines will be provided in a pharmacy manual for the site and an instruction guide for patients.

5.3 Selection and Timing of Dose for Each Patient

All patients will be randomly assigned in a ratio of 1:1 to receive CNSA-001 20 mg/kg/day (10 mg/kg BID) or placebo BID.

The CNSA-001 dose was selected following completion of two 14-day GLP toxicity studies in the rat and marmoset. The no observed adverse effect level from both studies was set at 1000 mg/kg/day, which represents a human equivalent dose of 161.3 mg/kg/day based on allometric scaling. Consequently, the proposed dose of 20 mg/kg/day represents an 8.1-fold safety margin.

Study drug will be dispensed on Day 1 (Section 6.11) with a dosing diary in which patients will record all doses taken and times they were taken (Section 5.8.1). The first dose on Day 1 will be taken in the clinic after patients undergo the nutrient satiety test (Section 6.7).

If a patient vomits after taking a dose of study drug, the patient 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.

5.4 Method of Assigning Patients to Treatment Groups

Patients 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. Patients who are randomized will be considered to be enrolled.

5.5 Blinding

This study has a double-blind design. The Investigator, study personnel, and patients will not make any effort to determine which study drug is being received. Unblinded pharmacy (or other qualified site) personnel will be utilized in this study to prepare the study drug.

Patients will be blinded to study drug assignment. Only in an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific patient, may the Investigator unblind a patient's study drug assignment. Copies of the randomization sequence and treatment codes will be kept in the pharmacy at the sites. If emergency unblinding is required, the Investigator will have immediate access to individual sealed codes containing treatment allocations. However, before any unblinding occurs, the Investigator is strongly advised to discuss options with the Sponsor's Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the patient's study drug assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to the unblinding. The Investigator will record in source documentation the date and reason for revealing the blinded study drug assignment for any patient and the names and roles of personnel unblinded.

5.6 Concomitant Therapy

Patients will be permitted to take:

- Analgesics, including narcotics, if the patient has been on a stable dose of the medication for >30 days before randomization; dose escalation is NOT permitted during the study through the EOT

- Promotility agents, including metoclopramide if the patient has been on a stable dose of the medication >30 days before randomization; dose changes are NOT permitted during the study through the EOT

- Neuromodulators, including any tricyclic antidepressant, gabapentin, and pregabalin, if the patient has been on a stable dose >30 days before randomization; dose changes are NOT permitted during the study through the EOT

- Rescue medications that patients would usually take, including ondansetron (Zofran®), promethazine (Phenergan®) or prochlorperazine (Compazine®) for nausea and tramadol (Ultram®), if symptoms related to gastroparesis require further treatment during the study through the EOT

All prescription and over-the-counter medications (including herbal medications) that the patient took within 30 days before Screening though the EOT should be recorded.

5.7 Restrictions

5.7.1 Prior Therapy and Concomitant Therapy

The following are prohibited:

- Any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening

- Domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT

- Dose escalation of analgesic or promotility agents or neuromodulators within 30 days before randomization or during the study through the EOT

- Erythromycin within 30 days before randomization or during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization

- Systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)

- Fundic-relaxing agents, including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT

- Medications that can alter GI sensation or accommodation or gastric emptying overnight before the nutrient satiety test (Section 6.7)

5.7.2 Food Intake

Patients will continue their usual diet without modification throughout the study. Patients are required to have been fasting overnight for the following assessments:

- Clinical laboratory, including glycosylated hemoglobin A1c (HbA1c), tests
- The nutrient satiety test (Section 6.7), which requires the consumption of Ensure™ (Abbott Laboratories, Abbott Park, IL, USA)
- The GEBT (Section 6.10), which requires consumption of a standardized 230 kCal meal, consisting of a standardized carbon-13 (^{13}C)-labeled egg component and 6 saltine crackers, with 6 ounces of water

5.7.3 Total Blood Volume

The total volume of blood obtained from an individual study patient is expected to be approximately 40 mL, for clinical laboratory tests inclusive of the HbA1c test.

5.7.4 Patient Activity and Tobacco Restrictions

Patients will not be confined during the study and will not require any activity restrictions. Patients must abstain from tobacco use (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks before Day 1 and during the study through the EOT.

5.8 Treatment Compliance

Patients will be instructed to return all used (empty containers) and unused study drug on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day). Compliance with the dosing regimen will be assessed by reconciliation of used and unused study drug. The quantities dispensed, returned, used, and lost will be recorded on the dispensing log provided for the study.

5.8.1 Dosing Diary

Patients will be provided with a dosing diary on Day 1 along with instructions for recording all doses of study drug and times they were taken. The dosing diary will be collected on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day), and the Investigator (or designee) will transcribe all entries into the electronic case report form (eCRF).

5.9 Packaging and Labeling

CNSA-001 Oral Powder for Suspension is packaged in 10 mL amber glass vials with black child proof caps. Each glass vial contains 175 mg of sepiapterin.

Each vial of CNSA-001 Oral Powder for Suspension will contain the product name, strength, content, expiry/retest date, and company name. Each vial label will contain the words, "Caution: Investigational medicine for clinical trial use only."

CNSA-001 PLACEBO suspension is packaged in 500 mL bottles. Each bottle of CNSA-001 PLACEBO suspension will contain the content and company name as well as "CNSA-001 PLACEBO" on its label.

The suspending vehicle, Medisca® Oral Mix, is commercially available and will be provided separately.

5.10 Storage and Accountability

All drug product required for completion of this study will be provided by Censa Pharmaceuticals. It is the responsibility of the pharmacy staff or study staff to ensure that a current record of drug inventory and drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the study monitor and are open to inspection at any time by applicable regulatory authorities.

CNSA-001 Oral Powder for Suspension (non-reconstituted) may be stored frozen at -20°C or at refrigerated conditions (2 to 8°C). If not administered on the same day of suspending, CNSA-001 suspension should be stored at refrigerated conditions (2 to 8°C) until time of dosing. Once suspended, CNSA-001 is stable for 14 days.

CNSA-001 PLACEBO suspension may be stored refrigerated at 2 to 8°C.

5.11 Investigational Product Retention at Study Site

Upon completion of the study and once inventoried by the study site, all used (empty) containers of study drug will be destroyed. Any unused containers of study drug may be either destroyed or returned to the Sponsor following discussion with the Sponsor. If study drug is destroyed, a certificate of destruction will be provided to the Sponsor by the appropriate facility performing the destruction.

6 STUDY PROCEDURES

6.1 Informed Consent

Consent forms describing in detail the study drug, study procedures, and risks are given to the patient, and written documentation of informed consent is required prior to conducting study-related procedures. See Section 10.4 for more information on the informed consent process.

6.2 Medical History and Demographic Data

A detailed medical/surgical history will be obtained at Screening. The history will include specific information related to any prior or existing medical conditions or surgical procedures involving the following systems: dermatologic; head, eyes, ears, nose, and throat (HEENT); lymphatic; cardiovascular; respiratory; GI; musculoskeletal; and neurological. The medical history will be updated on Day 1 before the start of study drug.

Demographic data obtained at Screening will include age, gender, and self-reported race/ethnicity.

6.3 Vital Signs, Weight, and Height

Vital signs, including blood pressure, pulse, respiratory rate, and temperature, will be measured at Screening, Day 1 (predose and 2 hours postdose), and at the EOT and EOS visits. Vital signs will be measured prior to collection of laboratory samples and after patients have rested for 5 minutes in the supine position. For timepoints other than Day 1, vital signs will be taken at any time during the visit after resting and laboratory sample collection.

Weight will only be collected at Screening as necessary to determine the response to Exclusion Criterion #5 (Section 4.3) and on Day -1. Height will only be collected at Screening.

6.4 Physical Examination

A complete physical examination will be performed at Screening, on Day 1 before start of study drug and at the EOT and EOS visits. The examination will assess general appearance, as well as dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters.

6.5 Clinical Laboratory Tests and Glycosylated Hemoglobin A1c

Clinical laboratory tests will be performed by qualified local laboratories. Blood and urine samples for clinical chemistry, hematology, and urinalysis will be collected at Screening, Day 1 (predose), and at the EOT and EOS visits. Patients should fast overnight prior to collection of blood samples (minimum of 8 hours before blood sample collection). Blood samples for HbA1c will be collected at Screening and at the EOT and EOS visits. Clinically significant laboratory abnormalities should be followed to a satisfactory resolution, as determined by the Investigator.

The following clinical laboratory and other laboratory parameters will be assessed:

Hematology:	**Serum Chemistry:**
Hematocrit (HCT)	Albumin (ALB)
Hemoglobin (HGB)	Alkaline phosphatase (AP)
Platelet count	Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT])
Red blood cell (RBC) count	Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT])
White blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)	Blood urea nitrogen (BUN)
Urinalysis:	Calcium (Ca)
Bilirubin	Carbon dioxide (CO_2)
Glucose	Chloride (Cl)
Ketones	Creatinine
Occult blood	Gamma glutamyl transferase (GGT)
pH	Glucose
Protein	Lactate dehydrogenase (LDH)
Specific gravity	Phosphorus
Urobilinogen	Potassium (K)
Microscopy:	Sodium (Na)
WBCs	Total bilirubin
RBCs	Direct bilirubin
Epithelial cells	Total cholesterol
Pregnancy Testing: [a]	Total protein
Serum human chorionic gonadotropin (HCG) at Screening	Uric acid
Urine HCG Day 1 (predose) and Day 14 (±1 day)	**Other:**
	Glycosylated hemoglobin A1(HbA1c)

[a] Required for all women who are of childbearing potential. Any positive urine pregnancy test should be confirmed by a serum pregnancy test.

6.6 Electrocardiogram

At Screening, 12-lead electrocardiograms (ECGs) will be obtained in triplicate, with 1 minute separating the first and second recordings and 1 minute separating second and third recordings. The following ECG parameters will be collected and recorded in the eCRF: RR, PR, QRS, QT, and QTc intervals. In addition, the ECG tracing should be reported as normal,

abnormal clinically significant, or abnormal not clinically significant. If abnormalities are noted on the ECG, these should be recorded in the eCRF.

6.7 Nutrient Satiety Test

For the nutrient satiety test, patients consume 120 mL of Ensure™ every 4 minutes. At 5-minute intervals, patients 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). Patients 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 patients 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. The sum of the four 100-mm visual analogue scales provides an aggregate symptom score (Park, 2011).

The nutrient satiety test will be administered in the clinic 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. A nutrient satiety test volume of ≤600 mL at Screening is required for patients to participate in this study.

6.8 Gastroparesis Cardinal Symptom Index

The GCSI (Appendix 2) consisting of a subset of items from the PAGI-SYM instrument (Section 6.9, Appendix 2), will be administered in the clinic at Screening and on Day 1 (predose), Day 14 (+1 day), and Day 28 (±1 day). A GCSI score >21 at Screening, indicating moderate to severe symptoms, is required for patients to participate in this study.

6.9 Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity

The PAGI-SYM (Appendix 2) is a 20-item upper GI symptom severity instrument with 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. It will be administered in the clinic on Day 1 (predose) and on Day 14 (+1 day), and Day 28 (±1 day).

6.10 Gastric Emptying Breath Test

The GEBT, which is a nonradioactive noninvasive test, will be administered in the clinic on Day -1, Day 15, and Day 27 or Day 29 after the patient 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 patient provides baseline (premeal) breath samples and then consumes 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. The meal is to be consumed within 10 minutes. Single postmeal breath samples are collected in capped glass tubes at 45, 90, 120, 150, 180, and 240 minutes after the meal is consumed and sent to the specified local laboratory for

analysis by Gas Isotope Ratio Mass Spectrometry. By adding ^{13}C to the test meal, the GEBT can determine how fast the stomach empties the meal by measuring the rate of carbon-13 dioxide ($^{13}CO_2$) excretion arising from the digested test meal. The rate of $^{13}CO_2$ excretion found in the patient's breath is proportional to the patient's rate of gastric emptying. The patient's $^{13}CO_2$ excretion rate at each breath collection time is reported using the GEBT metric "kPCD." The "k" is a multiplier of 1000, and "PCD" is an acronym for percent ^{13}C dose excreted (as $^{13}CO_2$). The test should not be administered to patients with a known allergy to egg, wheat, or algae (Spirulina) (Cairn Diagnostics™; Sutton et al, 2015; GEBT package insert, 2015; United States Food and Drug Administration, 2015).

6.11 Dispensing Study Drug

Study drug will be dispensed on Day 1 along with a dosing diary to record all doses taken and times they were taken. A sufficient supply of study drug will be dispensed for dosing through Day 14. Details on the preparation of study drug, dosing guidelines, and storage will be provided in a pharmacy manual for the site and an instruction guide for patients.

6.12 Adverse Events Assessments

An AE is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

The occurrence of an AE or serious adverse event (SAE) (Section 6.12.6) may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes, but is not limited to, the event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. Action taken regarding study medication (e.g., drug withdrawn, interrupted) will also be collected in the eCRF. All AEs that start during the study must be documented appropriately regardless of relationship. All treatment-related AEs or AEs leading to discontinuation will be followed to an adequate resolution, as determined by the Investigator.

Any medical condition that is present at the time that the patient is screened will be considered as medical history and not reported as an AE. However, if the patient's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. The AEs characterized as intermittent require documentation of onset and duration of each episode.

6.12.1 Reporting Timelines

The Investigator will record all reportable events with start dates occurring any time after informed consent and continue through clinical study completion or, in the case of withdrawal, until the outcome is determined. The AEs will be assessed at each visit and/or

through telephone contact with the patient. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

All SAEs should be reported after the patient signs the informed consent and followed until resolution, stabilization, or until the Investigator provides sufficient evidence that no further information can be obtained.

All SAEs and pregnancies (in a patient or partner of a male patient) occurring while the patient is on the study or within 30 (±3) days after the patient received the last dose of study drug must be reported within 24 hours of the knowledge of the event by study personnel whether or not considered to be related to study drug.

Deaths that occur ≥30 (±3) days after the patient's last study dose must be reported within 24 hours of knowledge of the event, if deemed related to study drug by the Investigator.

Although pregnancy is not considered an AE or SAE by regulatory definition, for this study pregnancies must be processed following SAE timelines (e.g., within 24 hours of knowledge of the pregnancy) for data transmission purposes. In the event that a pregnancy complication occurs, or elective termination of a pregnancy is required for medical reasons, then the complication will be recorded as an AE or SAE, as appropriate.

While elective and uncomplicated induced abortion not required for medical reasons does not constitute an AE or SAE (even if the patient or patient's partner is hospitalized to undergo abortion), spontaneous abortion is considered a fatal event and must be reported as an AE and SAE, as appropriate.

Any pregnancy and/or suspected pregnancy that occurs during the study in a female patient should be reported using Pregnancy Reporting Form within 24 hours of knowledge of the event by study personnel. Any pregnancy and/or suspected pregnancy will be followed for outcome.

If the patient has received the investigational drug prior to becoming pregnant, the patient will continue the efficacy assessment and Follow-up periods and measures of safety and efficacy will be obtained.

The patient will be followed until the outcome of the pregnancy is determined. It is the responsibility of the Investigator to obtain and document pregnancy information on the most recent Pregnancy Report Form. Furthermore, any SAE occurring as an outcome of the pregnancy must be reported according to the procedures outlined for SAE reporting.

6.12.2 Severity

The intensity of each AE will be graded as follows:

Mild:	Events require minimal or no treatment and do not interfere with the patient's daily activities.
Moderate:	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe:	Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but may not be considered an SAE. Alternatively, a stroke that results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE.

6.12.3 Relationship

The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. For purposes of consistency, guidelines for assessing causality are provided below:

Not Related	The AE is completely independent of study drug 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. No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state.
Unlikely to be 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 chemicals or underlying disease provides plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).
Possibly Related	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
Probably Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
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 response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to study drug administration, then an alternative explanation should be provided, if available.

6.12.4 Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigators' Brochure or is not listed at the specificity or severity that has been observed;

or, if an Investigators' Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the protocol.

The drug safety medical reviewer will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent (e.g., Investigators' Brochure).

6.12.5 Clinical Laboratory Adverse Events

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms or require medical intervention, as determined by the Investigator. However, each laboratory abnormality (e.g., clinically significant changes detected in hematology, serum chemistry panel, urinalysis, urine microscopic, and HbA1c evaluations) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to study drug interruption or discontinuation, must be recorded as an AE, or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (e.g., vital signs) performed that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described below.

6.12.6 Serious Adverse Events

6.12.6.1 Definition

An SAE is defined as an AE or suspected adverse reaction occurring at any dose that results in any of the following outcomes: death, life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

An AE or suspected adverse reaction is considered ''life-threatening'' if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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, or the development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in these other situations.

6.12.6.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Sponsor must submit a safety report for any suspected adverse reaction to study treatment that is both serious and unexpected. Before submitting a safety report, the Sponsor needs to ensure that the event meets all 3 of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the AE does not meet all 3 of the definitions, it should not be submitted as a safety report.

6.12.6.3 Reporting Serious Adverse Events

The Investigator will report all SAEs to the designated drug safety team within 24 hours of knowledge of the event whether or not considered to be related to study drug using the SAE Report Form provided.

Although not all information required for a complete SAE Report Form may be readily available at the time of the event, the Investigator must include sufficient information on the SAE Report Form to allow for a complete medical assessment. This should include at a minimum the patient number, site number, detailed description of the event, seriousness criteria, causality/relationship to study drug, and Investigator signature.

The designated drug safety team will acknowledge the receipt of the SAE via email to the clinical site. After submission of the initial report, the Investigator will provide follow-up information to the drug safety team as requested (e.g., concomitant medications, hospital discharge summary) to further evaluate the event and assure that all appropriate information is received. Once all information is received and the SAE has been deemed appropriate for closure, the SAE Report Form must be signed and dated by the Investigator.

The Investigator is responsible for informing the Institutional Review Board (IRB) of the SAE in accordance with institutional policies and procedures including relevant initial and follow-up information about the SAE.

Treatment-related SAEs or events leading to discontinuation of study drug will be followed for outcome information until resolution or stabilization. Other supporting documentation of the event may be requested by Censa Pharmaceuticals (or designee) and should be provided as soon as possible. The Medical Monitor should be contacted when the Investigator considers an SAE to be treatment-related.

6.12.7 Treatment-Emergent Adverse Events

Those AEs that start at the time of or after the first dose of study drug are TEAEs. Those AEs that worsen at or after the time of first dose of study drug are also considered treatment-emergent. All AEs that occur on or after the ICF has been signed, including all TEAEs, through Day 29 will be recorded in the eCRF.

All SAEs through Day 44 ±3 days [30 ±3 days after the patient received last dose of study drug] will be recorded in the eCRF and reported as described in Section 6.12.6.3.

6.13 Prior and Concomitant Medication Assessments

All prescription and over-the-counter medications (including herbal medications) taken by a patient starting from the 30-day period before Screening through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations will be recorded. Any concomitant medications added or discontinued during the study will be recorded at each visit.

6.14 Removal of Patients From the Trial or Study Drug

6.14.1 Early Discontinuation From Study Drug Administration

Premature discontinuation of study drug administration is defined as the discontinuation of study drug for an individual patient before the required full course of study drug is completed. Reasons for premature discontinuation from study drug administration should be recorded on the appropriate page(s) of the eCRF and may include, but are not limited to the following:

- Occurrence of an AE, SAE, or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from study drug administration
- In the judgment of the Investigator, the patient experiences a general or specific change(s) that renders the patient unsuitable for continued study drug administration
- There is a need for concomitant medication that makes the patient ineligible for further study drug administration
- Pregnancy

Given the requirement for pregnancy testing in women of childbearing potential at Screening and the requirement for highly effective methods of contraception during the study, it is unlikely that pregnancies will occur during study conduct. However, study drug will be discontinued should suspected or confirmed pregnancy or nursing during the study drug administration period occur.

Patients who prematurely discontinue study drug due to any of the above reasons will complete the EOT assessments within 24 hours of withdrawal.

6.14.2 Withdrawal From the Study

Patients may withdraw from the study for any reason or be withdrawn at the request of the Investigator or Sponsor. The reason for a patient's withdrawal must be recorded on the appropriate page(s) of the eCRF. Reasons for withdrawal from the study may include, but are not limited to:

- Withdrawal of consent
- AEs or SAEs
- Significant patient noncompliance, defined as refusal or inability to adhere to the protocol requirements
- The Investigator determines that it is in the best interest of the patient to withdraw from study participation, due to a reason other than safety

Each patient who withdraws from the study after receipt of any amount of study drug will be asked to undergo EOT assessments. However, patients may withdraw consent to participate in this study at any time without penalty. Withdrawn patients who receive any amount of study drug, will not be replaced. Withdrawn patients who do not receive any study drug will be replaced.

6.14.3 Study Stopping Criteria

The study may be terminated if significant violations of Good Clinical Practice (GCP) that compromise the ability to achieve the study objectives or compromise patient safety are observed at any time during the study. With regard to safety, the study may be temporarily suspended or terminated should the Investigator, Sponsor, or IRB determine that the safety of patients is significantly jeopardized. The decision for a temporary or permanent study hold will depend on the nature, frequency, and severity of AEs that were observed in all enrolled patients to date. In a temporary study hold, no additional patients will be enrolled into the study or dosed with study drug until the study team members (including the Investigator and the Medical Monitor) decide it is safe to proceed with the study.

6.15 Appropriateness of Measurements

Safety will be measured by AEs (including SAEs), vital signs, physical examinations, and clinical laboratory and HbA1c tests.

Because treatment with BH4 is hypothesized to restore nNOS function in the control of gastric accommodation, the nutrient satiety test (Section 6.7) was chosen for the primary endpoint for this study. Gastric accommodation has been measured using ultrasonography (Undeland et al, 1998), single-photon emission computed tomography (Bredenoord et al, 2003), and barostat testing (Coulie et al, 1998; Sarnelli et al, 2001). Barostat studies have been shown to be reproducible (Sarnelli et al, 2001) but are invasive and not widely available. Satiety testing using a nutrient liquid has been shown to be reproducible (Kindt et

al, 2008) and correlate with impairment in gastric accommodation but not gastric emptying or visceral sensitivity (Tack et al, 2003).

The GEBT is nonradioactive, noninvasive test of gastric emptying rate that has been validated against the reference method of gastric scintigraphy. It has been accepted by the United States Food and Drug Administration (FDA) for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastroparesis. The GEBT can determine how fast the stomach empties a standardized meal with a ^{13}C-labeled egg component by measuring the ratio of $^{13}CO_2$ to carbon-12 dioxide ($^{12}CO_2$) collected in breath samples at multiple time points after the meal is consumed compared to baseline. The breath samples are collected in capped glass tubes and sent to a specified local laboratory for analysis. By measuring the change in the ratio of $^{13}CO_2$ to $^{12}CO_2$ over time in comparison to the premeal value, the rate of $^{13}CO_2$ excretion can be calculated and the gastric emptying rate determined. The GEBT does not require administration by specially trained health care professionals or special precautions related to radiation-emitting compounds (Section 6.10).

The GCSI (Section 6.8, Appendix 2), consisting of a subset of items from the PAGI-SYM instrument (Section 6.9, Appendix 2) (described below), is based on reviews of the medical literature and results from clinician interviews and patient focus groups. Its reliability and validity were examined in 169 gastroparesis patients from 7 clinical centers in the US. Patients completed the GCSI, SF-36 Health Survey, and disability day questions at baseline and again at 8 weeks. Clinicians independently rated the severity of the patients' symptoms, and both clinicians and patients rated the changes in gastroparesis-related symptoms over the 8weeks. For the GCSI total score, the internal consistency reliability was 0.84, and the test-re-test reliability was 0.76. Significant relationships were observed between the clinician-assessed symptom severity and the GCSI total score, and significant associations were found between the GCSI scores and SF-36 physical and mental component summary scores and restricted activity and bed disability days. Patients with greater symptom severity, as rated by clinicians, reported greater symptom severity on the GCSI. The GCSI total scores were responsive to changes in overall gastroparesis symptoms as assessed by clinicians ($p = 0.0002$) and patients ($p = 0.002$) (Revicki et al, 2003).

The PAGI-SYM (Section 6.9, Appendix 2) is a 20-item upper GI symptom severity instrument with 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. To develop the instrument, patients with GERD (n = 810), dyspepsia (n = 767), or gastroparesis (n = 169) from the US, France, Germany, Italy, the Netherlands, and Poland completed the PAGI-SYM, the SF-36 Health Survey, a disease-specific health-related quality of life measure (Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life [PAGI-QOL]), and disability day questions. Two-week reproducibility was evaluated in 277 stable patients. Construct validity was evaluated by correlating subscale scores with SF-36, PAGI-QOL and global symptom severity scores and disability days. Internal consistency reliability ranged from 0.79 to 0.91, and test-retest reliability ranged from 0.60 to 0.82 for the PAGI-SYM subscales. The PAGI-SYM subscale scores correlated significantly with SF-36 scores (all $p < 0.0001$), PAGI-QOL scores (all $p < 0.0001$), disability days ($p < 0.0001$), and global symptom severity

($p < 0.0001$). Mean PAGI-SYM scores varied significantly in groups defined by disability days (all $p < 0.0001$), in which greater symptom severity was associated with more disability days (Rentz et al, 2004; Revicki et al, 2004).

7 STUDY ACTIVITIES

7.1 Screening Procedures (Day –28 to Day -1)

The following will be performed/collected during the Screening Period from Day -28 to Day -1 after obtaining informed consent with a properly signed ICF (Section 10.4):

- Obtain demographic data (age, gender, self-reported race/ethnicity)
- Obtain medical/surgical history, including specific information related to any prior or existing medical conditions or surgical procedures involving the dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological systems (Section 6.2)
- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) prior to collection of any laboratory samples and after patients have rested for 5 minutes in a supine position; obtain the patient's weight (as necessary to determine the response to Exclusion Criterion #5 [Section 4.3] and on Day -1) and height (Section 6.3)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4)
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5)
- Perform a serum pregnancy test for all women who are of childbearing potential
- Obtain 12-lead ECGs in triplicate, with 1 minute separating the first and second recordings and 1 minute separating second and third recordings (Section 6.6)
- Administer the GCSI (Section 6.8, Appendix 2)
- Record all prescription and over-the-counter medications (including herbal medications) taken within 30 days before the Screening
- Assess/record AEs from the time of informed consent
- Administer the nutrient satiety test (Section 6.76.10) after the patient has fasted overnight and after any medications that can alter GI sensation or accommodation or gastric emptying have been held overnight
- Confirm patient meets inclusion criteria and no exclusion criteria (Section 4.2 and Section 4.3, respectively)
- Administer the GEBT (Section 6.10) on Day -1 after the patient 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)

- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations (Section 6.5) and the nutrient satiety test (Section 6.7) is administered on Day 1 predose
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the days of the nutrient satiety test (Section 6.7)
- Randomize patient on Day -1

7.2 Day 1 Predose

The following will be performed/collected on Day 1 in the clinic before the patient receives study drug:

- Obtain medical/surgical history since Screening, including specific information related to any prior or existing medical conditions or surgical procedures involving the dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological systems (Section 6.2)
- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine position (Section 6.3)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4)
- Collect blood samples for clinical chemistry, and hematology after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5)
- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test
- Record all prior prescription and over-the-counter medications (including herbal medications) taken since Screening
- Assess/record AEs since Screening
- Administer:
  - Nutrient satiety test (Section 6.76.10)
  - GCSI (Section 6.8, Appendix 2)
  - PAGI-SYM (Section 6.9, Appendix 2)

7.3 Day 1 After Baseline Evaluations Through Day 13

7.3.1 Day 1

- Administer first dose of study drug in the clinic

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) 2 hours postdose after patients have rested 5 minutes in a supine position (Section 6.3)
- Dispense study drug and instruct the patient on its preparation and administration BID starting with the second dose on Day 1 and continuing through Day 14 (Section 5.2 and Section 6.11)
- Dispense dosing diary and instruct the patient on its completion (Section 5.8.1)
- Instruct the patient not to take any Day 14 doses of study drug before the Day 14 clinic visit, and to bring the dosing diary and all study drug supplies to the Day 14 visit
- Record all medications the patient received since the predose assessment
- Assess/record AEs since the predose assessment
- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations, the nutrient satiety test (Section 6.7), and the GEBT (Section 6.10) on Day 14 and/or on Day 15
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the Day 14 visit (for the nutrient satiety test)

7.4 Early Termination Procedures

If a patient discontinues study drug early (Section 6.14.1), the patient should return to the study site within 24 hours of withdrawal and complete all of the procedures outlined for the EOT (Section 7.5). If a patient withdraws early from the study (Section 6.14.2), 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 (Section 7.5). All study drug and supplies and the dosing diary will be collected.

7.5 End of Treatment Visits (Day 14 and Day 15)

Patients will complete EOT visit(s) at early termination (Section 7.4) or on Day 14 and Day 15. During the EOT visits, the following will be completed:

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature), prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine (Section 6.3) on Day 14 or Day 15
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4) on Day 14 or Day 15
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5) on Day 14 or Day 15

- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test on Day 14 or Day 15
- Administer:
  - Nutrient satiety test (Section 6.76.10) on Day 14
  - GCSI (Section 6.8, Appendix 2) on Day 14 or Day 15
  - PAGI-SYM (Section 6.9, Appendix 2) on Day 14 or Day 15
  - GEBT (Section 6.10) on Day 15
- Administer first Day 14 dose of study drug on Day 14; administer the second Day 14 dose of study drug on Day 14 or instruct patient to take second Day 14 dose of study drug on Day 14 after the patient leaves the clinic
- Record all prescription and over-the-counter medications (including herbal medications) taken since the Day 1 visit through Day 15 before the patient leaves the clinic
- Assess/record AEs since last visit through Day 15 before the patient leaves the clinic
- Collect study drug, dosing diary, and assess study drug compliance on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15
- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations on Day 28 (±1 day), the nutrient satiety test (Section 6.7) on Day 28, and the GEBT (Section 6.10) on Day 27 or Day 29
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the Day 28 visit (for the nutrient satiety test)

7.6 End of Study (Day 28 ±1 Day)

Patients will complete the EOS assessments on Days 27 through Day 29. The following EOS assessments will be completed:

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature), prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine position (Section 6.3) on Day 28 (±1 day)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4) on Day 28 (±1 day)
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5) on Day 28 (±1 day)

- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test on Day 28 (±1 day)
- Administer:
  - Nutrient satiety test (Section 6.76.10) on Day 28
  - GCSI (Section 6.8, Appendix 2) on Day 28 (±1 day)
  - PAGI-SYM (Section 6.9, Appendix 2) on Day 28 (±1 day)
  - GEBT (Section 6.10) on Day 27 or Day 29
- Collect study drug, dosing diary, and assess study drug compliance on Day 28 (±1 day) (if not done on Day 14 or Day 15)
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations
- Assess/record AEs since last visit through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations

7.7 Telephone Follow-up Day 44 (±3 Days) (30 ±3 Days After Last Dose)

During telephone Follow-up on Day 44 (±3 days), the following will be completed:

- Call the patient to see if any SAEs were experienced during the 30 ±3 days after the last dose of study drug
- Record SAEs in the eCRF, if applicable
- Report SAEs following SAE reporting timelines per Section 6.12.1

8 QUALITY CONTROL AND ASSURANCE

Regular monitoring and an independent audit, if conducted, must be performed according to International Council on Harmonisation (ICH)-GCP (Section 10.6).

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., GLPs, Good Manufacturing Practices).

The investigational site will provide direct access to all trial-related sites, source data/documents (including patient diaries), and reports for the purpose of monitoring and auditing by Censa Pharmaceuticals (or designee), and inspection by local and regulatory authorities.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Descriptive statistics, including numbers and percentages for categorical variables, and numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Exploratory analyses may also be performed. Listings of individual patient data will be produced. Additional details can be found in the statistical analysis plan.

9.2 Determination of 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 (Section 6.7), in women with moderate to severe diabetic gastroparesis. A total of 10 patients 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.

9.3 Analysis Populations

Two study populations will be analyzed:

- Safety population: all patients who were randomized and received any amount of study drug (CNSA-001 or placebo)
- Efficacy population: all patients who were randomized, received any amount of study drug (CNSA-001 or placebo), and had available Day 1 predose and Day 14 nutrient satiety test (Section 6.7) maximum tolerated volume results

9.4 Demographics, Baseline Characteristics, Enrollment, Protocol Deviations, and Patient Disposition

Enrollment, protocol deviations, demographics (age, sex, race/ethnicity), prior and concomitant medications, and medical history will be summarized by treatment group using descriptive statistics. Discontinuations from study drug and the study will be summarized by treatment group as well and the reasons for discontinuation will be listed.

9.5 Statistical Analysis of Efficacy Variables

Efficacy will be assessed in the Efficacy population.

The primary efficacy measure will be the changes in maximal tolerated volume consumed during the nutrient satiety test (Section 6.7) from Day 1 to Day 14 and Day 28. The changes from Day 1 to Day 14 and from Day 1 to Day 28 in maximal tolerated volume consumed

during the nutrient satiety test will be compared between treatment groups using a student's t-test.

Secondary efficacy measures will consist of changes in the following from baseline through Day 14 (±1 day) and through Day 28 (±1 day):

- PAGI-SYM (Section 6.9, Appendix 2) subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores
- Gastric emptying as measured by the GEBT (Section 6.10)

The primary and secondary measures will be summarized by treatment group at each visit as well as changes from baseline using summary statistics (number of patients, mean, standard deviation, median, and range) including 95% confidence intervals for changes from baseline. Additional analyses may be conducted, and details will be provided in the statistical analysis plan (SAP).

9.6 Safety Analysis

Safety will be assessed in the Safety population. The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and treatment group. Severity of AEs and SAEs will be summarized similarly. Those AEs leading to premature discontinuation from the study drug and the serious TEAEs will be presented in a table or a listing. Clinical laboratory and HbA1c test results and vital signs will be summarized at each visit as will changes from baseline for each treatment group. A frequency distribution of abnormal physical examination results will be provided. Additional details will be provided in the SAP.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Table 1 summarizes the administrative structure for this study.

Table 1: Administrative Structure for GAS-001 Study

Contract Research Organization	InClin, Inc. 2655 Campus Drive, Suite 100 San Mateo, CA, 94403 Phone: [redacted]

10.2 Institutional Review Board Approval

The Investigator will submit this protocol, any protocol modifications, and the patient consent form to be utilized in this study, to the appropriate IRB for review and approval. This committee must operate in accordance with the ICH GCP. Documentation of approval of the protocol and the informed consent document must be forwarded to Censa Pharmaceuticals (or designee) prior to initiation of this study.

The Investigator is responsible for assuring continuing review and approval of the clinical study. The Investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to his/her IRB. The Investigator will not make any changes in the protocol without IRB approval except as necessary to eliminate apparent immediate hazards to the patients. The Investigator will provide progress reports to the IRB as required by the IRB. If the study remains in progress for >1 year, the Investigator must obtain annual renewal and re-approval from the IRB. Documentation of renewal must be submitted to Censa Pharmaceuticals (or designee). The Investigator will provide notice to the IRB of completion of participation in the study.

10.3 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol; GCPs, including ICH Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; applicable regional regulatory requirements (i.e., ICH E6); and in accordance with the ethical principles of the Declaration of Helsinki.

10.4 Patient Information and Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion in understandable terms of the purposes, procedures, risks and possible benefits of participation, and rights of study patients will be conducted with patients, and, as appropriate, their legally authorized representatives (LARs; henceforth in the discussion of informed consent, study patient means "patient and/or LAR") and family members. The study patients should have

the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Study patients will be asked to carefully review the ICF approved by Censa Pharmaceuticals (or designee) and the IRB. After any needed discussion and consideration of study participation and before undergoing any procedures specifically for the study, the patient will sign the ICF. The ICF will be retained in the study patient's study records, and a copy of the ICF will be given to the study patient.

Patients may decline to participate in the study and withdraw consent at any time or for any reason throughout the course of the study without AEs on the quality of their medical care.

10.5 Confidentiality

The Investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. This extends to testing of biological samples and genetic tests in addition to the clinical information relating to participants. Only an identification code (i.e., not names) should be recorded on any form or document submitted to Censa Pharmaceuticals, the Contract Research Organization (CRO), or the IRB. The Investigator must keep logs on screened and enrolled patients. In addition, the Investigator must have a list where the identity of all treated patients can be found.

The Investigator agrees that all information received from Censa Pharmaceuticals, including, but not limited to, the Investigator's Brochure, this protocol, CRFs, and any other information related to the protocol-specified treatment of the study, remain the sole and exclusive property of Censa Pharmaceuticals during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Censa Pharmaceuticals. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

The study monitor, other authorized representatives of Censa Pharmaceuticals, and representatives of the IRB may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, and hospital) and pharmacy records for the participants in this study. The clinical study site's research staff will permit access to such records.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

10.6 Study Monitoring

A clinical monitor authorized to represent Censa Pharmaceuticals will conduct site visits to inspect study data, patient's medical records, and eCRFs in accordance with ICH guidelines GCP, and applicable regulations and guidelines. The clinical monitor will also monitor ongoing drug accountability and adherence to protocol procedures. Details of clinical site monitoring are specified in a Clinical Monitoring Plan.

Independent audits may be conducted to ensure that monitoring practices are performed consistently across all participating sites and that monitors are following the Clinical Monitoring Plan.

The Investigator will allow representatives of the Censa Pharmaceuticals and regulatory authorities to inspect facilities and records relevant to this study.

10.7 Case Report Forms and Study Records

The eCRFs will be supplied by Censa Pharmaceuticals or designee for the recording of all information and study data as specified by this protocol. Original eCRF data should be handled in accordance with instructions from Censa Pharmaceuticals or designee. All eCRFs must be completed by the clinical study site's research staff authorized to do so by the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data reported in the eCRF derived from source documents should be consistent with the source documents. Source documents are defined as records of documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or patient-specific email correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by Censa Pharmaceuticals or designee and by regulatory authorities. The original ICF for each participating patient shall be filed with records kept by the Investigator, and copies shall be given to the patient.

Once all data queries and issues have been resolved for each patient the Investigator will electronically sign each patient's eCRF. This signature will indicate that the data have been thoroughly inspected and will thereby certify the contents of the eCRF.

Clinical data will be entered into a 21 Code of Federal Regulations (CFR) Part 11-compliant electronic data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered by the clinical study site's research staff directly from the source documents.

10.8 Protocol Violations/Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly. This is consistent with the following sections in ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1

- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

10.9 Access to Source Documentation

The Investigator agrees by his/her participation that the results of this study may be used for submission for national or international registration. If required, national or international authorities will be provided with the name of the Investigator and his or her address, full disclosure of his or her qualifications, any potential conflicts of interests, payments, and extent of involvement.

During site visits, the clinical monitor will review original patient records, drug accountability records, and additional documents as needed. During the course of the study, Censa Pharmaceutical's (or designee's) Quality Assurance personnel may conduct an on-site audit visit. The Investigator will provide direct access to and allow verification and copying of all trial-related documents (e.g., source data) for trial-related monitoring, audits, IRB reviews, and regulatory inspections.

10.10 Data Generation and Analysis

Some or all of the obligations of implementing or conducting this study may be transferred from Censa Pharmaceuticals to the CRO.

A case report, comprised of individual eCRFs, will be completed for every patient who signs an ICF and is enrolled into the study.

All original source documentation (laboratory results, treatment records, audit query responses, etc.) will be retained by the Investigator or institution unless specified otherwise by the protocol. The results as they become available will be entered on the appropriate eCRFs. Legible reproductions of the original laboratory reports for selected tests or variables will be submitted to Censa Pharmaceuticals or CRO as requested.

The eCRFs will be reviewed by a clinical monitor who will evaluate the completeness and accuracy of the data. Queries will be generated for omissions, corrections, and clarifications. Data may also be reviewed in-house by a clinical auditor and data management or other personnel.

Data analyses will be performed after database lock, when all queries have been resolved.

10.11 Retention of Data

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Censa Pharmaceuticals, if

applicable. It is the responsibility of Censa Pharmaceuticals to inform the Investigator when these documents no longer need to be retained.

10.12 Financial Disclosure

Each Investigator must submit to Censa Pharmaceuticals (or designee) financial disclosure information according to national law and/or local regulations.

10.13 Publication and Disclosure Policy

The data generated in this clinical study are the exclusive property of Censa Pharmaceuticals and are confidential. Authorship on any publication of the results from this study will be based on contributions to study design, patient enrollment, data analysis, interpretation of results, and drafting and editing of any publication in accordance with published authorship ethical guidelines for publication of research studies. Independent analysis and/or publication of these data by the Investigator(s) or any member of their staff is not permitted without the prior, written consent of Censa Pharmaceuticals.

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APPENDIX 1 SCHEDULE OF EVENTS

	Screening Period		Treatment Period		Follow-up Period			
					EOT		EOS	Telephone Follow-up
Evaluation	**-28 to -1**	**Day 1 (Predose)**	**Day 1 Through Day 13**	**Day 14[a]**	**Day 14[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					X	X	
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 patient 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 patients 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). Patients will fast overnight before blood sample collections.

[g] Patients 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 patient 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 patient 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), patients 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 patient 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 patient vomits after taking a dose of study drug, the patient 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] Patients 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 patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day).

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; 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 2 GCSI AND PAGI-SYM ASSESSMENT INSTRUMENTS

Gastroparesis Cardinal Symptom Index Questionnaire (English Version):

GCSI

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please *circle the number* that best describes how *severe* the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5

Khoury V, Dubois, D. GCSI Gastroparesis Cardinal Symptom Index information booklet. 2nd ed. Lyon, France: Mapi Research Trust; 2015. p 30.

Gastroparesis Cardinal Symptom Index Questionnaire (United States Spanish Version):

Este cuestionario le pregunta acerca de la gravedad de los síntomas que usted pueda haber tenido relacionados con sus problemas de estómago. No hay respuestas correctas ni incorrectas. Por favor conteste cada pregunta lo más precisamente posible.

Para cada síntoma, por favor marque con un círculo el número que mejor describa qué tan grave ha sido el síntoma durante las últimas 2 semanas. Si usted no ha tenido este síntoma, marque con un círculo el 0. Si el síntoma ha sido muy leve, marque con un círculo el 1. Si el síntoma ha sido leve, marque con un círculo el 2. Si ha sido moderado, marque con un círculo el 3. Si ha sido grave, marque con un círculo el 4. Si ha sido muy grave, marque con un círculo el 5. Por favor, asegúrese de contestar cada pregunta.

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
1.	Náuseas (sentirse enfermo(a) del estómago como si fuera a vomitar)	0	1	2	3	4	5
2.	Arcadas/Ganas de vomitar (como si fuera a vomitar pero no sale nada)	0	1	2	3	4	5
3.	Vómitos	0	1	2	3	4	5
4.	Sensación de estómago lleno	0	1	2	3	4	5
5.	No poder terminar una comida de porción normal	0	1	2	3	4	5
6.	Sentirse excesivamente lleno(a) después de las comidas	0	1	2	3	4	5
7.	Pérdida del apetito	0	1	2	3	4	5
8.	Hinchado(a) de comer (sentir que necesita aflojar su ropa)	0	1	2	3	4	5
9.	Estómago o barriga visiblemente más grande	0	1	2	3	4	5

GCSI – USA / US Spanish – Final version – MAPI Research Institute
Spanish (USA)_ Versión 1.0 _Standard

Updated_cbe

Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (United States EnglishVersion)

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please circle the number that best describes how severe the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5
10. upper abdominal (above the navel) pain	0	1	2	3	4	5
11. upper abdominal (above the navel) discomfort	0	1	2	3	4	5
12. lower abdominal (below the navel) pain	0	1	2	3	4	5

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
13. lower abdominal (below the navel) discomfort	0	1	2	3	4	5
14. heartburn (burning pain rising in your chest or throat) during the day	0	1	2	3	4	5
15. heartburn (burning pain rising in your chest or throat) when lying down	0	1	2	3	4	5
16. feeling of discomfort inside your chest during the day	0	1	2	3	4	5
17. feeling of discomfort inside your chest at night (during sleep time)	0	1	2	3	4	5
18. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	0	1	2	3	4	5
19. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	0	1	2	3	4	5
20. bitter, acid or sour taste in your mouth	0	1	2	3	4	5

PAGI-SYM (Standard) - United States/English - Original version - Mapi
PAGI_SYM_AU2.1_standard_eng-USori doc

Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (United States Spanish Version)

Este cuestionario le pregunta acerca de la gravedad de los síntomas que usted pueda haber tenido relacionados con sus problemas de estómago. No hay respuestas correctas ni incorrectas. Por favor conteste cada pregunta lo más precisamente posible.

Para cada síntoma, por favor marque con un círculo el número que mejor describa qué tan grave ha sido el síntoma durante las últimas 2 semanas. Si usted no ha tenido este síntoma, marque con un círculo el 0. Si el síntoma ha sido muy leve, marque con un círculo el 1. Si el síntoma ha sido leve, marque con un círculo el 2. Si ha sido moderado, marque con un círculo el 3. Si ha sido grave, marque con un círculo el 4. Si ha sido muy grave, marque con un círculo el 5. Por favor, asegúrese de contestar cada pregunta.

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
1.	Náuseas (sentirse enfermo(a) del estómago como si fuera a vomitar)	0	1	2	3	4	5
2.	Arcadas/Ganas de vomitar (como si fuera a vomitar pero no sale nada)	0	1	2	3	4	5
3.	Vómitos	0	1	2	3	4	5
4.	Sensación de estómago lleno	0	1	2	3	4	5
5.	No poder terminar una comida de porción normal	0	1	2	3	4	5
6.	Sentirse excesivamente lleno(a) después de las comidas	0	1	2	3	4	5
7.	Pérdida del apetito	0	1	2	3	4	5
8.	Hinchado(a) de comer (sentir que necesita aflojar su ropa)	0	1	2	3	4	5
9.	Estómago o barriga visiblemente más grande	0	1	2	3	4	5
10.	Dolor abdominal superior (arriba del ombligo)	0	1	2	3	4	5
11.	Malestar abdominal superior (arriba del ombligo)	0	1	2	3	4	5

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
12.	Dolor abdominal inferior (abajo del ombligo)	0	1	2	3	4	5
13.	Malestar abdominal inferior (abajo del ombligo)	0	1	2	3	4	5
14.	Acidez (dolor ardiente que sube en su pecho o garganta) durante el día	0	1	2	3	4	5
15.	Acidez (dolor ardiente que sube en su pecho o garganta) cuando está recostado(a)	0	1	2	3	4	5
16.	Sentir malestar en el pecho durante el día	0	1	2	3	4	5
17.	Sentir malestar en el pecho durante la noche	0	1	2	3	4	5
18.	Regurgitación o reflujo (fluido o líquido que sube de su estómago hasta la garganta) durante el día	0	1	2	3	4	5
19.	Regurgitación o reflujo (fluido o líquido que sube de su estómago hasta la garganta) cuando está recostado(a)	0	1	2	3	4	5
20.	Sabor agrio, ácido o amargo en la boca	0	1	2	3	4	5

PAGI-SYM (Standard) - United States/Spanish - Version of 09 Nov 07 - Mapi.
ID4237/PAGI_SYM_AU2.1_standard_spa-US doc

CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Study Phase:	2 Pilot
Product Name:	CNSA-001 (sepiapterin)
Dosage Form:	Oral powder for suspension
Indication:	Treatment of women with moderate to severe diabetic gastroparesis
Investigators:	Multicenter study
Sponsor:	Censa Pharmaceuticals 65 William Street Wellesley, MA 02481
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	06 September 2018
Amendment 1:	09 October 2018

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

SPONSOR SIGNATURES

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Final Date:	06 September 2018
Amendment 1:	09 October 2018

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed [redacted] Date: 09 OCT 2018

[redacted]
Censa Pharmaceuticals, Inc.

Sig[redacted] Date: 09 OCT 2018

[redacted]
Censa Pharmaceuticals

INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Final Date:	06 September 2018
Amendment 1:	09 October 2018

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signature | Date (DD Month YYYY)

Printed Name, Credentials

Affiliation

Address

Phone Number

PROTOCOL AMENDMENT 1 (OCTOBER 9, 2018)

Protocol GAS-001 is amended primarily for the following reasons:

1. Added Exclusion Criterion to exclude patients with baseline cardiovascular instability.
2. Added Exclusion Criterion to exclude patients with PKU or hyperphenylalaninemia.
3. Updated the discontinuation criteria related to AEs in Section 6.14.1.
4. Updated the study stopping criteria to include specific examples of adverse event criteria for temporarily or permanently stopping the study.

Major changes to the protocol are as follows:

Synopsis and Section 4.3: Added two additional exclusion criteria for patients with baseline cardiovascular instability and for patients with PKU or hyperphenylalaninemia.

Section 6.14.1: Added drug class adverse events to individual discontinuation criteria, specifically, hypersensitivity reactions, anaphylaxis, and gastritis.

Section 6.14.3: Added examples of study stopping criteria associated with adverse event criteria of severity, frequency, and relatedness.

SYNOPSIS

Sponsor:
Censa Pharmaceuticals

Name of Finished Product:
CNSA-001

Name of Active Ingredient:
Sepiapterin

Name of Inactive Ingredients:
Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid

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

Study Number:
GAS-001

Study Phase: Phase 2 pilot

Primary Objective:

- 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:

In women with moderate to severe diabetic gastroparesis:

- To evaluate improvement of gastroparesis symptoms measured by global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]) (Section 6.8, Appendix 2)
- To evaluate patient-reported outcomes (PROs) as measured by the quality of life questionnaire Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) (Section 6.9, Appendix 2)
- To evaluate the emptying of the stomach as measured by the Gastric Emptying Breath Test (GEBT)
- To assess the safety and tolerability of CNSA-001 20 mg/kg/day

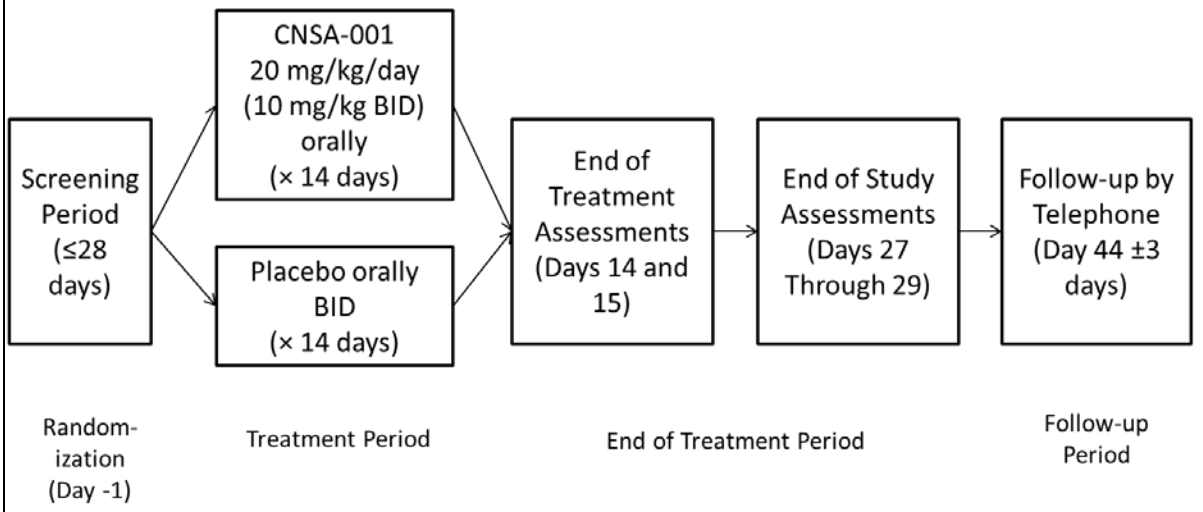
Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled pilot study of multiple doses of CNSA-001 (sepiapterin) powder for suspension administered orally in women with moderate to severe diabetic gastroparesis. Patients will be randomized in a ratio of 1:1 to receive CNSA-001 20 mg/kg/day or placebo, each dosed twice a day (BID); each group will consist of 10 patients. All patients will receive the standard of care for diabetic gastroparesis. Approximately 4 centers will participate in this study. The study design is summarized in the study schema below. A schedule of study events is provided in Appendix 1.

All study clinic visits will be outpatient visits.

Patients will continue their usual diet without modification throughout the study. Patients are required to have been fasting overnight for the following assessments:

- Clinical laboratory, including glycosylated hemoglobin A1c (HbA1c), tests
- The nutrient satiety test
- The GEBT



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, patients will undergo Screening procedures to determine study eligibility, as indicated in Appendix 1. Patients 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 patients will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Patients will undergo procedures during the Treatment Period as indicated in Appendix 1.

End of Treatment Period (Day 14 Through Day 15 Evaluations)
Patients will undergo End of Treatment (EOT) evaluations on Day 14 and Day 15 as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 14. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) 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)
Patients will undergo End of Study evaluations on Day 28 (±1 day) as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 28. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) 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])
Patients will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix 1.

Number of Patients:
Up to 20 women ≥18 and ≤65 years of age will be enrolled in this study and randomized in a ratio of 1:1 to receive CNSA-001 or placebo.

Main Criteria for Inclusion and Exclusion:
Patients are eligible to participate if they meet all the following inclusion criteria:

1. Informed consent
2. Females ≥18 and ≤65 years of age
3. Diagnosis of diabetes mellitus
4. Documentation of delayed gastric emptying on gastric emptying scintigraphy (within 1 year of enrollment)
5. Symptoms of gastroparesis for at least 6 months with GCSI (Section 6.8, Appendix 2) score >21 indicating moderate to severe symptoms
6. Gastric accommodation, as measured by nutrient satiety testing, of ≤600 mL
7. Negative upper endoscopy or upper gastrointestinal (GI) series within 3 years of enrollment (no evidence of mechanical obstruction or peptic ulcer disease)
8. Either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following:
   - Hormonal contraception (stable dose for 3 months)
   - Intrauterine device/Intrauterine Hormone-releasing System
   - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

   Patients who are abstinent will not be required to use a contraceptive method unless they become sexually active.
9. If on analgesics, including narcotics; promotility agents, including metoclopramide, or neuromodulators, including tricyclic antidepressants, gabapentin, and pregabalin, doses are stable for >30 days before randomization and the patient is not expected to require dose changes during the study through the EOT
10. Have not used tobacco (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks prior to Day 1 and willingness to abstain from these products during the study through the EOT

Patients are not eligible to participate if they meet any of the following exclusion criteria:

1. Male gender
2. Normal gastric emptying
3. Gastroparesis from postsurgical etiologies
4. Another active disorder that could, in the opinion of the Investigator, explain symptoms
5. Weight >100 kg
6. Alanine aminotransferase > 2× upper limit of normal (ULN)
7. Pregnant, breastfeeding, or considering pregnancy
8. Clinically significant cardiac arrhythmia at Screening
9. QT interval corrected for heart rate (QTc) ≥480 msec (based on triplicate measurements taken at Screening)
10. Resting heart rate ≤40 or ≥110 bpm or resting blood pressure <90/40 mmHg or >150/90 mmHg at Screening or prior to the first administration of study drug.
11. Recent clinically GI significant bleeding
12. Taking levodopa or domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT

13. Taking erythromycin within 30 days before randomization or expected to require erythromycin within 30 days before randomization or expected to require erythromycin during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization
14. Taking any fundic-relaxing agents including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT
15. Taking any systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)
16. Pulmonary dysfunction (e.g., chronic obstructive pulmonary disease)
17. Surgery for placement of a gastric stimulator within the past 6 months (patients postoperative >6 months with persistent symptoms and delayed gastric emptying are eligible)
18. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, small bowel malabsorption) that could affect the absorption of study drug or contraindicate undergoing the GEBT
19. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
20. History of allergies or adverse reactions to tetrahydrobiopterin or related compounds, to any excipients in the study drug formulation, or to egg, wheat, or algae (Spirulina)
21. Inability to tolerate oral medication
22. Current participation in any other investigational drug study or use of any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening
23. Any clinically significant laboratory abnormality; in general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range unless deemed not clinically significant by the Investigator
24. Major surgery within the previous 90 days
25. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study
26. History of alcohol or drug abuse within 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
27. Episodes of ketoacidosis or hypoglycemia that are frequent as defined by the Investigator
28. History of phenylketonuria (PKU) or hyperphenylalaninemia.
29. Any other conditions, including diabetic comorbidities, that, in the opinion of the Investigator or Sponsor, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

Test Product, Dose, and Mode of Administration:

The test product is CNSA-001 (sepiapterin) oral powder for suspension. CNSA-001 will be suspended in Medisca® Oral Mix prior to dispensing to the patient. Patients randomized to receive CNSA-001 will receive CNSA-001 20 mg/kg/day (i.e., 10 mg/kg BID) for 14 days.

Reference Therapy; Dose; and Mode of Administration:

The reference product is placebo. The placebo is a ready-made suspension containing microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, ascorbic acid, and colorant (Yellow No. 6) that is suspended in Medisca® Oral Mix.

Duration of Treatment:
Patients will be treated for a total of 14 days.

Criteria for Evaluation:

Safety:
Safety and tolerability of CNSA-001 as measured by severity and number of treatment-emergent adverse events (TEAEs), including assessment of severity of TEAEs, and changes in clinical laboratory and HbA1c tests, vital signs, and physical examinations

Efficacy:
The primary efficacy measure will be the change in maximal tolerated volume consumed during the nutrient satiety test from Day 1 to Day 14 and Day 1 to Day 28.
Secondary efficacy measures will consist of changes in the following from baseline to Day 14 and baseline to Day 28 (±1 day):

- GCSI (Section 6.8, Appendix 2) PAGI-SYM (Section 6.9, Appendix 2) subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores
- Gastric emptying as measured by the GEBT

Statistical Methods:
The following study populations will be analyzed:

- Safety population: all patients who were randomized and received any amount of study drug (CNSA-001 or placebo)
- Efficacy population: all patients who were randomized, received any amount of study drug (CNSA-001 or placebo), and had available Day 1 and Day 14 nutrient satiety test maximum tolerated volume results

Safety will be assessed in the Safety population. Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and treatment group. Severity of AEs and serious adverse events (SAEs) will be summarized similarly. Those AEs leading to premature discontinuation from the study drug and the serious TEAEs will be presented in a table or a listing. Clinical laboratory and HbA1c test results and vital signs will be summarized at each visit as will changes from baseline for each treatment group. A frequency distribution of abnormal physical examination results will be provided.
Efficacy will be assessed in the Efficacy population. The changes from Day 1 to Day 14 and from Day 1 to Day 28 in maximal tolerated volume consumed during the nutrient satiety test will be compared between treatment groups using a student's t-test. Results from the nutrient satiety test through Day 14 and Day 28, the GEBT through Day 15 and Day 27 or Day 29, and the GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) through Day 14 (+1) and through Day 28 (±1) will be summarized using summary statistics (number of patients, mean, standard deviation, median, and range) at each visit as well as changes from baseline within each treatment group. The 95% confidence intervals for the changes from baseline will be provided. Additional analyses may be conducted, and details will be provided in the statistical analysis plan.

Date of Original Protocol: 06 September 2018
Date of Amendment 1: 09 October 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALB	Albumin
ALT	Alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT])
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
$AUC_{0\text{-last}}$	Area under the concentration time curve from 0 to the last measurement
BH4	Tetrahydrobiopterin
BID	Twice a day
BUN	Blood urea nitrogen
^{13}C	Carbon-13
Ca	Calcium
CFR	Code of Federal Regulations
Cl	Chloride
C_{max}	Maximum concentration
CO_2	Carbon dioxide
$^{12}CO_2$	Carbon-12 dioxide
$^{13}CO_2$	Carbon-13 dioxide
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GCSI	Gastroparesis Cardinal Symptom Index
GEBT	Gastric Emptying Breath Test
GGT	Gamma glutamyl transferase
GI	Gastrointestinal

GLP	Good Laboratory Practice
HbA1c	Glycosylated hemoglobin A1c
HCG	Human chorionic gonadotropin
HCT	Hematocrit
HEENT	Head, eyes, ears, nose, and throat
HGB	Hemoglobin
ICF	Informed consent form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
K	Potassium
kPCD	the Gastric Emptying Breath Test metric; "k" is a multiplier of 1000, and "PCD" is an acronym for percent carbon-13 dose excreted (as carbon-13 dioxide)
LAR	legally authorized representative
LDH	Lactate dehydrogenase
MedDRA®	Medical Dictionary for Regulatory Activities
Na	Sodium
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
PAGI-QOL	Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity
PRO	Patient-reported outcome
QTc	QT interval corrected for heart rate
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction

TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell

1 INTRODUCTION

1.1 Diabetic Gastroparesis

Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction; symptoms are chronic with episodic symptom exacerbation (Parkman et al, 2004). Gastroparesis affects women 4 times more than men (Soykan, et al, 1998). Idiopathic gastroparesis accounts for most cases, but gastroparesis is frequently associated with diabetes (diabetic gastroparesis) (Soykan, et al, 1998; Karamanolis et al, 2007). Several cross-sectional studies have found delayed gastric emptying of solids and/or liquids in 30% to 50% of patients with Type 1 or Type 2 diabetes (Horowitz et al, 2002). Patients with diabetes mellitus commonly experience gastric and intestinal dysfunction (Feldman and Schiller, 1983).

The actual mechanism of diabetic gastroparesis is not well known. Vagal nerve dysfunction and/or damage, interstitial cells of Cajal loss, and smooth muscle and enteric neuron dysfunction have all been implicated in the pathogenesis of diabetic gastroparesis (Stacher, 2001; Parkman et al, 2004). In addition, acute hyperglycemia has the potential to slow gastric emptying (Camilleri et al, 2013).

At a molecular level, attention has been devoted to the potential role of altered nitrergic signaling in the enteric nervous system. Gastric motility is regulated in large part by neurons of the enteric nervous system located in the muscle wall (Wood et al, 1999). These neurons are either excitatory (releasing acetylcholine) or inhibitory (releasing nitric oxide [NO] and vasoactive intestinal peptide). Nerves throughout the luminal gastrointestinal (GI) tract express neuronal nitric oxide synthase (nNOS), which generates NO, a key neurotransmitter in the regulation of GI motility (Takahashi, 2003); it is the principal nonadrenergic noncholinergic inhibitory neurotransmitter in the GI tract. In diabetic rats, which serve as a model for type 1 diabetes, nNOS expression was found to be impaired. This impairment in nNOS messenger RNA expression was associated with impaired smooth muscle relaxation in response to electrical stimulation of circular muscle fibers obtained from the proximal stomach of these rats (Takahashi et al, 1997). It has been demonstrated that female diabetic rats had slower gastric emptying than age matched diabetic male rats, female control rats had greater nitrergic relaxation of circular antral muscle strips compared to male controls, and nitrergic relaxation was impaired in diabetic female rats but not matched diabetic male rats (Gangula et al, 2007).

The core signs and symptoms of gastroparesis by incidence are nausea (92% to 96%), vomiting (68% to 88%), postprandial fullness (54% to 77%), early satiety (42% to 60%), and upper abdominal pain (36% to 85%) (Soykan et al, 1998; Hoogerwerf et al, 1999; Anaparthy et al, 2009). Patients may experience any combination of signs and symptoms with varying degrees of severity. Pain is less prevalent in diabetic gastroparesis than idiopathic gastroparesis. Patients with diabetic gastroparesis may experience further derangement of glucose control because of unpredictable gastric emptying and altered absorption of orally administered hypoglycemic drugs, which may, in turn, affect measurement of core signs and symptoms. Severe signs and symptoms may cause complications such as malnutrition,

esophagitis, and Mallory-Weiss tears. Gastroparesis adversely affects the lives of patients with the disease, resulting in decreased social interaction, poor work functionality, and development of anxiety or depression (Soykan et al, 1998; Parkman et al, 2004).

1.2 Impaired Gastric Accommodation in Gastroparesis

Patients with diabetic gastroparesis have also been shown to have gastric hypersensitivity, especially in the postprandial state, and impairment of the postprandial accommodation response. (Kumar et al, 2008). The stomach functions as 2 separate regions: the fundus acts as a reservoir accommodating a meal without a significant increase in intragastric pressure, and the distal stomach/antrum triturates gastric contents. Receptive relaxation or accommodation is vagally mediated resulting in the release of NO and activation of nitrergic myenteric neurons. Nitrergic signaling is responsible for gastric accommodation and pyloric relaxation in response to a meal (Ishiguchi et al, 2001).

Impaired accommodation has been associated with symptoms of early satiety and weight loss in patients with idiopathic gastroparesis (Karamanolis et al, 2007). A study of patients with diabetic gastroparesis found that 90% of patients had impaired gastric accommodation to a nutrient meal (Kumar et al, 2008). In the distal stomach, NO is required for the propulsive contractions that triturate gastric contents and control of pyloric closure; lack of NO can lead to delayed gastric emptying and impaired gastric accommodation (Gangula et al, 2007).

Several co-factors are known to be important for nNOS activity, including nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), calcium, and tetrahydrobiopterin (BH4) (Werner et al, 2003). The homodimeric conformation of all 3 isoforms of nitric oxide synthase (NOS) is regulated by BH4 (Werner et al, 2003). In the absence of BH4, uncoupling of NO production occurs and leads to super oxide production, resulting in further impaired nNOS bioactivity.

1.3 Current Treatment of Diabetic Gastroparesis

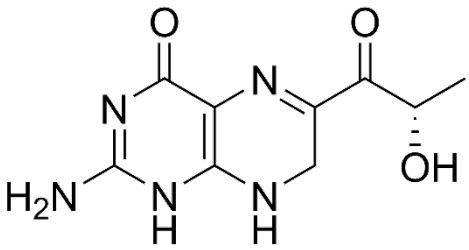
Therapies for gastroparesis have been targeted at accelerating gastric emptying or controlling symptoms. Available therapies for accelerating gastric emptying are limited in number and efficacy. These include metoclopramide (Snape et al, 1982), erythromycin (Arts et al, 2005), and domperidone (not available in the United States [US]) (Prakash and Wagstaff, 1998). There is also poor correlation between gastric emptying and baseline symptom severity (Karamanolis et al, 2007; Talley et al, 2001) and in response to therapeutic intervention. In part, as a result of lack of understanding of the underlying pathogenesis that leads to alterations in GI motility and sensation, medical therapies have not been targeted at the underlying pathophysiology of gastroparesis.

The first-line medical therapy for patients with diabetic gastroparesis is generally a combination of an antiemetic agent in addition to the promotility drug. Unfortunately, many patients with diabetic gastroparesis will not experience adequate symptom relief despite first-line therapy. For patients with refractory disease, options include combination prokinetic therapy, psychotropic medications, pyloric botulinum toxin injection, and gastric electric stimulation (Fass, 2010; Camilleri et al, 2013).

1.4 CNSA-001 (Sepiapterin)

Sepiapterin is 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$.

The chemical structure of sepiapterin is:



Sepiapterin serves as a substrate for BH4 synthesis via the pterin salvage pathway (Mayer and Werner, 1995). Oral administration of sepiapterin was shown to be more potent (>2 fold) than oral administration of BH4 in increasing intracellular BH4 in normal mice (Sawabe et al, 2002). Translation of this finding to humans has been confirmed in a Phase 1 study, PKU-001, conducted by Censa Pharmaceuticals.

1.5 Rationale for Study

BH4 biosynthesis is impaired in chronic diabetes. The mechanism of impairment is not well understood but is thought to be a result of hyperglycemia-induced proteasome-mediated degradation of GTP-cyclohydrolase, the rate-limiting enzyme in the synthesis pathway for BH4 (Xu et al, 2007).

CNSA-001 is the first viable formulation of sepiapterin, shown to increase intracellular BH4 (Section 1.4), intended for the treatment of female patients with diabetic gastroparesis. CNSA-001 was studied in a single and multiple ascending-dose study in healthy volunteers, the Phase 1 study, Study PKU-001. Part A of this study assessed the safety and pharmacokinetics of CNSA-001 at 6 dose levels inclusive of an assessment of food effect (i.e., 2.5 mg/kg, 7.5 mg/kg, 20 mg/kg, 40 mg/kg, 80 mg/kg, and 10 mg/kg [to assess food effect]). Additionally, Kuvan® (sapropterin dihydrochloride), a synthetic BH4 commercially available product, was administered at equivalent doses for the first 3 dose levels (2.5 mg/kg, 7.5 mg/kg, and 20 mg/kg). Dose-dependent correlations between CNSA-001 and plasma BH4 concentrations were observed with each successive dose level. Dose proportionality was observed between the top 2 dose levels (40 mg/kg and 80 mg/kg) and resultant BH4 concentrations. Administration with a standard high-fat (approximately 50 percent of total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) meal resulted in approximately 80% higher plasma BH4 concentrations (area under the concentration time curve from 0 to the last measurement [$AUC_{0\text{-last}}$] and maximum concentration [C_{max}]) than in subjects who had fasted before receipt of CNSA-001. Treatment-emergent adverse events (TEAEs) in Part A of Study PKU-001 were reported in 26 subjects (44.1%, 26/59). The TEAEs for CNSA-001 were generally mild and consistent with reported adverse events (AEs) for Kuvan® and placebo. The frequency of TEAEs did

not appear to increase with increasing dose. The TEAEs that were judged to be related to study treatment were reported in 17 subjects: 11 subjects (26.2%, 11/42) who received CNSA-001, 4 subjects (44.4%, 4/9) who received Kuvan®, and 2 subjects (25.0%, 2/8) who received placebo. No TEAEs were severe or serious or led to discontinuation of study drug. Headache and dizziness were the most common TEAEs , but these TEAEs occurred at a similar frequency as with placebo.

Part B of Study PKU-001 assessed multiple ascending doses CNSA-001 in healthy volunteers. Data indicate CNSA-001 was well tolerated following daily doses of 5, 20, and 60 mg/kg/day for 7 days and that TEAEs were reported in 14 subjects (58.3%, 14/24). The TEAEs in subjects who received CNSA 001 were mild or moderate and consistent with the TEAEs in subjects who received placebo: TEAEs were experienced by 10 subjects (55.6%, 10/18) who received CNSA-001 at doses from 5 mg/kg to 60 mg/kg daily for 7 days and by 4 subjects (66.7%, 4/6) who received placebo. No TEAEs were severe, serious, or led to discontinuation. Of the 10 TEAEs reported in subjects who received CNSA-001, only 4 were judged to be related to study drug, and, of the 4 TEAEs reported in subjects who received placebo, only 1 was judged to be related to study drug. Somnolence, fatigue, headache, and procedural pain (secondary to performance of 2 sequential lumbar punctures 7 days apart) were the most common TEAEs reported, and they occurred at a similar frequency when compared with placebo with the exception of fatigue and headache, which were each reported in 2 subjects who received CNSA-001 (11.1%, 2/18).

This Phase 2 pilot study will assess CNSA-001 doses of 20 mg/kg/day administered as 10 mg/kg twice a day (BID) in comparison to placebo administered BID in female patients with diabetic gastroparesis. This study will help support the design of future Phase 2/3 studies in patients with diabetic gastroparesis.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the impact of CNSA-001 on gastric accommodation, as measured by nutrient satiety testing (Section 6.7), in women with moderate to severe diabetic gastroparesis.

2.2 Secondary Objectives

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

- To evaluate improvement of gastroparesis symptoms measured by global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]) (Section 6.8, Appendix 2)
- To evaluate patient-reported outcomes (PROs) as measured by the quality of life questionnaire Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) (Section 6.9, Appendix 2)
- To evaluate the emptying of the stomach, as measured by the Gastric Emptying Breath Test (GEBT) (Section 6.10)
- To assess the safety and tolerability of CNSA-001 20 mg/kg/day

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Study GAS-001 is a Phase 2, randomized, double-blind, placebo-controlled pilot study of multiple doses of CNSA-001 (sepiapterin) powder for suspension administered orally in women with moderate to severe diabetic gastroparesis. This is an outpatient study in which up to 20 patients will be enrolled at approximately 4 centers.

The Schedule of Events is provided in Appendix 1. The study schema is displayed in Figure 1.

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, patients will undergo Screening procedures to determine study eligibility, as indicated in Appendix 1. Patients 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 patients will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Patients will undergo procedures during the Treatment Period as indicated in Appendix 1.

Study drug may be prematurely discontinued for safety reasons, as described in Section 6.14.1. Patients may also withdraw from the study for any reason, as described in Section 6.14.2. 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) (Section 7.5, Appendix 1). 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 (Section 7.5, Appendix 1). 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 (Section 7.6, Appendix 1).

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

Patients will undergo EOT evaluations on Day 14 and Day 15 as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test (Section 6.7) on Day 14. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) will also be administered on Day 14 (+1 day), and the GEBT (Section 6.10) will be conducted on Day 15.

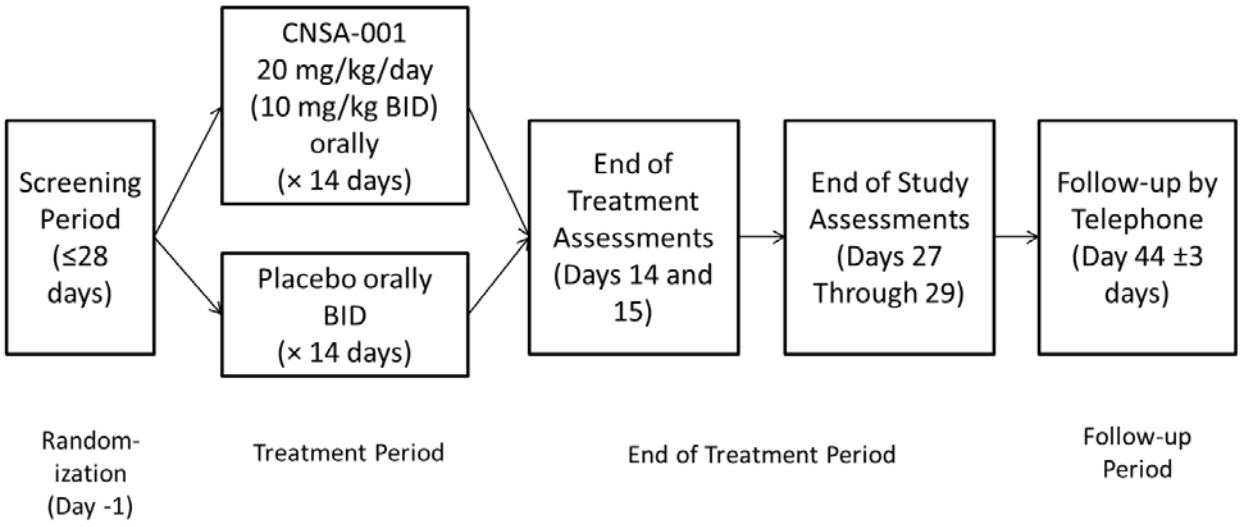
End of Study Period (Day 15 After Evaluations Through Day 28 [±1 Day] Evaluations)

Patients will undergo EOS evaluations on Day 28 (±1 day) as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test (Section 6.7) on Day 28. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) will also be administered on Day 28 ±1, and the GEBT (Section 6.10) will be conducted on Day 27 or Day 29.

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

Patients will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix 1.

Figure 1: Study Schema



Abbreviations: BID = twice a day.

3.2 Rationale for Study Design and Control Group

CNSA-001 (sepiapterin) is a new chemical entity that is an endogenous, naturally occurring precursor of BH4 via the pterin salvage pathway. Animal studies and data from a Phase 1 single and multiple ascending-dose study in healthy volunteers conducted by Censa Pharmaceuticals indicate rapid intracellular conversion of sepiapterin to BH4. It is expected that oral administration of CNSA-001 to women with diabetic gastroparesis will result in increases in both intracellular and circulating BH4 concentrations. In chronic diabetes, BH4 biosynthesis is impaired (Xu et al, 2007).

CNSA-001 was studied in two 14-day Good Laboratory Practice (GLP) toxicity studies, as described in Section 5.3, and in a single and multiple ascending-dose study in healthy volunteers, Study PKU-001, as described in Section 1.5.

Because all patients will receive the standard of care for diabetic gastroparesis in addition to their assigned study drug, the study design of a randomized study of CNSA-001 versus

placebo in female patients with diabetic gastroparesis will not expose patients to the risk of no treatment.

This study has a double-blind design intended to reduce bias.

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).

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 4 study centers will enroll up to 20 women with moderate to severe diabetic gastroparesis this study.

4.2 Inclusion Criteria

Patients are eligible to participate in this study if they meet all the following inclusion criteria:

1. Informed consent
2. Females ≥18 and ≤65 years of age
3. Diagnosis of diabetes mellitus
4. Documentation of delayed gastric emptying on gastric emptying scintigraphy (within 1 year of enrollment)
5. Symptoms of gastroparesis for at least 6 months with GCSI (Section 6.8, Appendix 2) score >21 indicating moderate to severe symptoms
6. Gastric accommodation, as measured by nutrient satiety testing, of ≤600 mL
7. Negative upper endoscopy or upper GI series within 3 years of enrollment (no evidence of mechanical obstruction or peptic ulcer disease)
8. Either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following:
   - Hormonal contraception (stable dose for 3 months)
   - Intrauterine device/Intrauterine Hormone-releasing System
   - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

   Patients who are abstinent will not be required to use a contraceptive method unless they become sexually active
9. If on analgesics (including narcotics), promotility agents (including metoclopramide), or neuromodulators (including tricyclic antidepressants, gabapentin, and pregabalin), doses are stable for >30 days before randomization and the patient is not expected to require dose changes during the study through the EOT
10. Have not used tobacco (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks prior to Day 1 and willingness to abstain from these products during the study through the EOT

4.3 Exclusion Criteria

Patients are not eligible to participate in this study if they meet any of the following exclusion criteria:

1. Male gender
2. Normal gastric emptying
3. Gastroparesis from postsurgical etiologies
4. Another active disorder that could, in the opinion of the Investigator, explain symptoms
5. Weight >100 kg
6. Alanine aminotransferase > 2× upper limit of normal (ULN)
7. Pregnant, breastfeeding, or considering pregnancy
8. Clinically significant cardiac arrhythmia at Screening
9. QT interval corrected for heart rate (QTc) ≥480 msec (based on triplicate measurements taken at Screening)
10. Resting heart rate ≤40 or ≥110 bpm or resting blood pressure <90/40 mmHg or >150/90 mmHg at Screening or prior to the first administration of study drug.
11. Recent clinically significant GI bleeding
12. Taking levodopa or domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT
13. Taking erythromycin within 30 days before randomization or expected to require erythromycin within 30 days before randomization or expected to require erythromycin during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization
14. Taking any fundic-relaxing agents including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT
15. Taking any systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)
16. Pulmonary dysfunction (e.g., chronic obstructive pulmonary disease)
17. Surgery for placement of a gastric stimulator within the past 6 months (patients postoperative >6 months with persistent symptoms and delayed gastric emptying are eligible)

18. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, small bowel malabsorption) that could affect the absorption of study drug or contraindicate undergoing the GEBT (Section 6.10)
19. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
20. History of allergies or adverse reactions to BH4 or related compounds, to any excipients in the study drug formulation, or to egg, wheat, or algae (Spirulina)
21. Inability to tolerate oral medication
22. Current participation in any other investigational drug study or use of any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening
23. Any clinically significant laboratory abnormality; in general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range unless deemed not clinically significant by the Investigator
24. Major surgery within the previous 90 days
25. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study
26. History of alcohol or drug abuse within 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
27. Episodes of ketoacidosis or hypoglycemia that are frequent as defined by the Investigator
28. History of phenylketonuria (PKU) or hyperphenylalaninemia.
29. Any other conditions, including diabetic comorbidities, that, in the opinion of the Investigator or Sponsor, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Test Product

The test product is CNSA-001 (sepiapterin) oral powder for suspension. CNSA-001 contains the new chemical entity, sepiapterin. Sepiapterin is 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$. Inactive ingredients in CNSA-001 include microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid. CNSA-001 will be suspended in Medisca® Oral Mix prior to dispensing it to the patient.

5.1.2 Placebo Control

The placebo is a ready-made suspension containing microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, ascorbic acid, and colorant (Yellow No. 6) that is suspended in Medisca® Oral Mix.

5.2 Treatments Administered

Patients will be randomized in a ratio of 1:1 to the following treatment groups:

- CNSA-001 20 mg/kg/day (10 mg/kg BID) for 14 days
- Placebo BID for 14 days

Dosing of CNSA-001 is based on the patient's weight. The weight obtained on Day -1 will be used to calculate the exact amount (mg) of CNSA-001 active ingredient (sepiapterin) required for each patient's daily dose.

The placebo is formulated as ready-made suspension. The placebo will be administered in the same manner (volume) as CNSA-001.

Details on preparation of study drug and dosing guidelines will be provided in a pharmacy manual for the site and an instruction guide for patients.

5.3 Selection and Timing of Dose for Each Patient

All patients will be randomly assigned in a ratio of 1:1 to receive CNSA-001 20 mg/kg/day (10 mg/kg BID) or placebo BID.

The CNSA-001 dose was selected following completion of two 14-day GLP toxicity studies in the rat and marmoset. The no observed adverse effect level from both studies was set at 1000 mg/kg/day, which represents a human equivalent dose of 161.3 mg/kg/day based on allometric scaling. Consequently, the proposed dose of 20 mg/kg/day represents an 8.1-fold safety margin.

Study drug will be dispensed on Day 1 (Section 6.11) with a dosing diary in which patients will record all doses taken and times they were taken (Section 5.8.1). The first dose on Day 1 will be taken in the clinic after patients undergo the nutrient satiety test (Section 6.7).

If a patient vomits after taking a dose of study drug, the patient 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.

5.4 Method of Assigning Patients to Treatment Groups

Patients 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. Patients who are randomized will be considered to be enrolled.

5.5 Blinding

This study has a double-blind design. The Investigator, study personnel, and patients will not make any effort to determine which study drug is being received. Unblinded pharmacy (or other qualified site) personnel will be utilized in this study to prepare the study drug.

Patients will be blinded to study drug assignment. Only in an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific patient, may the Investigator unblind a patient's study drug assignment. Copies of the randomization sequence and treatment codes will be kept in the pharmacy at the sites. If emergency unblinding is required, the Investigator will have immediate access to individual sealed codes containing treatment allocations. However, before any unblinding occurs, the Investigator is strongly advised to discuss options with the Sponsor's Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the patient's study drug assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to the unblinding. The Investigator will record in source documentation the date and reason for revealing the blinded study drug assignment for any patient and the names and roles of personnel unblinded.

5.6 Concomitant Therapy

Patients will be permitted to take:

- Analgesics, including narcotics, if the patient has been on a stable dose of the medication for >30 days before randomization; dose escalation is NOT permitted during the study through the EOT

- Promotility agents, including metoclopramide if the patient has been on a stable dose of the medication >30 days before randomization; dose changes are NOT permitted during the study through the EOT

- Neuromodulators, including any tricyclic antidepressant, gabapentin, and pregabalin, if the patient has been on a stable dose >30 days before randomization; dose changes are NOT permitted during the study through the EOT

- Rescue medications that patients would usually take, including ondansetron (Zofran®), promethazine (Phenergan®) or prochlorperazine (Compazine®) for nausea and tramadol (Ultram®), if symptoms related to gastroparesis require further treatment during the study through the EOT

All prescription and over-the-counter medications (including herbal medications) that the patient took within 30 days before Screening though the EOT should be recorded.

5.7 Restrictions

5.7.1 Prior Therapy and Concomitant Therapy

The following are prohibited:

- Any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening

- Domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT

- Dose escalation of analgesic or promotility agents or neuromodulators within 30 days before randomization or during the study through the EOT

- Erythromycin within 30 days before randomization or during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization

- Systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)

- Fundic-relaxing agents, including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT

- Medications that can alter GI sensation or accommodation or gastric emptying overnight before the nutrient satiety test (Section 6.7)

5.7.2 Food Intake

Patients will continue their usual diet without modification throughout the study. Patients are required to have been fasting overnight for the following assessments:

- Clinical laboratory, including glycosylated hemoglobin A1c (HbA1c), tests
- The nutrient satiety test (Section 6.7), which requires the consumption of Ensure™ (Abbott Laboratories, Abbott Park, IL, USA)
- The GEBT (Section 6.10), which requires consumption of a standardized 230 kCal meal, consisting of a standardized carbon-13 (^{13}C)-labeled egg component and 6 saltine crackers, with 6 ounces of water

5.7.3 Total Blood Volume

The total volume of blood obtained from an individual study patient is expected to be approximately 40 mL, for clinical laboratory tests inclusive of the HbA1c test.

5.7.4 Patient Activity and Tobacco Restrictions

Patients will not be confined during the study and will not require any activity restrictions. Patients must abstain from tobacco use (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks before Day 1 and during the study through the EOT.

5.8 Treatment Compliance

Patients will be instructed to return all used (empty containers) and unused study drug on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day). Compliance with the dosing regimen will be assessed by reconciliation of used and unused study drug. The quantities dispensed, returned, used, and lost will be recorded on the dispensing log provided for the study.

5.8.1 Dosing Diary

Patients will be provided with a dosing diary on Day 1 along with instructions for recording all doses of study drug and times they were taken. The dosing diary will be collected on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day), and the Investigator (or designee) will transcribe all entries into the electronic case report form (eCRF).

5.9 Packaging and Labeling

CNSA-001 Oral Powder for Suspension is packaged in 10 mL amber glass vials with black child proof caps. Each glass vial contains 175 mg of sepiapterin.

Each vial of CNSA-001 Oral Powder for Suspension will contain the product name, strength, content, expiry/retest date, and company name. Each vial label will contain the words, "Caution: Investigational medicine for clinical trial use only."

CNSA-001 PLACEBO suspension is packaged in 500 mL bottles. Each bottle of CNSA-001 PLACEBO suspension will contain the content and company name as well as "CNSA-001 PLACEBO" on its label.

The suspending vehicle, Medisca® Oral Mix, is commercially available and will be provided separately.

5.10 Storage and Accountability

All drug product required for completion of this study will be provided by Censa Pharmaceuticals. It is the responsibility of the pharmacy staff or study staff to ensure that a current record of drug inventory and drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the study monitor and are open to inspection at any time by applicable regulatory authorities.

CNSA-001 Oral Powder for Suspension (non-reconstituted) may be stored frozen at -20°C or at refrigerated conditions (2 to 8°C). If not administered on the same day of suspending, CNSA-001 suspension should be stored at refrigerated conditions (2 to 8°C) until time of dosing. Once suspended, CNSA-001 is stable for 14 days.

CNSA-001 PLACEBO suspension may be stored refrigerated at 2 to 8°C.

5.11 Investigational Product Retention at Study Site

Upon completion of the study and once inventoried by the study site, all used (empty) containers of study drug will be destroyed. Any unused containers of study drug may be either destroyed or returned to the Sponsor following discussion with the Sponsor. If study drug is destroyed, a certificate of destruction will be provided to the Sponsor by the appropriate facility performing the destruction.

6 STUDY PROCEDURES

6.1 Informed Consent

Consent forms describing in detail the study drug, study procedures, and risks are given to the patient, and written documentation of informed consent is required prior to conducting study-related procedures. See Section 10.4 for more information on the informed consent process.

6.2 Medical History and Demographic Data

A detailed medical/surgical history will be obtained at Screening. The history will include specific information related to any prior or existing medical conditions or surgical procedures involving the following systems: dermatologic; head, eyes, ears, nose, and throat (HEENT); lymphatic; cardiovascular; respiratory; GI; musculoskeletal; and neurological. The medical history will be updated on Day 1 before the start of study drug.

Demographic data obtained at Screening will include age, gender, and self-reported race/ethnicity.

6.3 Vital Signs, Weight, and Height

Vital signs, including blood pressure, pulse, respiratory rate, and temperature, will be measured at Screening, Day 1 (predose and 2 hours postdose), and at the EOT and EOS visits. Vital signs will be measured prior to collection of laboratory samples and after patients have rested for 5 minutes in the supine position. For timepoints other than Day 1, vital signs will be taken at any time during the visit after resting and laboratory sample collection.

Weight will only be collected at Screening as necessary to determine the response to Exclusion Criterion #5 (Section 4.3) and on Day -1. Height will only be collected at Screening.

6.4 Physical Examination

A complete physical examination will be performed at Screening, on Day 1 before start of study drug and at the EOT and EOS visits. The examination will assess general appearance, as well as dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters.

6.5 Clinical Laboratory Tests and Glycosylated Hemoglobin A1c

Clinical laboratory tests will be performed by qualified local laboratories. Blood and urine samples for clinical chemistry, hematology, and urinalysis will be collected at Screening, Day 1 (predose), and at the EOT and EOS visits. Patients should fast overnight prior to collection of blood samples (minimum of 8 hours before blood sample collection). Blood samples for HbA1c will be collected at Screening and at the EOT and EOS visits. Clinically significant laboratory abnormalities should be followed to a satisfactory resolution, as determined by the Investigator.

The following clinical laboratory and other laboratory parameters will be assessed:

Hematology:	**Serum Chemistry:**
Hematocrit (HCT)	Albumin (ALB)
Hemoglobin (HGB)	Alkaline phosphatase (AP)
Platelet count	Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT])
Red blood cell (RBC) count	Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT])
White blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)	Blood urea nitrogen (BUN)
Urinalysis:	Calcium (Ca)
Bilirubin	Carbon dioxide (CO_2)
Glucose	Chloride (Cl)
Ketones	Creatinine
Occult blood	Gamma glutamyl transferase (GGT)
pH	Glucose
Protein	Lactate dehydrogenase (LDH)
Specific gravity	Phosphorus
Urobilinogen	Potassium (K)
Microscopy:	Sodium (Na)
WBCs	Total bilirubin
RBCs	Direct bilirubin
Epithelial cells	Total cholesterol
Pregnancy Testing: [a]	Total protein
Serum human chorionic gonadotropin (HCG) at Screening	Uric acid
Urine HCG Day 1 (predose) and Day 14 (±1 day)	**Other:**
	Glycosylated hemoglobin A1(HbA1c)

[a] Required for all women who are of childbearing potential. Any positive urine pregnancy test should be confirmed by a serum pregnancy test.

6.6 Electrocardiogram

At Screening, 12-lead electrocardiograms (ECGs) will be obtained in triplicate, with 1 minute separating the first and second recordings and 1 minute separating second and third recordings. The following ECG parameters will be collected and recorded in the eCRF: RR, PR, QRS, QT, and QTc intervals. In addition, the ECG tracing should be reported as normal,

abnormal clinically significant, or abnormal not clinically significant. If abnormalities are noted on the ECG, these should be recorded in the eCRF.

6.7 Nutrient Satiety Test

For the nutrient satiety test, patients consume 120 mL of Ensure™ every 4 minutes. At 5-minute intervals, patients 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). Patients 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 patients 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. The sum of the four 100-mm visual analogue scales provides an aggregate symptom score (Park, 2011).

The nutrient satiety test will be administered in the clinic 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. A nutrient satiety test volume of ≤600 mL at Screening is required for patients to participate in this study.

6.8 Gastroparesis Cardinal Symptom Index

The GCSI (Appendix 2) consisting of a subset of items from the PAGI-SYM instrument (Section 6.9, Appendix 2), will be administered in the clinic at Screening and on Day 1 (predose), Day 14 (+1 day), and Day 28 (±1 day). A GCSI score >21 at Screening, indicating moderate to severe symptoms, is required for patients to participate in this study.

6.9 Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity

The PAGI-SYM (Appendix 2) is a 20-item upper GI symptom severity instrument with 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. It will be administered in the clinic on Day 1 (predose) and on Day 14 (+1 day), and Day 28 (±1 day).

6.10 Gastric Emptying Breath Test

The GEBT, which is a nonradioactive noninvasive test, will be administered in the clinic on Day -1, Day 15, and Day 27 or Day 29 after the patient 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 patient provides baseline (premeal) breath samples and then consumes 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. The meal is to be consumed within 10 minutes. Single postmeal breath samples are collected in capped glass tubes at 45, 90, 120, 150, 180, and 240 minutes after the meal is consumed and sent to the specified local laboratory for

analysis by Gas Isotope Ratio Mass Spectrometry. By adding ^{13}C to the test meal, the GEBT can determine how fast the stomach empties the meal by measuring the rate of carbon-13 dioxide ($^{13}CO_2$) excretion arising from the digested test meal. The rate of $^{13}CO_2$ excretion found in the patient's breath is proportional to the patient's rate of gastric emptying. The patient's $^{13}CO_2$ excretion rate at each breath collection time is reported using the GEBT metric "kPCD." The "k" is a multiplier of 1000, and "PCD" is an acronym for percent ^{13}C dose excreted (as $^{13}CO_2$). The test should not be administered to patients with a known allergy to egg, wheat, or algae (Spirulina) (Cairn Diagnostics™; Sutton et al, 2015; GEBT package insert, 2015; United States Food and Drug Administration, 2015).

6.11 Dispensing Study Drug

Study drug will be dispensed on Day 1 along with a dosing diary to record all doses taken and times they were taken. A sufficient supply of study drug will be dispensed for dosing through Day 14. Details on the preparation of study drug, dosing guidelines, and storage will be provided in a pharmacy manual for the site and an instruction guide for patients.

6.12 Adverse Events Assessments

An AE is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

The occurrence of an AE or serious adverse event (SAE) (Section 6.12.6) may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes, but is not limited to, the event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. Action taken regarding study medication (e.g., drug withdrawn, interrupted) will also be collected in the eCRF. All AEs that start during the study must be documented appropriately regardless of relationship. All treatment-related AEs or AEs leading to discontinuation will be followed to an adequate resolution, as determined by the Investigator.

Any medical condition that is present at the time that the patient is screened will be considered as medical history and not reported as an AE. However, if the patient's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. The AEs characterized as intermittent require documentation of onset and duration of each episode.

6.12.1 Reporting Timelines

The Investigator will record all reportable events with start dates occurring any time after informed consent and continue through clinical study completion or, in the case of withdrawal, until the outcome is determined. The AEs will be assessed at each visit and/or

through telephone contact with the patient. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

All SAEs should be reported after the patient signs the informed consent and followed until resolution, stabilization, or until the Investigator provides sufficient evidence that no further information can be obtained.

All SAEs and pregnancies (in a patient or partner of a male patient) occurring while the patient is on the study or within 30 (±3) days after the patient received the last dose of study drug must be reported within 24 hours of the knowledge of the event by study personnel whether or not considered to be related to study drug.

Deaths that occur ≥30 (±3) days after the patient's last study dose must be reported within 24 hours of knowledge of the event, if deemed related to study drug by the Investigator.

Although pregnancy is not considered an AE or SAE by regulatory definition, for this study pregnancies must be processed following SAE timelines (e.g., within 24 hours of knowledge of the pregnancy) for data transmission purposes. In the event that a pregnancy complication occurs, or elective termination of a pregnancy is required for medical reasons, then the complication will be recorded as an AE or SAE, as appropriate.

While elective and uncomplicated induced abortion not required for medical reasons does not constitute an AE or SAE (even if the patient or patient's partner is hospitalized to undergo abortion), spontaneous abortion is considered a fatal event and must be reported as an AE and SAE, as appropriate.

Any pregnancy and/or suspected pregnancy that occurs during the study in a female patient should be reported using Pregnancy Reporting Form within 24 hours of knowledge of the event by study personnel. Any pregnancy and/or suspected pregnancy will be followed for outcome.

If the patient has received the investigational drug prior to becoming pregnant, the patient will continue the efficacy assessment and Follow-up periods and measures of safety and efficacy will be obtained.

The patient will be followed until the outcome of the pregnancy is determined. It is the responsibility of the Investigator to obtain and document pregnancy information on the most recent Pregnancy Report Form. Furthermore, any SAE occurring as an outcome of the pregnancy must be reported according to the procedures outlined for SAE reporting.

6.12.2 Severity

The intensity of each AE will be graded as follows:

Mild:	Events require minimal or no treatment and do not interfere with the patient's daily activities.
Moderate:	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe:	Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but may not be considered an SAE. Alternatively, a stroke that results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE.

6.12.3 Relationship

The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. For purposes of consistency, guidelines for assessing causality are provided below:

Not Related	The AE is completely independent of study drug 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. No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state.
Unlikely to be 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 chemicals or underlying disease provides plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).
Possibly Related	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
Probably Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
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 response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to study drug administration, then an alternative explanation should be provided, if available.

6.12.4 Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigators' Brochure or is not listed at the specificity or severity that has been observed;

or, if an Investigators' Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the protocol.

The drug safety medical reviewer will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent (e.g., Investigators' Brochure).

6.12.5 Clinical Laboratory Adverse Events

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms or require medical intervention, as determined by the Investigator. However, each laboratory abnormality (e.g., clinically significant changes detected in hematology, serum chemistry panel, urinalysis, urine microscopic, and HbA1c evaluations) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to study drug interruption or discontinuation, must be recorded as an AE, or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (e.g., vital signs) performed that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described below.

6.12.6 Serious Adverse Events

6.12.6.1 Definition

An SAE is defined as an AE or suspected adverse reaction occurring at any dose that results in any of the following outcomes: death, life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

An AE or suspected adverse reaction is considered ''life-threatening'' if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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, or the development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in these other situations.

6.12.6.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Sponsor must submit a safety report for any suspected adverse reaction to study treatment that is both serious and unexpected. Before submitting a safety report, the Sponsor needs to ensure that the event meets all 3 of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the AE does not meet all 3 of the definitions, it should not be submitted as a safety report.

6.12.6.3 Reporting Serious Adverse Events

The Investigator will report all SAEs to the designated drug safety team within 24 hours of knowledge of the event whether or not considered to be related to study drug using the SAE Report Form provided.

Although not all information required for a complete SAE Report Form may be readily available at the time of the event, the Investigator must include sufficient information on the SAE Report Form to allow for a complete medical assessment. This should include at a minimum the patient number, site number, detailed description of the event, seriousness criteria, causality/relationship to study drug, and Investigator signature.

The designated drug safety team will acknowledge the receipt of the SAE via email to the clinical site. After submission of the initial report, the Investigator will provide follow-up information to the drug safety team as requested (e.g., concomitant medications, hospital discharge summary) to further evaluate the event and assure that all appropriate information is received. Once all information is received and the SAE has been deemed appropriate for closure, the SAE Report Form must be signed and dated by the Investigator.

The Investigator is responsible for informing the Institutional Review Board (IRB) of the SAE in accordance with institutional policies and procedures including relevant initial and follow-up information about the SAE.

Treatment-related SAEs or events leading to discontinuation of study drug will be followed for outcome information until resolution or stabilization. Other supporting documentation of the event may be requested by Censa Pharmaceuticals (or designee) and should be provided as soon as possible. The Medical Monitor should be contacted when the Investigator considers an SAE to be treatment-related.

6.12.7 Treatment-Emergent Adverse Events

Those AEs that start at the time of or after the first dose of study drug are TEAEs. Those AEs that worsen at or after the time of first dose of study drug are also considered treatment-emergent. All AEs that occur on or after the ICF has been signed, including all TEAEs, through Day 29 will be recorded in the eCRF.

All SAEs through Day 44 ±3 days [30 ±3 days after the patient received last dose of study drug] will be recorded in the eCRF and reported as described in Section 6.12.6.3.

6.13 Prior and Concomitant Medication Assessments

All prescription and over-the-counter medications (including herbal medications) taken by a patient starting from the 30-day period before Screening through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations will be recorded. Any concomitant medications added or discontinued during the study will be recorded at each visit.

6.14 Removal of Patients From the Trial or Study Drug

6.14.1 Early Discontinuation From Study Drug Administration

Premature discontinuation of study drug administration is defined as the discontinuation of study drug for an individual patient before the required full course of study drug is completed. Reasons for premature discontinuation from study drug administration should be recorded on the appropriate page(s) of the eCRF and may include, but are not limited to the following:

- Occurrence of an AE, SAE, or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from study drug administration
- In the judgment of the Investigator, the patient experiences a general or specific change(s) that renders the patient unsuitable for continued study drug administration
- There is a need for concomitant medication that makes the patient ineligible for further study drug administration
- Pregnancy
- Specific reasons related to adverse events that have been observed in pre- and post-marketing treatment with the same drug class of CNSA-001 (i.e., sapropterin):
    - Hypersensitivity reactions including anaphylaxis
    - Gastritis
    - Abnormal liver function tests in patients with liver impairment
    - Unexplained hyperactivity

Given the requirement for pregnancy testing in women of childbearing potential at Screening and the requirement for highly effective methods of contraception during the study, it is unlikely that pregnancies will occur during study conduct. However, study drug will be discontinued should suspected or confirmed pregnancy or nursing during the study drug administration period occur.

Patients who prematurely discontinue study drug due to any of the above reasons will complete the EOT assessments within 24 hours of withdrawal.

6.14.2 Withdrawal From the Study

Patients may withdraw from the study for any reason or be withdrawn at the request of the Investigator or Sponsor. The reason for a patient's withdrawal must be recorded on the appropriate page(s) of the eCRF. Reasons for withdrawal from the study may include, but are not limited to:

- Withdrawal of consent
- AEs or SAEs
- Significant patient noncompliance, defined as refusal or inability to adhere to the protocol requirements
- The Investigator determines that it is in the best interest of the patient to withdraw from study participation, due to a reason other than safety

Each patient who withdraws from the study after receipt of any amount of study drug will be asked to undergo EOT assessments. However, patients may withdraw consent to participate in this study at any time without penalty. Withdrawn patients who receive any amount of study drug, will not be replaced. Withdrawn patients who do not receive any study drug will be replaced.

6.14.3 Study Stopping Criteria

The study may be terminated if significant violations of Good Clinical Practice (GCP) that compromise the ability to achieve the study objectives or compromise patient safety are observed at any time during the study. With regard to safety, the study may be temporarily suspended or terminated should the Investigator, Sponsor, or IRB determine that the safety of patients is significantly jeopardized. The decision for a temporary or permanent study hold will depend on the nature, frequency, and severity of AEs that were observed in all enrolled patients to date. For example, the study will be temporarily or permanently halted should either of the following occur:

- The presence of the same system organ class (e,g., gastrointestinal, cardiac, etc.) severe AE for which no other alternative etiology can be identified, considered related to study drug, in 2 or more patients (Severity defined in Section 6.12.2).
- The presence of life-threatening AE or AE requiring urgent intervention in 1 or more patients.
- Death related to Adverse Event.

In a temporary study hold, no additional patients will be enrolled into the study or dosed with study drug until the study team members (including the Investigator and the Medical Monitor) decide it is safe to proceed with the study.

6.15 Appropriateness of Measurements

Safety will be measured by AEs (including SAEs), vital signs, physical examinations, and clinical laboratory and HbA1c tests.

Because treatment with BH4 is hypothesized to restore nNOS function in the control of gastric accommodation, the nutrient satiety test (Section 6.7) was chosen for the primary endpoint for this study. Gastric accommodation has been measured using ultrasonography (Undeland et al, 1998), single-photon emission computed tomography (Bredenoord et al, 2003), and barostat testing (Coulie et al, 1998; Sarnelli et al, 2001). Barostat studies have been shown to be reproducible (Sarnelli et al, 2001) but are invasive and not widely available. Satiety testing using a nutrient liquid has been shown to be reproducible (Kindt et al, 2008) and correlate with impairment in gastric accommodation but not gastric emptying or visceral sensitivity (Tack et al, 2003).

The GEBT is nonradioactive, noninvasive test of gastric emptying rate that has been validated against the reference method of gastric scintigraphy. It has been accepted by the United States Food and Drug Administration (FDA) for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastroparesis. The GEBT can determine how fast the stomach empties a standardized meal with a ^{13}C-labeled egg component by measuring the ratio of $^{13}CO_2$ to carbon-12 dioxide ($^{12}CO_2$) collected in breath samples at multiple time points after the meal is consumed compared to baseline. The breath samples are collected in capped glass tubes and sent to a specified local laboratory for analysis. By measuring the change in the ratio of $^{13}CO_2$ to $^{12}CO_2$ over time in comparison to the premeal value, the rate of $^{13}CO_2$ excretion can be calculated and the gastric emptying rate determined. The GEBT does not require administration by specially trained health care professionals or special precautions related to radiation-emitting compounds (Section 6.10).

The GCSI (Section 6.8, Appendix 2), consisting of a subset of items from the PAGI-SYM instrument (Section 6.9, Appendix 2) (described below), is based on reviews of the medical literature and results from clinician interviews and patient focus groups. Its reliability and validity were examined in 169 gastroparesis patients from 7 clinical centers in the US. Patients completed the GCSI, SF-36 Health Survey, and disability day questions at baseline and again at 8 weeks. Clinicians independently rated the severity of the patients' symptoms, and both clinicians and patients rated the changes in gastroparesis-related symptoms over the 8weeks. For the GCSI total score, the internal consistency reliability was 0.84, and the test-re-test reliability was 0.76. Significant relationships were observed between the clinician-assessed symptom severity and the GCSI total score, and significant associations were found between the GCSI scores and SF-36 physical and mental component summary scores and restricted activity and bed disability days. Patients with greater symptom severity, as rated by

clinicians, reported greater symptom severity on the GCSI. The GCSI total scores were responsive to changes in overall gastroparesis symptoms as assessed by clinicians ($p = 0.0002$) and patients ($p = 0.002$) (Revicki et al, 2003).

The PAGI-SYM (Section 6.9, Appendix 2) is a 20-item upper GI symptom severity instrument with 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. To develop the instrument, patients with GERD (n = 810), dyspepsia (n = 767), or gastroparesis (n = 169) from the US, France, Germany, Italy, the Netherlands, and Poland completed the PAGI-SYM, the SF-36 Health Survey, a disease-specific health-related quality of life measure (Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life [PAGI-QOL]), and disability day questions. Two-week reproducibility was evaluated in 277 stable patients. Construct validity was evaluated by correlating subscale scores with SF-36, PAGI-QOL and global symptom severity scores and disability days. Internal consistency reliability ranged from 0.79 to 0.91, and test-retest reliability ranged from 0.60 to 0.82 for the PAGI-SYM subscales. The PAGI-SYM subscale scores correlated significantly with SF-36 scores (all $p < 0.0001$), PAGI-QOL scores (all $p < 0.0001$), disability days ($p < 0.0001$), and global symptom severity ($p < 0.0001$). Mean PAGI-SYM scores varied significantly in groups defined by disability days (all $p < 0.0001$), in which greater symptom severity was associated with more disability days (Rentz et al, 2004; Revicki et al, 2004).

7 STUDY ACTIVITIES

7.1 Screening Procedures (Day –28 to Day -1)

The following will be performed/collected during the Screening Period from Day -28 to Day -1 after obtaining informed consent with a properly signed ICF (Section 10.4):

- Obtain demographic data (age, gender, self-reported race/ethnicity)
- Obtain medical/surgical history, including specific information related to any prior or existing medical conditions or surgical procedures involving the dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological systems (Section 6.2)
- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) prior to collection of any laboratory samples and after patients have rested for 5 minutes in a supine position; obtain the patient's weight (as necessary to determine the response to Exclusion Criterion #5 [Section 4.3] and on Day -1) and height (Section 6.3)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4)
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5)
- Perform a serum pregnancy test for all women who are of childbearing potential
- Obtain 12-lead ECGs in triplicate, with 1 minute separating the first and second recordings and 1 minute separating second and third recordings (Section 6.6)
- Administer the GCSI (Section 6.8, Appendix 2)
- Record all prescription and over-the-counter medications (including herbal medications) taken within 30 days before the Screening
- Assess/record AEs from the time of informed consent
- Administer the nutrient satiety test (Section 6.76.10) after the patient has fasted overnight and after any medications that can alter GI sensation or accommodation or gastric emptying have been held overnight
- Confirm patient meets inclusion criteria and no exclusion criteria (Section 4.2 and Section 4.3, respectively)
- Administer the GEBT (Section 6.10) on Day -1 after the patient 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)

- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations (Section 6.5) and the nutrient satiety test (Section 6.7) is administered on Day 1 predose
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the days of the nutrient satiety test (Section 6.7)
- Randomize patient on Day -1

7.2 Day 1 Predose

The following will be performed/collected on Day 1 in the clinic before the patient receives study drug:

- Obtain medical/surgical history since Screening, including specific information related to any prior or existing medical conditions or surgical procedures involving the dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological systems (Section 6.2)
- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine position (Section 6.3)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4)
- Collect blood samples for clinical chemistry, and hematology after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5)
- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test
- Record all prior prescription and over-the-counter medications (including herbal medications) taken since Screening
- Assess/record AEs since Screening
- Administer:
  - Nutrient satiety test (Section 6.76.10)
  - GCSI (Section 6.8, Appendix 2)
  - PAGI-SYM (Section 6.9, Appendix 2)

7.3 Day 1 After Baseline Evaluations Through Day 13

7.3.1 Day 1

- Administer first dose of study drug in the clinic

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) 2 hours postdose after patients have rested 5 minutes in a supine position (Section 6.3)
- Dispense study drug and instruct the patient on its preparation and administration BID starting with the second dose on Day 1 and continuing through Day 14 (Section 5.2 and Section 6.11)
- Dispense dosing diary and instruct the patient on its completion (Section 5.8.1)
- Instruct the patient not to take any Day 14 doses of study drug before the Day 14 clinic visit, and to bring the dosing diary and all study drug supplies to the Day 14 visit
- Record all medications the patient received since the predose assessment
- Assess/record AEs since the predose assessment
- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations, the nutrient satiety test (Section 6.7), and the GEBT (Section 6.10) on Day 14 and/or on Day 15
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the Day 14 visit (for the nutrient satiety test)

7.4 Early Termination Procedures

If a patient discontinues study drug early (Section 6.14.1), the patient should return to the study site within 24 hours of withdrawal and complete all of the procedures outlined for the EOT (Section 7.5). If a patient withdraws early from the study (Section 6.14.2), 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 (Section 7.5). All study drug and supplies and the dosing diary will be collected.

7.5 End of Treatment Visits (Day 14 and Day 15)

Patients will complete EOT visit(s) at early termination (Section 7.4) or on Day 14 and Day 15. During the EOT visits, the following will be completed:

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature), prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine (Section 6.3) on Day 14 or Day 15
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4) on Day 14 or Day 15
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5) on Day 14 or Day 15

- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test on Day 14 or Day 15
- Administer:
  - Nutrient satiety test (Section 6.76.10) on Day 14
  - GCSI (Section 6.8, Appendix 2) on Day 14 or Day 15
  - PAGI-SYM (Section 6.9, Appendix 2) on Day 14 or Day 15
  - GEBT (Section 6.10) on Day 15
- Administer first Day 14 dose of study drug on Day 14; administer the second Day 14 dose of study drug on Day 14 or instruct patient to take second Day 14 dose of study drug on Day 14 after the patient leaves the clinic
- Record all prescription and over-the-counter medications (including herbal medications) taken since the Day 1 visit through Day 15 before the patient leaves the clinic
- Assess/record AEs since last visit through Day 15 before the patient leaves the clinic
- Collect study drug, dosing diary, and assess study drug compliance on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15
- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations on Day 28 (±1 day), the nutrient satiety test (Section 6.7) on Day 28, and the GEBT (Section 6.10) on Day 27 or Day 29
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the Day 28 visit (for the nutrient satiety test)

7.6 End of Study (Day 28 ±1 Day)

Patients will complete the EOS assessments on Days 27 through Day 29. The following EOS assessments will be completed:

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature), prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine position (Section 6.3) on Day 28 (±1 day)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4) on Day 28 (±1 day)
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5) on Day 28 (±1 day)

- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test on Day 28 (±1 day)
- Administer:
  - Nutrient satiety test (Section 6.76.10) on Day 28
  - GCSI (Section 6.8, Appendix 2) on Day 28 (±1 day)
  - PAGI-SYM (Section 6.9, Appendix 2) on Day 28 (±1 day)
  - GEBT (Section 6.10) on Day 27 or Day 29
- Collect study drug, dosing diary, and assess study drug compliance on Day 28 (±1 day) (if not done on Day 14 or Day 15)
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations
- Assess/record AEs since last visit through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations

7.7 Telephone Follow-up Day 44 (±3 Days) (30 ±3 Days After Last Dose)

During telephone Follow-up on Day 44 (±3 days), the following will be completed:

- Call the patient to see if any SAEs were experienced during the 30 ±3 days after the last dose of study drug
- Record SAEs in the eCRF, if applicable
- Report SAEs following SAE reporting timelines per Section 6.12.1

8 QUALITY CONTROL AND ASSURANCE

Regular monitoring and an independent audit, if conducted, must be performed according to International Council on Harmonisation (ICH)-GCP (Section 10.6).

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., GLPs, Good Manufacturing Practices).

The investigational site will provide direct access to all trial-related sites, source data/documents (including patient diaries), and reports for the purpose of monitoring and auditing by Censa Pharmaceuticals (or designee), and inspection by local and regulatory authorities.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Descriptive statistics, including numbers and percentages for categorical variables, and numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Exploratory analyses may also be performed. Listings of individual patient data will be produced. Additional details can be found in the statistical analysis plan.

9.2 Determination of 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 (Section 6.7), in women with moderate to severe diabetic gastroparesis. A total of 10 patients 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.

9.3 Analysis Populations

Two study populations will be analyzed:

- Safety population: all patients who were randomized and received any amount of study drug (CNSA-001 or placebo)
- Efficacy population: all patients who were randomized, received any amount of study drug (CNSA-001 or placebo), and had available Day 1 predose and Day 14 nutrient satiety test (Section 6.7) maximum tolerated volume results

9.4 Demographics, Baseline Characteristics, Enrollment, Protocol Deviations, and Patient Disposition

Enrollment, protocol deviations, demographics (age, sex, race/ethnicity), prior and concomitant medications, and medical history will be summarized by treatment group using descriptive statistics. Discontinuations from study drug and the study will be summarized by treatment group as well and the reasons for discontinuation will be listed.

9.5 Statistical Analysis of Efficacy Variables

Efficacy will be assessed in the Efficacy population.

The primary efficacy measure will be the changes in maximal tolerated volume consumed during the nutrient satiety test (Section 6.7) from Day 1 to Day 14 and Day 28. The changes from Day 1 to Day 14 and from Day 1 to Day 28 in maximal tolerated volume consumed

during the nutrient satiety test will be compared between treatment groups using a student's t-test.

Secondary efficacy measures will consist of changes in the following from baseline through Day 14 (±1 day) and through Day 28 (±1 day):

- PAGI-SYM (Section 6.9, Appendix 2) subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores
- Gastric emptying as measured by the GEBT (Section 6.10)

The primary and secondary measures will be summarized by treatment group at each visit as well as changes from baseline using summary statistics (number of patients, mean, standard deviation, median, and range) including 95% confidence intervals for changes from baseline. Additional analyses may be conducted, and details will be provided in the statistical analysis plan (SAP).

9.6 Safety Analysis

Safety will be assessed in the Safety population. The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and treatment group. Severity of AEs and SAEs will be summarized similarly. Those AEs leading to premature discontinuation from the study drug and the serious TEAEs will be presented in a table or a listing. Clinical laboratory and HbA1c test results and vital signs will be summarized at each visit as will changes from baseline for each treatment group. A frequency distribution of abnormal physical examination results will be provided. Additional details will be provided in the SAP.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Table 1 summarizes the administrative structure for this study.

Table 1: Administrative Structure for GAS-001 Study

Contract Research Organization	InClin, Inc. 2655 Campus Drive, Suite 100 San Mateo, CA, 94403 Phone: [redacted]

10.2 Institutional Review Board Approval

The Investigator will submit this protocol, any protocol modifications, and the patient consent form to be utilized in this study, to the appropriate IRB for review and approval. This committee must operate in accordance with the ICH GCP. Documentation of approval of the protocol and the informed consent document must be forwarded to Censa Pharmaceuticals (or designee) prior to initiation of this study.

The Investigator is responsible for assuring continuing review and approval of the clinical study. The Investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to his/her IRB. The Investigator will not make any changes in the protocol without IRB approval except as necessary to eliminate apparent immediate hazards to the patients. The Investigator will provide progress reports to the IRB as required by the IRB. If the study remains in progress for >1 year, the Investigator must obtain annual renewal and re-approval from the IRB. Documentation of renewal must be submitted to Censa Pharmaceuticals (or designee). The Investigator will provide notice to the IRB of completion of participation in the study.

10.3 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol; GCPs, including ICH Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; applicable regional regulatory requirements (i.e., ICH E6); and in accordance with the ethical principles of the Declaration of Helsinki.

10.4 Patient Information and Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion in understandable terms of the purposes, procedures, risks and possible benefits of participation, and rights of study patients will be conducted with patients, and, as appropriate, their legally authorized representatives (LARs; henceforth in the discussion of informed consent, study patient means "patient and/or LAR") and family members. The study patients should have

the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Study patients will be asked to carefully review the ICF approved by Censa Pharmaceuticals (or designee) and the IRB. After any needed discussion and consideration of study participation and before undergoing any procedures specifically for the study, the patient will sign the ICF. The ICF will be retained in the study patient's study records, and a copy of the ICF will be given to the study patient.

Patients may decline to participate in the study and withdraw consent at any time or for any reason throughout the course of the study without AEs on the quality of their medical care.

10.5 Confidentiality

The Investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. This extends to testing of biological samples and genetic tests in addition to the clinical information relating to participants. Only an identification code (i.e., not names) should be recorded on any form or document submitted to Censa Pharmaceuticals, the Contract Research Organization (CRO), or the IRB. The Investigator must keep logs on screened and enrolled patients. In addition, the Investigator must have a list where the identity of all treated patients can be found.

The Investigator agrees that all information received from Censa Pharmaceuticals, including, but not limited to, the Investigator's Brochure, this protocol, CRFs, and any other information related to the protocol-specified treatment of the study, remain the sole and exclusive property of Censa Pharmaceuticals during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Censa Pharmaceuticals. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

The study monitor, other authorized representatives of Censa Pharmaceuticals, and representatives of the IRB may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, and hospital) and pharmacy records for the participants in this study. The clinical study site's research staff will permit access to such records.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

10.6 Study Monitoring

A clinical monitor authorized to represent Censa Pharmaceuticals will conduct site visits to inspect study data, patient's medical records, and eCRFs in accordance with ICH guidelines GCP, and applicable regulations and guidelines. The clinical monitor will also monitor ongoing drug accountability and adherence to protocol procedures. Details of clinical site monitoring are specified in a Clinical Monitoring Plan.

Independent audits may be conducted to ensure that monitoring practices are performed consistently across all participating sites and that monitors are following the Clinical Monitoring Plan.

The Investigator will allow representatives of the Censa Pharmaceuticals and regulatory authorities to inspect facilities and records relevant to this study.

10.7 Case Report Forms and Study Records

The eCRFs will be supplied by Censa Pharmaceuticals or designee for the recording of all information and study data as specified by this protocol. Original eCRF data should be handled in accordance with instructions from Censa Pharmaceuticals or designee. All eCRFs must be completed by the clinical study site's research staff authorized to do so by the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data reported in the eCRF derived from source documents should be consistent with the source documents. Source documents are defined as records of documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or patient-specific email correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by Censa Pharmaceuticals or designee and by regulatory authorities. The original ICF for each participating patient shall be filed with records kept by the Investigator, and copies shall be given to the patient.

Once all data queries and issues have been resolved for each patient the Investigator will electronically sign each patient's eCRF. This signature will indicate that the data have been thoroughly inspected and will thereby certify the contents of the eCRF.

Clinical data will be entered into a 21 Code of Federal Regulations (CFR) Part 11-compliant electronic data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered by the clinical study site's research staff directly from the source documents.

10.8 Protocol Violations/Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly. This is consistent with the following sections in ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1

- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

10.9 Access to Source Documentation

The Investigator agrees by his/her participation that the results of this study may be used for submission for national or international registration. If required, national or international authorities will be provided with the name of the Investigator and his or her address, full disclosure of his or her qualifications, any potential conflicts of interests, payments, and extent of involvement.

During site visits, the clinical monitor will review original patient records, drug accountability records, and additional documents as needed. During the course of the study, Censa Pharmaceutical's (or designee's) Quality Assurance personnel may conduct an on-site audit visit. The Investigator will provide direct access to and allow verification and copying of all trial-related documents (e.g., source data) for trial-related monitoring, audits, IRB reviews, and regulatory inspections.

10.10 Data Generation and Analysis

Some or all of the obligations of implementing or conducting this study may be transferred from Censa Pharmaceuticals to the CRO.

A case report, comprised of individual eCRFs, will be completed for every patient who signs an ICF and is enrolled into the study.

All original source documentation (laboratory results, treatment records, audit query responses, etc.) will be retained by the Investigator or institution unless specified otherwise by the protocol. The results as they become available will be entered on the appropriate eCRFs. Legible reproductions of the original laboratory reports for selected tests or variables will be submitted to Censa Pharmaceuticals or CRO as requested.

The eCRFs will be reviewed by a clinical monitor who will evaluate the completeness and accuracy of the data. Queries will be generated for omissions, corrections, and clarifications. Data may also be reviewed in-house by a clinical auditor and data management or other personnel.

Data analyses will be performed after database lock, when all queries have been resolved.

10.11 Retention of Data

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Censa Pharmaceuticals, if

applicable. It is the responsibility of Censa Pharmaceuticals to inform the Investigator when these documents no longer need to be retained.

10.12 Financial Disclosure

Each Investigator must submit to Censa Pharmaceuticals (or designee) financial disclosure information according to national law and/or local regulations.

10.13 Publication and Disclosure Policy

The data generated in this clinical study are the exclusive property of Censa Pharmaceuticals and are confidential. Authorship on any publication of the results from this study will be based on contributions to study design, patient enrollment, data analysis, interpretation of results, and drafting and editing of any publication in accordance with published authorship ethical guidelines for publication of research studies. Independent analysis and/or publication of these data by the Investigator(s) or any member of their staff is not permitted without the prior, written consent of Censa Pharmaceuticals.

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APPENDIX 1 SCHEDULE OF EVENTS

	Screening Period		Treatment Period		Follow-up Period			
					EOT		EOS	Telephone Follow-up
Evaluation	-28 to -1	Day 1 (Predose)	Day 1 Through Day 13	Day 14[a]	Day 14[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					X	X	
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 patient 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 patients 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). Patients will fast overnight before blood sample collections.

[g] Patients 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 patient 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 patient 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), patients 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 patient 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 patient vomits after taking a dose of study drug, the patient 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] Patients 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 patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day).

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; 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 2 GCSI AND PAGI-SYM ASSESSMENT INSTRUMENTS

Gastroparesis Cardinal Symptom Index Questionnaire (English Version):

GCSI

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please *circle the number* that best describes how *severe* the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5

Khoury V, Dubois, D. GCSI Gastroparesis Cardinal Symptom Index information booklet. 2nd ed. Lyon, France: Mapi Research Trust; 2015. p 30.

Gastroparesis Cardinal Symptom Index Questionnaire (United States Spanish Version):

Este cuestionario le pregunta acerca de la gravedad de los síntomas que usted pueda haber tenido relacionados con sus problemas de estómago. No hay respuestas correctas ni incorrectas. Por favor conteste cada pregunta lo más precisamente posible.

Para cada síntoma, por favor marque con un círculo el número que mejor describa qué tan grave ha sido el síntoma durante las últimas 2 semanas. Si usted no ha tenido este síntoma, marque con un círculo el 0. Si el síntoma ha sido muy leve, marque con un círculo el 1. Si el síntoma ha sido leve, marque con un círculo el 2. Si ha sido moderado, marque con un círculo el 3. Si ha sido grave, marque con un círculo el 4. Si ha sido muy grave, marque con un círculo el 5. Por favor, asegúrese de contestar cada pregunta.

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
1.	Náuseas (sentirse enfermo(a) del estómago como si fuera a vomitar)	0	1	2	3	4	5
2.	Arcadas/Ganas de vomitar (como si fuera a vomitar pero no sale nada)	0	1	2	3	4	5
3.	Vómitos	0	1	2	3	4	5
4.	Sensación de estómago lleno	0	1	2	3	4	5
5.	No poder terminar una comida de porción normal	0	1	2	3	4	5
6.	Sentirse excesivamente lleno(a) después de las comidas	0	1	2	3	4	5
7.	Pérdida del apetito	0	1	2	3	4	5
8.	Hinchado(a) de comer (sentir que necesita aflojar su ropa)	0	1	2	3	4	5
9.	Estómago o barriga visiblemente más grande	0	1	2	3	4	5

GCSI – USA / US Spanish – Final version – MAPI Research Institute
Spanish (USA)_ Versión 1.0 _Standard

Updated_cbe

Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (United States EnglishVersion)

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please circle the number that best describes how severe the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5
10. upper abdominal (above the navel) pain	0	1	2	3	4	5
11. upper abdominal (above the navel) discomfort	0	1	2	3	4	5
12. lower abdominal (below the navel) pain	0	1	2	3	4	5

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
13. lower abdominal (below the navel) discomfort	0	1	2	3	4	5
14. heartburn (burning pain rising in your chest or throat) during the day	0	1	2	3	4	5
15. heartburn (burning pain rising in your chest or throat) when lying down	0	1	2	3	4	5
16. feeling of discomfort inside your chest during the day	0	1	2	3	4	5
17. feeling of discomfort inside your chest at night (during sleep time)	0	1	2	3	4	5
18. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	0	1	2	3	4	5
19. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	0	1	2	3	4	5
20. bitter, acid or sour taste in your mouth	0	1	2	3	4	5

PAGI-SYM (Standard) - United States/English - Original version - Mapi
PAGI_SYM_AU2.1_standard_eng-USori.doc

Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (United States Spanish Version)

Este cuestionario le pregunta acerca de la gravedad de los síntomas que usted pueda haber tenido relacionados con sus problemas de estómago. No hay respuestas correctas ni incorrectas. Por favor conteste cada pregunta lo más precisamente posible.

Para cada síntoma, por favor marque con un círculo el número que mejor describa qué tan grave ha sido el síntoma durante las últimas 2 semanas. Si usted no ha tenido este síntoma, marque con un círculo el 0. Si el síntoma ha sido muy leve, marque con un círculo el 1. Si el síntoma ha sido leve, marque con un círculo el 2. Si ha sido moderado, marque con un círculo el 3. Si ha sido grave, marque con un círculo el 4. Si ha sido muy grave, marque con un círculo el 5. Por favor, asegúrese de contestar cada pregunta.

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
1.	Náuseas (sentirse enfermo(a) del estómago como si fuera a vomitar)	0	1	2	3	4	5
2.	Arcadas/Ganas de vomitar (como si fuera a vomitar pero no sale nada)	0	1	2	3	4	5
3.	Vómitos	0	1	2	3	4	5
4.	Sensación de estómago lleno	0	1	2	3	4	5
5.	No poder terminar una comida de porción normal	0	1	2	3	4	5
6.	Sentirse excesivamente lleno(a) después de las comidas	0	1	2	3	4	5
7.	Pérdida del apetito	0	1	2	3	4	5
8.	Hinchado(a) de comer (sentir que necesita aflojar su ropa)	0	1	2	3	4	5
9.	Estómago o barriga visiblemente más grande	0	1	2	3	4	5
10.	Dolor abdominal superior (arriba del ombligo)	0	1	2	3	4	5
11.	Malestar abdominal superior (arriba del ombligo)	0	1	2	3	4	5

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
12.	Dolor abdominal inferior (abajo del ombligo)	0	1	2	3	4	5
13.	Malestar abdominal inferior (abajo del ombligo)	0	1	2	3	4	5
14.	Acidez (dolor ardiente que sube en su pecho o garganta) durante el día	0	1	2	3	4	5
15.	Acidez (dolor ardiente que sube en su pecho o garganta) cuando está recostado(a)	0	1	2	3	4	5
16.	Sentir malestar en el pecho durante el día	0	1	2	3	4	5
17.	Sentir malestar en el pecho durante la noche	0	1	2	3	4	5
18.	Regurgitación o reflujo (fluido o líquido que sube de su estómago hasta la garganta) durante el día	0	1	2	3	4	5
19.	Regurgitación o reflujo (fluido o líquido que sube de su estómago hasta la garganta) cuando está recostado(a)	0	1	2	3	4	5
20.	Sabor agrio, ácido o amargo en la boca	0	1	2	3	4	5

PAGI-SYM (Standard) - United States/Spanish - Version of 09 Nov 07 - Mapi.
ID4237/PAGI_SYM_AU2.1_standard_spa-US doc

CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Study Phase:	2 Pilot
Product Name:	CNSA-001 (sepiapterin)
Dosage Form:	Oral powder for suspension
Indication:	Treatment of women with moderate to severe diabetic gastroparesis
Investigators:	Multicenter study
Sponsor:	Censa Pharmaceuticals 65 William Street Wellesley, MA 02481
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	06 September 2018
Amendment 1:	09 October 2018
Amendment 2:	12 November 2018

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

SPONSOR SIGNATURES

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Final Date:	06 September 2018
Amendment 1:	09 October 2018
Amendment 2:	12 November 2018

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed [redacted] Date: 12 Nov 2018

[redacted]
Censa Pharmaceuticals, Inc.

Sig[redacted] Date: [redacted] nov 12th 2018

[redacted]
Censa Pharmaceuticals

INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Final Date:	06 September 2018
Amendment 1:	09 October 2018
Amendment 2:	12 November 2018

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signature | Date (DD Month YYYY)

Printed Name, Credentials

Affiliation

Address

Phone Number

PROTOCOL AMENDMENT 2 (NOVEMBER 12, 2018)

Protocol GAS-001 is amended primarily for the following reasons:

1. Modified Exclusion Criterion #9 to exclude patients with a marked baseline prolongation of QT/QTc interval of ≥470 msec (based on triplicate measurements taken at screening).
2. Removed reference to Quality of Life measurements using the PAGI-SYM.
3. Corrected wording of secondary endpoints to more accurately reference change resulting from CNSA-001 treatment.
4. Corrected the methods of administration of the nutrient satiety test to 150mL of Ensure every 5 minutes.

Major changes to the protocol are as follows:

Synopsis and Section 4.3: Modified exclusion criterion #9 to QTc ≥470 msec.

Synopsis and Section 2.2: Corrected wording of secondary endpoints to reflect an effect of CNSA-001 treatment. Corrected the usage of PAGI-SYM as a symptom scale versus a quality of life scale.

Section 6.7: Corrected the methods for administering the nutrient satiety test.

PROTOCOL AMENDMENT 1 (OCTOBER 9, 2018)

Protocol GAS-001 is amended primarily for the following reasons:

1. Added Exclusion Criterion to exclude patients with baseline cardiovascular instability.
2. Added Exclusion Criterion to exclude patients with PKU or hyperphenylalaninemia.
3. Updated the discontinuation criteria related to AEs in Section 6.14.1.
4. Updated the study stopping criteria to include specific examples of adverse event criteria for temporarily or permanently stopping the study.

Major changes to the protocol are as follows:

Synopsis and Section 4.3: Added two additional exclusion criteria for patients with baseline cardiovascular instability and for patients with PKU or hyperphenylalaninemia.

Section 6.14.1: Added drug class adverse events to individual discontinuation criteria, specifically, hypersensitivity reactions, anaphylaxis, and gastritis.

Section 6.14.3: Added examples of study stopping criteria associated with adverse event criteria of severity, frequency, and relatedness.

SYNOPSIS

Sponsor:
Censa Pharmaceuticals

Name of Finished Product:
CNSA-001

Name of Active Ingredient:
Sepiapterin

Name of Inactive Ingredients:
Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid

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

Study Number:
GAS-001

Study Phase: Phase 2 pilot

Primary Objective:

- 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:

In women with moderate to severe diabetic gastroparesis:

- To evaluate the effect of CNSA-001 on improvement of gastroparesis symptoms as measured by the change from baseline in the global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]) (Section 6.8, Appendix 2)
- To evaluate the effect of CNSA-001 on patient-reported symptoms as measured by the change from baseline in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) (Section 6.9, Appendix 2)
- 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

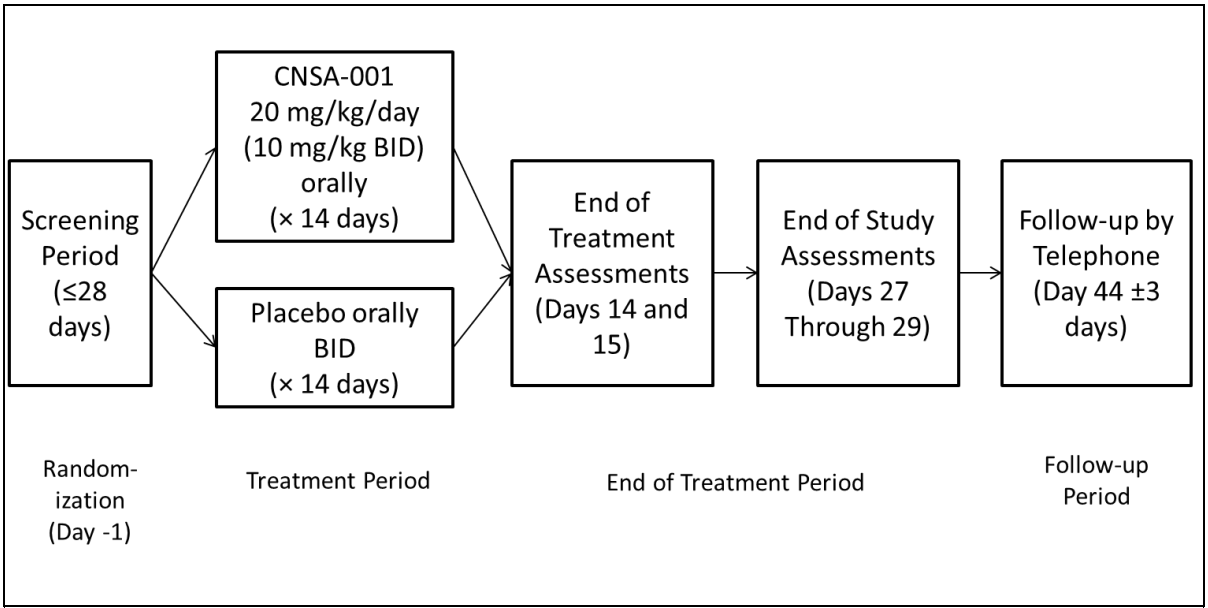
Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled pilot study of multiple doses of CNSA-001 (sepiapterin) powder for suspension administered orally in women with moderate to severe diabetic gastroparesis. Patients will be randomized in a ratio of 1:1 to receive CNSA-001 20 mg/kg/day or placebo, each dosed twice a day (BID); each group will consist of 10 patients. All patients will receive the standard of care for diabetic gastroparesis. Approximately 4 centers will participate in this study. The study design is summarized in the study schema below. A schedule of study events is provided in Appendix 1.

All study clinic visits will be outpatient visits.

Patients will continue their usual diet without modification throughout the study. Patients are required to have been fasting overnight for the following assessments:

- Clinical laboratory, including glycosylated hemoglobin A1c (HbA1c), tests
- The nutrient satiety test
- The GEBT



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, patients will undergo Screening procedures to determine study eligibility, as indicated in Appendix 1. Patients 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 patients will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Patients will undergo procedures during the Treatment Period as indicated in Appendix 1.

End of Treatment Period (Day 14 Through Day 15 Evaluations)
Patients will undergo End of Treatment (EOT) evaluations on Day 14 and Day 15 as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 14. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) 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)
Patients will undergo End of Study evaluations on Day 28 (±1 day) as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 28. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) 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])
Patients will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix 1.

Number of Patients:
Up to 20 women ≥18 and ≤65 years of age will be enrolled in this study and randomized in a ratio of 1:1 to receive CNSA-001 or placebo.

Main Criteria for Inclusion and Exclusion:
Patients are eligible to participate if they meet all the following inclusion criteria:

1. Informed consent
2. Females ≥18 and ≤65 years of age
3. Diagnosis of diabetes mellitus
4. Documentation of delayed gastric emptying on gastric emptying scintigraphy (within 1 year of enrollment)
5. Symptoms of gastroparesis for at least 6 months with GCSI (Section 6.8, Appendix 2) score >21 indicating moderate to severe symptoms
6. Gastric accommodation, as measured by nutrient satiety testing, of ≤600 mL
7. Negative upper endoscopy or upper gastrointestinal (GI) series within 3 years of enrollment (no evidence of mechanical obstruction or peptic ulcer disease)
8. Either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following:
   - Hormonal contraception (stable dose for 3 months)
   - Intrauterine device/Intrauterine Hormone-releasing System
   - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

   Patients who are abstinent will not be required to use a contraceptive method unless they become sexually active.
9. If on analgesics, including narcotics; promotility agents, including metoclopramide, or neuromodulators, including tricyclic antidepressants, gabapentin, and pregabalin, doses are stable for >30 days before randomization and the patient is not expected to require dose changes during the study through the EOT
10. Have not used tobacco (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks prior to Day 1 and willingness to abstain from these products during the study through the EOT

Patients are not eligible to participate if they meet any of the following exclusion criteria:

1. Male gender
2. Normal gastric emptying
3. Gastroparesis from postsurgical etiologies
4. Another active disorder that could, in the opinion of the Investigator, explain symptoms
5. Weight >100 kg
6. Alanine aminotransferase > 2× upper limit of normal (ULN)
7. Pregnant, breastfeeding, or considering pregnancy
8. Clinically significant cardiac arrhythmia at Screening
9. QT interval corrected for heart rate (QTc) ≥470 msec (based on triplicate measurements taken at Screening)
10. Resting heart rate ≤40 or ≥110 bpm or resting blood pressure <90/40 mmHg or >150/90 mmHg at Screening or prior to the first administration of study drug.
11. Recent clinically GI significant bleeding
12. Taking levodopa or domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT

13. Taking erythromycin within 30 days before randomization or expected to require erythromycin within 30 days before randomization or expected to require erythromycin during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization
14. Taking any fundic-relaxing agents including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT
15. Taking any systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)
16. Pulmonary dysfunction (e.g., chronic obstructive pulmonary disease)
17. Surgery for placement of a gastric stimulator within the past 6 months (patients postoperative >6 months with persistent symptoms and delayed gastric emptying are eligible)
18. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, small bowel malabsorption) that could affect the absorption of study drug or contraindicate undergoing the GEBT
19. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
20. History of allergies or adverse reactions to tetrahydrobiopterin or related compounds, to any excipients in the study drug formulation, or to egg, wheat, or algae (Spirulina)
21. Inability to tolerate oral medication
22. Current participation in any other investigational drug study or use of any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening
23. Any clinically significant laboratory abnormality; in general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range unless deemed not clinically significant by the Investigator
24. Major surgery within the previous 90 days
25. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study
26. History of alcohol or drug abuse within 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
27. Episodes of ketoacidosis or hypoglycemia that are frequent as defined by the Investigator
28. History of phenylketonuria (PKU) or hyperphenylalaninemia.
29. Any other conditions, including diabetic comorbidities, that, in the opinion of the Investigator or Sponsor, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

Test Product, Dose, and Mode of Administration:

The test product is CNSA-001 (sepiapterin) oral powder for suspension. CNSA-001 will be suspended in Medisca® Oral Mix prior to dispensing to the patient. Patients randomized to receive CNSA-001 will receive CNSA-001 20 mg/kg/day (i.e., 10 mg/kg BID) for 14 days.

Reference Therapy; Dose; and Mode of Administration:

The reference product is placebo. The placebo is a ready-made suspension containing microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, ascorbic acid, and colorant (Yellow No. 6) that is suspended in Medisca® Oral Mix.
Duration of Treatment: Patients will be treated for a total of 14 days.
Criteria for Evaluation: **Safety:** Safety and tolerability of CNSA-001 as measured by severity and number of treatment-emergent adverse events (TEAEs), including assessment of severity of TEAEs, and changes in clinical laboratory and HbA1c tests, vital signs, and physical examinations **Efficacy:** The primary efficacy measure will be the change in maximal tolerated volume consumed during the nutrient satiety test from Day 1 to Day 14 and Day 1 to Day 28. Secondary efficacy measures will consist of changes in the following from baseline to Day 14 and baseline to Day 28 (±1 day): • GCSI (Section 6.8, Appendix 2) PAGI-SYM (Section 6.9, Appendix 2) subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores • Gastric emptying as measured by the GEBT
Statistical Methods: The following study populations will be analyzed: • Safety population: all patients who were randomized and received any amount of study drug (CNSA-001 or placebo) • Efficacy population: all patients who were randomized, received any amount of study drug (CNSA-001 or placebo), and had available Day 1 and Day 14 nutrient satiety test maximum tolerated volume results Safety will be assessed in the Safety population. Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and treatment group. Severity of AEs and serious adverse events (SAEs) will be summarized similarly. Those AEs leading to premature discontinuation from the study drug and the serious TEAEs will be presented in a table or a listing. Clinical laboratory and HbA1c test results and vital signs will be summarized at each visit as will changes from baseline for each treatment group. A frequency distribution of abnormal physical examination results will be provided. Efficacy will be assessed in the Efficacy population. The changes from Day 1 to Day 14 and from Day 1 to Day 28 in maximal tolerated volume consumed during the nutrient satiety test will be compared between treatment groups using a student's t-test. Results from the nutrient satiety test through Day 14 and Day 28, the GEBT through Day 15 and Day 27 or Day 29, and the GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) through Day 14 (+1) and through Day 28 (±1) will be summarized using summary statistics (number of patients, mean, standard deviation, median, and range) at each visit as well as changes from baseline within each treatment group. The 95% confidence intervals for the changes from baseline will be provided. Additional analyses may be conducted, and details will be provided in the statistical analysis plan.
Date of Original Protocol: 06 September 2018 **Date of Amendment 1:** 09 October 2018 Date of Amendment 2: 12 November 2018

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LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALB	Albumin
ALT	Alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT])
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
$AUC_{0\text{-last}}$	Area under the concentration time curve from 0 to the last measurement
BH4	Tetrahydrobiopterin
BID	Twice a day
BUN	Blood urea nitrogen
^{13}C	Carbon-13
Ca	Calcium
CFR	Code of Federal Regulations
Cl	Chloride
C_{max}	Maximum concentration
CO_2	Carbon dioxide
$^{12}CO_2$	Carbon-12 dioxide
$^{13}CO_2$	Carbon-13 dioxide
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GCSI	Gastroparesis Cardinal Symptom Index
GEBT	Gastric Emptying Breath Test
GGT	Gamma glutamyl transferase
GI	Gastrointestinal

GLP	Good Laboratory Practice
HbA1c	Glycosylated hemoglobin A1c
HCG	Human chorionic gonadotropin
HCT	Hematocrit
HEENT	Head, eyes, ears, nose, and throat
HGB	Hemoglobin
ICF	Informed consent form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
K	Potassium
kPCD	the Gastric Emptying Breath Test metric; "k" is a multiplier of 1000, and "PCD" is an acronym for percent carbon-13 dose excreted (as carbon-13 dioxide)
LAR	legally authorized representative
LDH	Lactate dehydrogenase
MedDRA®	Medical Dictionary for Regulatory Activities
Na	Sodium
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
PAGI-QOL	Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity
PRO	Patient-reported outcome
QTc	QT interval corrected for heart rate
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction

TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell

1 INTRODUCTION

1.1 Diabetic Gastroparesis

Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction; symptoms are chronic with episodic symptom exacerbation (Parkman et al, 2004). Gastroparesis affects women 4 times more than men (Soykan, et al, 1998). Idiopathic gastroparesis accounts for most cases, but gastroparesis is frequently associated with diabetes (diabetic gastroparesis) (Soykan, et al, 1998; Karamanolis et al, 2007). Several cross-sectional studies have found delayed gastric emptying of solids and/or liquids in 30% to 50% of patients with Type 1 or Type 2 diabetes (Horowitz et al, 2002). Patients with diabetes mellitus commonly experience gastric and intestinal dysfunction (Feldman and Schiller, 1983).

The actual mechanism of diabetic gastroparesis is not well known. Vagal nerve dysfunction and/or damage, interstitial cells of Cajal loss, and smooth muscle and enteric neuron dysfunction have all been implicated in the pathogenesis of diabetic gastroparesis (Stacher, 2001; Parkman et al, 2004). In addition, acute hyperglycemia has the potential to slow gastric emptying (Camilleri et al, 2013).

At a molecular level, attention has been devoted to the potential role of altered nitrergic signaling in the enteric nervous system. Gastric motility is regulated in large part by neurons of the enteric nervous system located in the muscle wall (Wood et al, 1999). These neurons are either excitatory (releasing acetylcholine) or inhibitory (releasing nitric oxide [NO] and vasoactive intestinal peptide). Nerves throughout the luminal gastrointestinal (GI) tract express neuronal nitric oxide synthase (nNOS), which generates NO, a key neurotransmitter in the regulation of GI motility (Takahashi, 2003); it is the principal nonadrenergic noncholinergic inhibitory neurotransmitter in the GI tract. In diabetic rats, which serve as a model for type 1 diabetes, nNOS expression was found to be impaired. This impairment in nNOS messenger RNA expression was associated with impaired smooth muscle relaxation in response to electrical stimulation of circular muscle fibers obtained from the proximal stomach of these rats (Takahashi et al, 1997). It has been demonstrated that female diabetic rats had slower gastric emptying than age matched diabetic male rats, female control rats had greater nitrergic relaxation of circular antral muscle strips compared to male controls, and nitrergic relaxation was impaired in diabetic female rats but not matched diabetic male rats (Gangula et al, 2007).

The core signs and symptoms of gastroparesis by incidence are nausea (92% to 96%), vomiting (68% to 88%), postprandial fullness (54% to 77%), early satiety (42% to 60%), and upper abdominal pain (36% to 85%) (Soykan et al, 1998; Hoogerwerf et al, 1999; Anaparthy et al, 2009). Patients may experience any combination of signs and symptoms with varying degrees of severity. Pain is less prevalent in diabetic gastroparesis than idiopathic gastroparesis. Patients with diabetic gastroparesis may experience further derangement of glucose control because of unpredictable gastric emptying and altered absorption of orally administered hypoglycemic drugs, which may, in turn, affect measurement of core signs and symptoms. Severe signs and symptoms may cause complications such as malnutrition,

esophagitis, and Mallory-Weiss tears. Gastroparesis adversely affects the lives of patients with the disease, resulting in decreased social interaction, poor work functionality, and development of anxiety or depression (Soykan et al, 1998; Parkman et al, 2004).

1.2 Impaired Gastric Accommodation in Gastroparesis

Patients with diabetic gastroparesis have also been shown to have gastric hypersensitivity, especially in the postprandial state, and impairment of the postprandial accommodation response. (Kumar et al, 2008). The stomach functions as 2 separate regions: the fundus acts as a reservoir accommodating a meal without a significant increase in intragastric pressure, and the distal stomach/antrum triturates gastric contents. Receptive relaxation or accommodation is vagally mediated resulting in the release of NO and activation of nitrergic myenteric neurons. Nitrergic signaling is responsible for gastric accommodation and pyloric relaxation in response to a meal (Ishiguchi et al, 2001).

Impaired accommodation has been associated with symptoms of early satiety and weight loss in patients with idiopathic gastroparesis (Karamanolis et al, 2007). A study of patients with diabetic gastroparesis found that 90% of patients had impaired gastric accommodation to a nutrient meal (Kumar et al, 2008). In the distal stomach, NO is required for the propulsive contractions that triturate gastric contents and control of pyloric closure; lack of NO can lead to delayed gastric emptying and impaired gastric accommodation (Gangula et al, 2007).

Several co-factors are known to be important for nNOS activity, including nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), calcium, and tetrahydrobiopterin (BH4) (Werner et al, 2003). The homodimeric conformation of all 3 isoforms of nitric oxide synthase (NOS) is regulated by BH4 (Werner et al, 2003). In the absence of BH4, uncoupling of NO production occurs and leads to super oxide production, resulting in further impaired nNOS bioactivity.

1.3 Current Treatment of Diabetic Gastroparesis

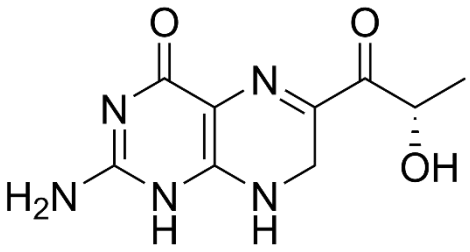
Therapies for gastroparesis have been targeted at accelerating gastric emptying or controlling symptoms. Available therapies for accelerating gastric emptying are limited in number and efficacy. These include metoclopramide (Snape et al, 1982), erythromycin (Arts et al, 2005), and domperidone (not available in the United States [US]) (Prakash and Wagstaff, 1998). There is also poor correlation between gastric emptying and baseline symptom severity (Karamanolis et al, 2007; Talley et al, 2001) and in response to therapeutic intervention. In part, as a result of lack of understanding of the underlying pathogenesis that leads to alterations in GI motility and sensation, medical therapies have not been targeted at the underlying pathophysiology of gastroparesis.

The first-line medical therapy for patients with diabetic gastroparesis is generally a combination of an antiemetic agent in addition to the promotility drug. Unfortunately, many patients with diabetic gastroparesis will not experience adequate symptom relief despite first-line therapy. For patients with refractory disease, options include combination prokinetic therapy, psychotropic medications, pyloric botulinum toxin injection, and gastric electric stimulation (Fass, 2010; Camilleri et al, 2013).

1.4 CNSA-001 (Sepiapterin)

Sepiapterin is 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$.

The chemical structure of sepiapterin is:



Sepiapterin serves as a substrate for BH4 synthesis via the pterin salvage pathway (Mayer and Werner, 1995). Oral administration of sepiapterin was shown to be more potent (>2 fold) than oral administration of BH4 in increasing intracellular BH4 in normal mice (Sawabe et al, 2002). Translation of this finding to humans has been confirmed in a Phase 1 study, PKU-001, conducted by Censa Pharmaceuticals.

1.5 Rationale for Study

BH4 biosynthesis is impaired in chronic diabetes. The mechanism of impairment is not well understood but is thought to be a result of hyperglycemia-induced proteasome-mediated degradation of GTP-cyclohydrolase, the rate-limiting enzyme in the synthesis pathway for BH4 (Xu et al, 2007).

CNSA-001 is the first viable formulation of sepiapterin, shown to increase intracellular BH4 (Section 1.4), intended for the treatment of female patients with diabetic gastroparesis. CNSA-001 was studied in a single and multiple ascending-dose study in healthy volunteers, the Phase 1 study, Study PKU-001. Part A of this study assessed the safety and pharmacokinetics of CNSA-001 at 6 dose levels inclusive of an assessment of food effect (i.e., 2.5 mg/kg, 7.5 mg/kg, 20 mg/kg, 40 mg/kg, 80 mg/kg, and 10 mg/kg [to assess food effect]). Additionally, Kuvan® (sapropterin dihydrochloride), a synthetic BH4 commercially available product, was administered at equivalent doses for the first 3 dose levels (2.5 mg/kg, 7.5 mg/kg, and 20 mg/kg). Dose-dependent correlations between CNSA-001 and plasma BH4 concentrations were observed with each successive dose level. Dose proportionality was observed between the top 2 dose levels (40 mg/kg and 80 mg/kg) and resultant BH4 concentrations. Administration with a standard high-fat (approximately 50 percent of total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) meal resulted in approximately 80% higher plasma BH4 concentrations (area under the concentration time curve from 0 to the last measurement [$AUC_{0\text{-last}}$] and maximum concentration [C_{max}]) than in subjects who had fasted before receipt of CNSA-001. Treatment-emergent adverse events (TEAEs) in Part A of Study PKU-001 were reported in 26 subjects (44.1%, 26/59). The TEAEs for CNSA-001 were generally mild and consistent with reported adverse events (AEs) for Kuvan® and placebo. The frequency of TEAEs did

not appear to increase with increasing dose. The TEAEs that were judged to be related to study treatment were reported in 17 subjects: 11 subjects (26.2%, 11/42) who received CNSA-001, 4 subjects (44.4%, 4/9) who received Kuvan®, and 2 subjects (25.0%, 2/8) who received placebo. No TEAEs were severe or serious or led to discontinuation of study drug. Headache and dizziness were the most common TEAEs , but these TEAEs occurred at a similar frequency as with placebo.

Part B of Study PKU-001 assessed multiple ascending doses CNSA-001 in healthy volunteers. Data indicate CNSA-001 was well tolerated following daily doses of 5, 20, and 60 mg/kg/day for 7 days and that TEAEs were reported in 14 subjects (58.3%, 14/24). The TEAEs in subjects who received CNSA 001 were mild or moderate and consistent with the TEAEs in subjects who received placebo: TEAEs were experienced by 10 subjects (55.6%, 10/18) who received CNSA-001 at doses from 5 mg/kg to 60 mg/kg daily for 7 days and by 4 subjects (66.7%, 4/6) who received placebo. No TEAEs were severe, serious, or led to discontinuation. Of the 10 TEAEs reported in subjects who received CNSA-001, only 4 were judged to be related to study drug, and, of the 4 TEAEs reported in subjects who received placebo, only 1 was judged to be related to study drug. Somnolence, fatigue, headache, and procedural pain (secondary to performance of 2 sequential lumbar punctures 7 days apart) were the most common TEAEs reported, and they occurred at a similar frequency when compared with placebo with the exception of fatigue and headache, which were each reported in 2 subjects who received CNSA-001 (11.1%, 2/18).

This Phase 2 pilot study will assess CNSA-001 doses of 20 mg/kg/day administered as 10 mg/kg twice a day (BID) in comparison to placebo administered BID in female patients with diabetic gastroparesis. This study will help support the design of future Phase 2/3 studies in patients with diabetic gastroparesis.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the impact of CNSA-001 on gastric accommodation, as measured by nutrient satiety testing (Section 6.7), in women with moderate to severe diabetic gastroparesis.

2.2 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 as measured by the change from baseline in the global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]) (Section 6.8, Appendix 2)
- To evaluate the effect of CNSA-001 on patient-reported symptoms as measured by the change from baseline in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) (Section 6.9, Appendix 2)
- 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) (Section 6.10)
- To assess the safety and tolerability of CNSA-001 20 mg/kg/day

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Study GAS-001 is a Phase 2, randomized, double-blind, placebo-controlled pilot study of multiple doses of CNSA-001 (sepiapterin) powder for suspension administered orally in women with moderate to severe diabetic gastroparesis. This is an outpatient study in which up to 20 patients will be enrolled at approximately 4 centers.

The Schedule of Events is provided in Appendix 1. The study schema is displayed in Figure 1.

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, patients will undergo Screening procedures to determine study eligibility, as indicated in Appendix 1. Patients 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 patients will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Patients will undergo procedures during the Treatment Period as indicated in Appendix 1.

Study drug may be prematurely discontinued for safety reasons, as described in Section 6.14.1. Patients may also withdraw from the study for any reason, as described in Section 6.14.2. 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) (Section 7.5, Appendix 1). 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 (Section 7.5, Appendix 1). 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 (Section 7.6, Appendix 1).

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

Patients will undergo EOT evaluations on Day 14 and Day 15 as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test (Section 6.7) on Day 14. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) will also be administered on Day 14 (+1 day), and the GEBT (Section 6.10) will be conducted on Day 15.

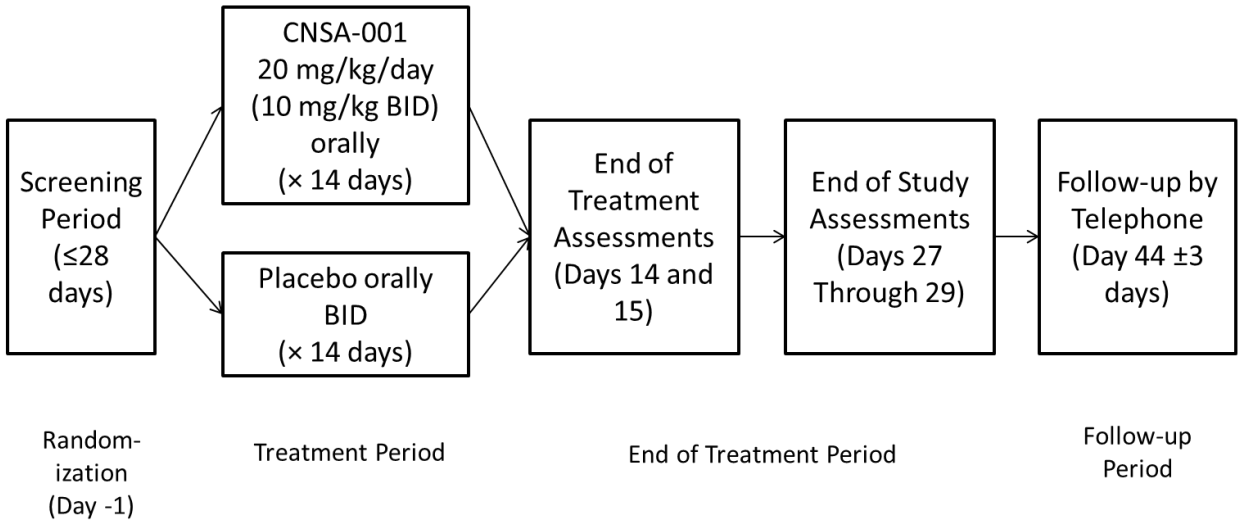
End of Study Period (Day 15 After Evaluations Through Day 28 [±1 Day] Evaluations)

Patients will undergo EOS evaluations on Day 28 (±1 day) as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test (Section 6.7) on Day 28. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) will also be administered on Day 28 ±1, and the GEBT (Section 6.10) will be conducted on Day 27 or Day 29.

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

Patients will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix 1.

Figure 1: Study Schema



Abbreviations: BID = twice a day.

3.2 Rationale for Study Design and Control Group

CNSA-001 (sepiapterin) is a new chemical entity that is an endogenous, naturally occurring precursor of BH4 via the pterin salvage pathway. Animal studies and data from a Phase 1 single and multiple ascending-dose study in healthy volunteers conducted by Censa Pharmaceuticals indicate rapid intracellular conversion of sepiapterin to BH4. It is expected that oral administration of CNSA-001 to women with diabetic gastroparesis will result in increases in both intracellular and circulating BH4 concentrations. In chronic diabetes, BH4 biosynthesis is impaired (Xu et al, 2007).

CNSA-001 was studied in two 14-day Good Laboratory Practice (GLP) toxicity studies, as described in Section 5.3, and in a single and multiple ascending-dose study in healthy volunteers, Study PKU-001, as described in Section 1.5.

Because all patients will receive the standard of care for diabetic gastroparesis in addition to their assigned study drug, the study design of a randomized study of CNSA-001 versus

placebo in female patients with diabetic gastroparesis will not expose patients to the risk of no treatment.

This study has a double-blind design intended to reduce bias.

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).

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 4 study centers will enroll up to 20 women with moderate to severe diabetic gastroparesis this study.

4.2 Inclusion Criteria

Patients are eligible to participate in this study if they meet all the following inclusion criteria:

1. Informed consent
2. Females ≥18 and ≤65 years of age
3. Diagnosis of diabetes mellitus
4. Documentation of delayed gastric emptying on gastric emptying scintigraphy (within 1 year of enrollment)
5. Symptoms of gastroparesis for at least 6 months with GCSI (Section 6.8, Appendix 2) score >21 indicating moderate to severe symptoms
6. Gastric accommodation, as measured by nutrient satiety testing, of ≤600 mL
7. Negative upper endoscopy or upper GI series within 3 years of enrollment (no evidence of mechanical obstruction or peptic ulcer disease)
8. Either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following:
   - Hormonal contraception (stable dose for 3 months)
   - Intrauterine device/Intrauterine Hormone-releasing System
   - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

   Patients who are abstinent will not be required to use a contraceptive method unless they become sexually active
9. If on analgesics (including narcotics), promotility agents (including metoclopramide), or neuromodulators (including tricyclic antidepressants, gabapentin, and pregabalin), doses are stable for >30 days before randomization and the patient is not expected to require dose changes during the study through the EOT
10. Have not used tobacco (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks prior to Day 1 and willingness to abstain from these products during the study through the EOT

4.3 Exclusion Criteria

Patients are not eligible to participate in this study if they meet any of the following exclusion criteria:

1. Male gender
2. Normal gastric emptying
3. Gastroparesis from postsurgical etiologies
4. Another active disorder that could, in the opinion of the Investigator, explain symptoms
5. Weight >100 kg
6. Alanine aminotransferase > 2× upper limit of normal (ULN)
7. Pregnant, breastfeeding, or considering pregnancy
8. Clinically significant cardiac arrhythmia at Screening
9. QT interval corrected for heart rate (QTc) ≥470 msec (based on triplicate measurements taken at Screening)
10. Resting heart rate ≤40 or ≥110 bpm or resting blood pressure <90/40 mmHg or >150/90 mmHg at Screening or prior to the first administration of study drug.
11. Recent clinically significant GI bleeding
12. Taking levodopa or domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT
13. Taking erythromycin within 30 days before randomization or expected to require erythromycin within 30 days before randomization or expected to require erythromycin during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization
14. Taking any fundic-relaxing agents including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT
15. Taking any systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)
16. Pulmonary dysfunction (e.g., chronic obstructive pulmonary disease)
17. Surgery for placement of a gastric stimulator within the past 6 months (patients postoperative >6 months with persistent symptoms and delayed gastric emptying are eligible)

18. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, small bowel malabsorption) that could affect the absorption of study drug or contraindicate undergoing the GEBT (Section 6.10)
19. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
20. History of allergies or adverse reactions to BH4 or related compounds, to any excipients in the study drug formulation, or to egg, wheat, or algae (Spirulina)
21. Inability to tolerate oral medication
22. Current participation in any other investigational drug study or use of any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening
23. Any clinically significant laboratory abnormality; in general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range unless deemed not clinically significant by the Investigator
24. Major surgery within the previous 90 days
25. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study
26. History of alcohol or drug abuse within 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
27. Episodes of ketoacidosis or hypoglycemia that are frequent as defined by the Investigator
28. History of phenylketonuria (PKU) or hyperphenylalaninemia.
29. Any other conditions, including diabetic comorbidities, that, in the opinion of the Investigator or Sponsor, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Test Product

The test product is CNSA-001 (sepiapterin) oral powder for suspension. CNSA-001 contains the new chemical entity, sepiapterin. Sepiapterin is 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$. Inactive ingredients in CNSA-001 include microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid. CNSA-001 will be suspended in Medisca® Oral Mix prior to dispensing it to the patient.

5.1.2 Placebo Control

The placebo is a ready-made suspension containing microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, ascorbic acid, and colorant (Yellow No. 6) that is suspended in Medisca® Oral Mix.

5.2 Treatments Administered

Patients will be randomized in a ratio of 1:1 to the following treatment groups:

- CNSA-001 20 mg/kg/day (10 mg/kg BID) for 14 days
- Placebo BID for 14 days

Dosing of CNSA-001 is based on the patient's weight. The weight obtained on Day -1 will be used to calculate the exact amount (mg) of CNSA-001 active ingredient (sepiapterin) required for each patient's daily dose.

The placebo is formulated as ready-made suspension. The placebo will be administered in the same manner (volume) as CNSA-001.

Details on preparation of study drug and dosing guidelines will be provided in a pharmacy manual for the site and an instruction guide for patients.

5.3 Selection and Timing of Dose for Each Patient

All patients will be randomly assigned in a ratio of 1:1 to receive CNSA-001 20 mg/kg/day (10 mg/kg BID) or placebo BID.

The CNSA-001 dose was selected following completion of two 14-day GLP toxicity studies in the rat and marmoset. The no observed adverse effect level from both studies was set at 1000 mg/kg/day, which represents a human equivalent dose of 161.3 mg/kg/day based on allometric scaling. Consequently, the proposed dose of 20 mg/kg/day represents an 8.1-fold safety margin.

Study drug will be dispensed on Day 1 (Section 6.11) with a dosing diary in which patients will record all doses taken and times they were taken (Section 5.8.1). The first dose on Day 1 will be taken in the clinic after patients undergo the nutrient satiety test (Section 6.7).

If a patient vomits after taking a dose of study drug, the patient 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.

5.4 Method of Assigning Patients to Treatment Groups

Patients 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. Patients who are randomized will be considered to be enrolled.

5.5 Blinding

This study has a double-blind design. The Investigator, study personnel, and patients will not make any effort to determine which study drug is being received. Unblinded pharmacy (or other qualified site) personnel will be utilized in this study to prepare the study drug.

Patients will be blinded to study drug assignment. Only in an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific patient, may the Investigator unblind a patient's study drug assignment. Copies of the randomization sequence and treatment codes will be kept in the pharmacy at the sites. If emergency unblinding is required, the Investigator will have immediate access to individual sealed codes containing treatment allocations. However, before any unblinding occurs, the Investigator is strongly advised to discuss options with the Sponsor's Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the patient's study drug assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to the unblinding. The Investigator will record in source documentation the date and reason for revealing the blinded study drug assignment for any patient and the names and roles of personnel unblinded.

5.6 Concomitant Therapy

Patients will be permitted to take:

- Analgesics, including narcotics, if the patient has been on a stable dose of the medication for >30 days before randomization; dose escalation is NOT permitted during the study through the EOT

- Promotility agents, including metoclopramide if the patient has been on a stable dose of the medication >30 days before randomization; dose changes are NOT permitted during the study through the EOT

- Neuromodulators, including any tricyclic antidepressant, gabapentin, and pregabalin, if the patient has been on a stable dose >30 days before randomization; dose changes are NOT permitted during the study through the EOT

- Rescue medications that patients would usually take, including ondansetron (Zofran®), promethazine (Phenergan®) or prochlorperazine (Compazine®) for nausea and tramadol (Ultram®), if symptoms related to gastroparesis require further treatment during the study through the EOT

All prescription and over-the-counter medications (including herbal medications) that the patient took within 30 days before Screening though the EOT should be recorded.

5.7 Restrictions

5.7.1 Prior Therapy and Concomitant Therapy

The following are prohibited:

- Any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening

- Domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT

- Dose escalation of analgesic or promotility agents or neuromodulators within 30 days before randomization or during the study through the EOT

- Erythromycin within 30 days before randomization or during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization

- Systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)

- Fundic-relaxing agents, including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT

- Medications that can alter GI sensation or accommodation or gastric emptying overnight before the nutrient satiety test (Section 6.7)

5.7.2 Food Intake

Patients will continue their usual diet without modification throughout the study. Patients are required to have been fasting overnight for the following assessments:

- Clinical laboratory, including glycosylated hemoglobin A1c (HbA1c), tests
- The nutrient satiety test (Section 6.7), which requires the consumption of Ensure™ (Abbott Laboratories, Abbott Park, IL, USA)
- The GEBT (Section 6.10), which requires consumption of a standardized 230 kCal meal, consisting of a standardized carbon-13 (^{13}C)-labeled egg component and 6 saltine crackers, with 6 ounces of water

5.7.3 Total Blood Volume

The total volume of blood obtained from an individual study patient is expected to be approximately 40 mL, for clinical laboratory tests inclusive of the HbA1c test.

5.7.4 Patient Activity and Tobacco Restrictions

Patients will not be confined during the study and will not require any activity restrictions. Patients must abstain from tobacco use (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks before Day 1 and during the study through the EOT.

5.8 Treatment Compliance

Patients will be instructed to return all used (empty containers) and unused study drug on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day). Compliance with the dosing regimen will be assessed by reconciliation of used and unused study drug. The quantities dispensed, returned, used, and lost will be recorded on the dispensing log provided for the study.

5.8.1 Dosing Diary

Patients will be provided with a dosing diary on Day 1 along with instructions for recording all doses of study drug and times they were taken. The dosing diary will be collected on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day), and the Investigator (or designee) will transcribe all entries into the electronic case report form (eCRF).

5.9 Packaging and Labeling

CNSA-001 Oral Powder for Suspension is packaged in 10 mL amber glass vials with black child proof caps. Each glass vial contains 175 mg of sepiapterin.

Each vial of CNSA-001 Oral Powder for Suspension will contain the product name, strength, content, expiry/retest date, and company name. Each vial label will contain the words, "Caution: Investigational medicine for clinical trial use only."

CNSA-001 PLACEBO suspension is packaged in 500 mL bottles. Each bottle of CNSA-001 PLACEBO suspension will contain the content and company name as well as "CNSA-001 PLACEBO" on its label.

The suspending vehicle, Medisca® Oral Mix, is commercially available and will be provided separately.

5.10 Storage and Accountability

All drug product required for completion of this study will be provided by Censa Pharmaceuticals. It is the responsibility of the pharmacy staff or study staff to ensure that a current record of drug inventory and drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the study monitor and are open to inspection at any time by applicable regulatory authorities.

CNSA-001 Oral Powder for Suspension (non-reconstituted) may be stored frozen at -20°C or at refrigerated conditions (2 to 8°C). If not administered on the same day of suspending, CNSA-001 suspension should be stored at refrigerated conditions (2 to 8°C) until time of dosing. Once suspended, CNSA-001 is stable for 14 days.

CNSA-001 PLACEBO suspension may be stored refrigerated at 2 to 8°C.

5.11 Investigational Product Retention at Study Site

Upon completion of the study and once inventoried by the study site, all used (empty) containers of study drug will be destroyed. Any unused containers of study drug may be either destroyed or returned to the Sponsor following discussion with the Sponsor. If study drug is destroyed, a certificate of destruction will be provided to the Sponsor by the appropriate facility performing the destruction.

6 STUDY PROCEDURES

6.1 Informed Consent

Consent forms describing in detail the study drug, study procedures, and risks are given to the patient, and written documentation of informed consent is required prior to conducting study-related procedures. See Section 10.4 for more information on the informed consent process.

6.2 Medical History and Demographic Data

A detailed medical/surgical history will be obtained at Screening. The history will include specific information related to any prior or existing medical conditions or surgical procedures involving the following systems: dermatologic; head, eyes, ears, nose, and throat (HEENT); lymphatic; cardiovascular; respiratory; GI; musculoskeletal; and neurological. The medical history will be updated on Day 1 before the start of study drug.

Demographic data obtained at Screening will include age, gender, and self-reported race/ethnicity.

6.3 Vital Signs, Weight, and Height

Vital signs, including blood pressure, pulse, respiratory rate, and temperature, will be measured at Screening, Day 1 (predose and 2 hours postdose), and at the EOT and EOS visits. Vital signs will be measured prior to collection of laboratory samples and after patients have rested for 5 minutes in the supine position. For timepoints other than Day 1, vital signs will be taken at any time during the visit after resting and laboratory sample collection.

Weight will only be collected at Screening as necessary to determine the response to Exclusion Criterion #5 (Section 4.3) and on Day -1. Height will only be collected at Screening.

6.4 Physical Examination

A complete physical examination will be performed at Screening, on Day 1 before start of study drug and at the EOT and EOS visits. The examination will assess general appearance, as well as dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters.

6.5 Clinical Laboratory Tests and Glycosylated Hemoglobin A1c

Clinical laboratory tests will be performed by qualified local laboratories. Blood and urine samples for clinical chemistry, hematology, and urinalysis will be collected at Screening, Day 1 (predose), and at the EOT and EOS visits. Patients should fast overnight prior to collection of blood samples (minimum of 8 hours before blood sample collection). Blood samples for HbA1c will be collected at Screening and at the EOT and EOS visits. Clinically significant laboratory abnormalities should be followed to a satisfactory resolution, as determined by the Investigator.

The following clinical laboratory and other laboratory parameters will be assessed:

Hematology:	**Serum Chemistry:**
Hematocrit (HCT)	Albumin (ALB)
Hemoglobin (HGB)	Alkaline phosphatase (AP)
Platelet count	Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT])
Red blood cell (RBC) count	Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT])
White blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)	Blood urea nitrogen (BUN)
Urinalysis:	Calcium (Ca)
Bilirubin	Carbon dioxide (CO_2)
Glucose	Chloride (Cl)
Ketones	Creatinine
Occult blood	Gamma glutamyl transferase (GGT)
pH	Glucose
Protein	Lactate dehydrogenase (LDH)
Specific gravity	Phosphorus
Urobilinogen	Potassium (K)
Microscopy:	Sodium (Na)
WBCs	Total bilirubin
RBCs	Direct bilirubin
Epithelial cells	Total cholesterol
Pregnancy Testing: [a]	Total protein
Serum human chorionic gonadotropin (HCG) at Screening	Uric acid
Urine HCG Day 1 (predose) and Day 14 (±1 day)	**Other:**
	Glycosylated hemoglobin A1(HbA1c)

[a] Required for all women who are of childbearing potential. Any positive urine pregnancy test should be confirmed by a serum pregnancy test.

6.6 Electrocardiogram

At Screening, 12-lead electrocardiograms (ECGs) will be obtained in triplicate, with 1 minute separating the first and second recordings and 1 minute separating second and third recordings. The following ECG parameters will be collected and recorded in the eCRF: RR, PR, QRS, QT, and QTc intervals. In addition, the ECG tracing should be reported as normal,

abnormal clinically significant, or abnormal not clinically significant. If abnormalities are noted on the ECG, these should be recorded in the eCRF.

6.7 Nutrient Satiety Test

For the nutrient satiety test, patients consume 150 mL of Ensure™ every 5 minutes. At 5-minute intervals, patients 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). Patients 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 patients 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. The sum of the four 100-mm visual analogue scales provides an aggregate symptom score (Park, 2011).

The nutrient satiety test will be administered in the clinic 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. A nutrient satiety test volume of ≤600 mL at Screening is required for patients to participate in this study.

6.8 Gastroparesis Cardinal Symptom Index

The GCSI (Appendix 2) consisting of a subset of items from the PAGI-SYM instrument (Section 6.9, Appendix 2), will be administered in the clinic at Screening and on Day 1 (predose), Day 14 (+1 day), and Day 28 (±1 day). A GCSI score >21 at Screening, indicating moderate to severe symptoms, is required for patients to participate in this study.

6.9 Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity

The PAGI-SYM (Appendix 2) is a 20-item upper GI symptom severity instrument with 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. It will be administered in the clinic on Day 1 (predose) and on Day 14 (+1 day), and Day 28 (±1 day).

6.10 Gastric Emptying Breath Test

The GEBT, which is a nonradioactive noninvasive test, will be administered in the clinic on Day -1, Day 15, and Day 27 or Day 29 after the patient 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 patient provides baseline (premeal) breath samples and then consumes 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. The meal is to be consumed within 10 minutes. Single postmeal breath samples are collected in capped glass tubes at 45, 90, 120, 150, 180, and 240 minutes after the meal is consumed and sent to the specified local laboratory for

analysis by Gas Isotope Ratio Mass Spectrometry. By adding ^{13}C to the test meal, the GEBT can determine how fast the stomach empties the meal by measuring the rate of carbon-13 dioxide ($^{13}CO_2$) excretion arising from the digested test meal. The rate of $^{13}CO_2$ excretion found in the patient's breath is proportional to the patient's rate of gastric emptying. The patient's $^{13}CO_2$ excretion rate at each breath collection time is reported using the GEBT metric "kPCD." The "k" is a multiplier of 1000, and "PCD" is an acronym for percent ^{13}C dose excreted (as $^{13}CO_2$). The test should not be administered to patients with a known allergy to egg, wheat, or algae (Spirulina) (Cairn Diagnostics™; Sutton et al, 2015; GEBT package insert, 2015; United States Food and Drug Administration, 2015).

6.11 Dispensing Study Drug

Study drug will be dispensed on Day 1 along with a dosing diary to record all doses taken and times they were taken. A sufficient supply of study drug will be dispensed for dosing through Day 14. Details on the preparation of study drug, dosing guidelines, and storage will be provided in a pharmacy manual for the site and an instruction guide for patients.

6.12 Adverse Events Assessments

An AE is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

The occurrence of an AE or serious adverse event (SAE) (Section 6.12.6) may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes, but is not limited to, the event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. Action taken regarding study medication (e.g., drug withdrawn, interrupted) will also be collected in the eCRF. All AEs that start during the study must be documented appropriately regardless of relationship. All treatment-related AEs or AEs leading to discontinuation will be followed to an adequate resolution, as determined by the Investigator.

Any medical condition that is present at the time that the patient is screened will be considered as medical history and not reported as an AE. However, if the patient's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. The AEs characterized as intermittent require documentation of onset and duration of each episode.

6.12.1 Reporting Timelines

The Investigator will record all reportable events with start dates occurring any time after informed consent and continue through clinical study completion or, in the case of withdrawal, until the outcome is determined. The AEs will be assessed at each visit and/or

through telephone contact with the patient. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

All SAEs should be reported after the patient signs the informed consent and followed until resolution, stabilization, or until the Investigator provides sufficient evidence that no further information can be obtained.

All SAEs and pregnancies (in a patient or partner of a male patient) occurring while the patient is on the study or within 30 (±3) days after the patient received the last dose of study drug must be reported within 24 hours of the knowledge of the event by study personnel whether or not considered to be related to study drug.

Deaths that occur ≥30 (±3) days after the patient's last study dose must be reported within 24 hours of knowledge of the event, if deemed related to study drug by the Investigator.

Although pregnancy is not considered an AE or SAE by regulatory definition, for this study pregnancies must be processed following SAE timelines (e.g., within 24 hours of knowledge of the pregnancy) for data transmission purposes. In the event that a pregnancy complication occurs, or elective termination of a pregnancy is required for medical reasons, then the complication will be recorded as an AE or SAE, as appropriate.

While elective and uncomplicated induced abortion not required for medical reasons does not constitute an AE or SAE (even if the patient or patient's partner is hospitalized to undergo abortion), spontaneous abortion is considered a fatal event and must be reported as an AE and SAE, as appropriate.

Any pregnancy and/or suspected pregnancy that occurs during the study in a female patient should be reported using Pregnancy Reporting Form within 24 hours of knowledge of the event by study personnel. Any pregnancy and/or suspected pregnancy will be followed for outcome.

If the patient has received the investigational drug prior to becoming pregnant, the patient will continue the efficacy assessment and Follow-up periods and measures of safety and efficacy will be obtained.

The patient will be followed until the outcome of the pregnancy is determined. It is the responsibility of the Investigator to obtain and document pregnancy information on the most recent Pregnancy Report Form. Furthermore, any SAE occurring as an outcome of the pregnancy must be reported according to the procedures outlined for SAE reporting.

6.12.2 Severity

The intensity of each AE will be graded as follows:

Mild:	Events require minimal or no treatment and do not interfere with the patient's daily activities.
Moderate:	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe:	Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but may not be considered an SAE. Alternatively, a stroke that results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE.

6.12.3 Relationship

The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. For purposes of consistency, guidelines for assessing causality are provided below:

Not Related	The AE is completely independent of study drug 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. No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state.
Unlikely to be 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 chemicals or underlying disease provides plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).
Possibly Related	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
Probably Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
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 response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to study drug administration, then an alternative explanation should be provided, if available.

6.12.4 Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigators' Brochure or is not listed at the specificity or severity that has been observed;

or, if an Investigators' Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the protocol.

The drug safety medical reviewer will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent (e.g., Investigators' Brochure).

6.12.5 Clinical Laboratory Adverse Events

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms or require medical intervention, as determined by the Investigator. However, each laboratory abnormality (e.g., clinically significant changes detected in hematology, serum chemistry panel, urinalysis, urine microscopic, and HbA1c evaluations) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to study drug interruption or discontinuation, must be recorded as an AE, or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (e.g., vital signs) performed that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described below.

6.12.6 Serious Adverse Events

6.12.6.1 Definition

An SAE is defined as an AE or suspected adverse reaction occurring at any dose that results in any of the following outcomes: death, life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

An AE or suspected adverse reaction is considered ''life-threatening'' if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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, or the development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in these other situations.

6.12.6.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Sponsor must submit a safety report for any suspected adverse reaction to study treatment that is both serious and unexpected. Before submitting a safety report, the Sponsor needs to ensure that the event meets all 3 of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the AE does not meet all 3 of the definitions, it should not be submitted as a safety report.

6.12.6.3 Reporting Serious Adverse Events

The Investigator will report all SAEs to the designated drug safety team within 24 hours of knowledge of the event whether or not considered to be related to study drug using the SAE Report Form provided.

Although not all information required for a complete SAE Report Form may be readily available at the time of the event, the Investigator must include sufficient information on the SAE Report Form to allow for a complete medical assessment. This should include at a minimum the patient number, site number, detailed description of the event, seriousness criteria, causality/relationship to study drug, and Investigator signature.

The designated drug safety team will acknowledge the receipt of the SAE via email to the clinical site. After submission of the initial report, the Investigator will provide follow-up information to the drug safety team as requested (e.g., concomitant medications, hospital discharge summary) to further evaluate the event and assure that all appropriate information is received. Once all information is received and the SAE has been deemed appropriate for closure, the SAE Report Form must be signed and dated by the Investigator.

The Investigator is responsible for informing the Institutional Review Board (IRB) of the SAE in accordance with institutional policies and procedures including relevant initial and follow-up information about the SAE.

Treatment-related SAEs or events leading to discontinuation of study drug will be followed for outcome information until resolution or stabilization. Other supporting documentation of the event may be requested by Censa Pharmaceuticals (or designee) and should be provided as soon as possible. The Medical Monitor should be contacted when the Investigator considers an SAE to be treatment-related.

6.12.7 Treatment-Emergent Adverse Events

Those AEs that start at the time of or after the first dose of study drug are TEAEs. Those AEs that worsen at or after the time of first dose of study drug are also considered treatment-emergent. All AEs that occur on or after the ICF has been signed, including all TEAEs, through Day 29 will be recorded in the eCRF.

All SAEs through Day 44 ±3 days [30 ±3 days after the patient received last dose of study drug] will be recorded in the eCRF and reported as described in Section 6.12.6.3.

6.13 Prior and Concomitant Medication Assessments

All prescription and over-the-counter medications (including herbal medications) taken by a patient starting from the 30-day period before Screening through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations will be recorded. Any concomitant medications added or discontinued during the study will be recorded at each visit.

6.14 Removal of Patients From the Trial or Study Drug

6.14.1 Early Discontinuation From Study Drug Administration

Premature discontinuation of study drug administration is defined as the discontinuation of study drug for an individual patient before the required full course of study drug is completed. Reasons for premature discontinuation from study drug administration should be recorded on the appropriate page(s) of the eCRF and may include, but are not limited to the following:

- Occurrence of an AE, SAE, or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from study drug administration
- In the judgment of the Investigator, the patient experiences a general or specific change(s) that renders the patient unsuitable for continued study drug administration
- There is a need for concomitant medication that makes the patient ineligible for further study drug administration
- Pregnancy
- Specific reasons related to adverse events that have been observed in pre- and post-marketing treatment with the same drug class of CNSA-001 (i.e., sapropterin):
    - Hypersensitivity reactions including anaphylaxis
    - Gastritis
    - Abnormal liver function tests in patients with liver impairment
    - Unexplained hyperactivity

Given the requirement for pregnancy testing in women of childbearing potential at Screening and the requirement for highly effective methods of contraception during the study, it is unlikely that pregnancies will occur during study conduct. However, study drug will be discontinued should suspected or confirmed pregnancy or nursing during the study drug administration period occur.

Patients who prematurely discontinue study drug due to any of the above reasons will complete the EOT assessments within 24 hours of withdrawal.

6.14.2 Withdrawal From the Study

Patients may withdraw from the study for any reason or be withdrawn at the request of the Investigator or Sponsor. The reason for a patient's withdrawal must be recorded on the appropriate page(s) of the eCRF. Reasons for withdrawal from the study may include, but are not limited to:

- Withdrawal of consent
- AEs or SAEs
- Significant patient noncompliance, defined as refusal or inability to adhere to the protocol requirements
- The Investigator determines that it is in the best interest of the patient to withdraw from study participation, due to a reason other than safety

Each patient who withdraws from the study after receipt of any amount of study drug will be asked to undergo EOT assessments. However, patients may withdraw consent to participate in this study at any time without penalty. Withdrawn patients who receive any amount of study drug, will not be replaced. Withdrawn patients who do not receive any study drug will be replaced.

6.14.3 Study Stopping Criteria

The study may be terminated if significant violations of Good Clinical Practice (GCP) that compromise the ability to achieve the study objectives or compromise patient safety are observed at any time during the study. With regard to safety, the study may be temporarily suspended or terminated should the Investigator, Sponsor, or IRB determine that the safety of patients is significantly jeopardized. The decision for a temporary or permanent study hold will depend on the nature, frequency, and severity of AEs that were observed in all enrolled patients to date. For example, the study will be temporarily or permanently halted should either of the following occur:

- The presence of the same system organ class (e,g., gastrointestinal, cardiac, etc.) severe AE for which no other alternative etiology can be identified, considered related to study drug, in 2 or more patients (Severity defined in Section 6.12.2).
- The presence of life-threatening AE or AE requiring urgent intervention in 1 or more patients.
- Death related to Adverse Event.

In a temporary study hold, no additional patients will be enrolled into the study or dosed with study drug until the study team members (including the Investigator and the Medical Monitor) decide it is safe to proceed with the study.

6.15 Appropriateness of Measurements

Safety will be measured by AEs (including SAEs), vital signs, physical examinations, and clinical laboratory and HbA1c tests.

Because treatment with BH4 is hypothesized to restore nNOS function in the control of gastric accommodation, the nutrient satiety test (Section 6.7) was chosen for the primary endpoint for this study. Gastric accommodation has been measured using ultrasonography (Undeland et al, 1998), single-photon emission computed tomography (Bredenoord et al, 2003), and barostat testing (Coulie et al, 1998; Sarnelli et al, 2001). Barostat studies have been shown to be reproducible (Sarnelli et al, 2001) but are invasive and not widely available. Satiety testing using a nutrient liquid has been shown to be reproducible (Kindt et al, 2008) and correlate with impairment in gastric accommodation but not gastric emptying or visceral sensitivity (Tack et al, 2003).

The GEBT is nonradioactive, noninvasive test of gastric emptying rate that has been validated against the reference method of gastric scintigraphy. It has been accepted by the United States Food and Drug Administration (FDA) for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastroparesis. The GEBT can determine how fast the stomach empties a standardized meal with a ^{13}C-labeled egg component by measuring the ratio of $^{13}CO_2$ to carbon-12 dioxide ($^{12}CO_2$) collected in breath samples at multiple time points after the meal is consumed compared to baseline. The breath samples are collected in capped glass tubes and sent to a specified local laboratory for analysis. By measuring the change in the ratio of $^{13}CO_2$ to $^{12}CO_2$ over time in comparison to the premeal value, the rate of $^{13}CO_2$ excretion can be calculated and the gastric emptying rate determined. The GEBT does not require administration by specially trained health care professionals or special precautions related to radiation-emitting compounds (Section 6.10).

The GCSI (Section 6.8, Appendix 2), consisting of a subset of items from the PAGI-SYM instrument (Section 6.9, Appendix 2) (described below), is based on reviews of the medical literature and results from clinician interviews and patient focus groups. Its reliability and validity were examined in 169 gastroparesis patients from 7 clinical centers in the US. Patients completed the GCSI, SF-36 Health Survey, and disability day questions at baseline and again at 8 weeks. Clinicians independently rated the severity of the patients' symptoms, and both clinicians and patients rated the changes in gastroparesis-related symptoms over the 8weeks. For the GCSI total score, the internal consistency reliability was 0.84, and the test-re-test reliability was 0.76. Significant relationships were observed between the clinician-assessed symptom severity and the GCSI total score, and significant associations were found between the GCSI scores and SF-36 physical and mental component summary scores and restricted activity and bed disability days. Patients with greater symptom severity, as rated by

clinicians, reported greater symptom severity on the GCSI. The GCSI total scores were responsive to changes in overall gastroparesis symptoms as assessed by clinicians ($p = 0.0002$) and patients ($p = 0.002$) (Revicki et al, 2003).

The PAGI-SYM (Section 6.9, Appendix 2) is a 20-item upper GI symptom severity instrument with 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. To develop the instrument, patients with GERD (n = 810), dyspepsia (n = 767), or gastroparesis (n = 169) from the US, France, Germany, Italy, the Netherlands, and Poland completed the PAGI-SYM, the SF-36 Health Survey, a disease-specific health-related quality of life measure (Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life [PAGI-QOL]), and disability day questions. Two-week reproducibility was evaluated in 277 stable patients. Construct validity was evaluated by correlating subscale scores with SF-36, PAGI-QOL and global symptom severity scores and disability days. Internal consistency reliability ranged from 0.79 to 0.91, and test-retest reliability ranged from 0.60 to 0.82 for the PAGI-SYM subscales. The PAGI-SYM subscale scores correlated significantly with SF-36 scores (all $p < 0.0001$), PAGI-QOL scores (all $p < 0.0001$), disability days ($p < 0.0001$), and global symptom severity ($p < 0.0001$). Mean PAGI-SYM scores varied significantly in groups defined by disability days (all $p < 0.0001$), in which greater symptom severity was associated with more disability days (Rentz et al, 2004; Revicki et al, 2004).

7 STUDY ACTIVITIES

7.1 Screening Procedures (Day –28 to Day -1)

The following will be performed/collected during the Screening Period from Day -28 to Day -1 after obtaining informed consent with a properly signed ICF (Section 10.4):

- Obtain demographic data (age, gender, self-reported race/ethnicity)
- Obtain medical/surgical history, including specific information related to any prior or existing medical conditions or surgical procedures involving the dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological systems (Section 6.2)
- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) prior to collection of any laboratory samples and after patients have rested for 5 minutes in a supine position; obtain the patient's weight (as necessary to determine the response to Exclusion Criterion #5 [Section 4.3] and on Day -1) and height (Section 6.3)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4)
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5)
- Perform a serum pregnancy test for all women who are of childbearing potential
- Obtain 12-lead ECGs in triplicate, with 1 minute separating the first and second recordings and 1 minute separating second and third recordings (Section 6.6)
- Administer the GCSI (Section 6.8, Appendix 2)
- Record all prescription and over-the-counter medications (including herbal medications) taken within 30 days before the Screening
- Assess/record AEs from the time of informed consent
- Administer the nutrient satiety test (Section 6.76.10) after the patient has fasted overnight and after any medications that can alter GI sensation or accommodation or gastric emptying have been held overnight
- Confirm patient meets inclusion criteria and no exclusion criteria (Section 4.2 and Section 4.3, respectively)
- Administer the GEBT (Section 6.10) on Day -1 after the patient 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)

- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations (Section 6.5) and the nutrient satiety test (Section 6.7) is administered on Day 1 predose
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the days of the nutrient satiety test (Section 6.7)
- Randomize patient on Day -1

7.2 Day 1 Predose

The following will be performed/collected on Day 1 in the clinic before the patient receives study drug:

- Obtain medical/surgical history since Screening, including specific information related to any prior or existing medical conditions or surgical procedures involving the dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological systems (Section 6.2)
- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine position (Section 6.3)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4)
- Collect blood samples for clinical chemistry, and hematology after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5)
- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test
- Record all prior prescription and over-the-counter medications (including herbal medications) taken since Screening
- Assess/record AEs since Screening
- Administer:
  - Nutrient satiety test (Section 6.76.10)
  - GCSI (Section 6.8, Appendix 2)
  - PAGI-SYM (Section 6.9, Appendix 2)

7.3 Day 1 After Baseline Evaluations Through Day 13

7.3.1 Day 1

- Administer first dose of study drug in the clinic

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) 2 hours postdose after patients have rested 5 minutes in a supine position (Section 6.3)
- Dispense study drug and instruct the patient on its preparation and administration BID starting with the second dose on Day 1 and continuing through Day 14 (Section 5.2 and Section 6.11)
- Dispense dosing diary and instruct the patient on its completion (Section 5.8.1)
- Instruct the patient not to take any Day 14 doses of study drug before the Day 14 clinic visit, and to bring the dosing diary and all study drug supplies to the Day 14 visit
- Record all medications the patient received since the predose assessment
- Assess/record AEs since the predose assessment
- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations, the nutrient satiety test (Section 6.7), and the GEBT (Section 6.10) on Day 14 and/or on Day 15
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the Day 14 visit (for the nutrient satiety test)

7.4 Early Termination Procedures

If a patient discontinues study drug early (Section 6.14.1), the patient should return to the study site within 24 hours of withdrawal and complete all of the procedures outlined for the EOT (Section 7.5). If a patient withdraws early from the study (Section 6.14.2), 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 (Section 7.5). All study drug and supplies and the dosing diary will be collected.

7.5 End of Treatment Visits (Day 14 and Day 15)

Patients will complete EOT visit(s) at early termination (Section 7.4) or on Day 14 and Day 15. During the EOT visits, the following will be completed:

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature), prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine (Section 6.3) on Day 14 or Day 15
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4) on Day 14 or Day 15
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5) on Day 14 or Day 15

- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test on Day 14 or Day 15
- Administer:
  - Nutrient satiety test (Section 6.76.10) on Day 14
  - GCSI (Section 6.8, Appendix 2) on Day 14 or Day 15
  - PAGI-SYM (Section 6.9, Appendix 2) on Day 14 or Day 15
  - GEBT (Section 6.10) on Day 15
- Administer first Day 14 dose of study drug on Day 14; administer the second Day 14 dose of study drug on Day 14 or instruct patient to take second Day 14 dose of study drug on Day 14 after the patient leaves the clinic
- Record all prescription and over-the-counter medications (including herbal medications) taken since the Day 1 visit through Day 15 before the patient leaves the clinic
- Assess/record AEs since last visit through Day 15 before the patient leaves the clinic
- Collect study drug, dosing diary, and assess study drug compliance on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15
- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations on Day 28 (±1 day), the nutrient satiety test (Section 6.7) on Day 28, and the GEBT (Section 6.10) on Day 27 or Day 29
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the Day 28 visit (for the nutrient satiety test)

7.6 End of Study (Day 28 ±1 Day)

Patients will complete the EOS assessments on Days 27 through Day 29. The following EOS assessments will be completed:

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature), prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine position (Section 6.3) on Day 28 (±1 day)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4) on Day 28 (±1 day)
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5) on Day 28 (±1 day)

- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test on Day 28 (±1 day)
- Administer:
  - Nutrient satiety test (Section 6.76.10) on Day 28
  - GCSI (Section 6.8, Appendix 2) on Day 28 (±1 day)
  - PAGI-SYM (Section 6.9, Appendix 2) on Day 28 (±1 day)
  - GEBT (Section 6.10) on Day 27 or Day 29
- Collect study drug, dosing diary, and assess study drug compliance on Day 28 (±1 day) (if not done on Day 14 or Day 15)
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations
- Assess/record AEs since last visit through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations

7.7 Telephone Follow-up Day 44 (±3 Days) (30 ±3 Days After Last Dose)

During telephone Follow-up on Day 44 (±3 days), the following will be completed:

- Call the patient to see if any SAEs were experienced during the 30 ±3 days after the last dose of study drug
- Record SAEs in the eCRF, if applicable
- Report SAEs following SAE reporting timelines per Section 6.12.1

8 QUALITY CONTROL AND ASSURANCE

Regular monitoring and an independent audit, if conducted, must be performed according to International Council on Harmonisation (ICH)-GCP (Section 10.6).

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., GLPs, Good Manufacturing Practices).

The investigational site will provide direct access to all trial-related sites, source data/documents (including patient diaries), and reports for the purpose of monitoring and auditing by Censa Pharmaceuticals (or designee), and inspection by local and regulatory authorities.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Descriptive statistics, including numbers and percentages for categorical variables, and numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Exploratory analyses may also be performed. Listings of individual patient data will be produced. Additional details can be found in the statistical analysis plan.

9.2 Determination of 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 (Section 6.7), in women with moderate to severe diabetic gastroparesis. A total of 10 patients 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.

9.3 Analysis Populations

Two study populations will be analyzed:

- Safety population: all patients who were randomized and received any amount of study drug (CNSA-001 or placebo)
- Efficacy population: all patients who were randomized, received any amount of study drug (CNSA-001 or placebo), and had available Day 1 predose and Day 14 nutrient satiety test (Section 6.7) maximum tolerated volume results

9.4 Demographics, Baseline Characteristics, Enrollment, Protocol Deviations, and Patient Disposition

Enrollment, protocol deviations, demographics (age, sex, race/ethnicity), prior and concomitant medications, and medical history will be summarized by treatment group using descriptive statistics. Discontinuations from study drug and the study will be summarized by treatment group as well and the reasons for discontinuation will be listed.

9.5 Statistical Analysis of Efficacy Variables

Efficacy will be assessed in the Efficacy population.

The primary efficacy measure will be the changes in maximal tolerated volume consumed during the nutrient satiety test (Section 6.7) from Day 1 to Day 14 and Day 28. The changes from Day 1 to Day 14 and from Day 1 to Day 28 in maximal tolerated volume consumed

during the nutrient satiety test will be compared between treatment groups using a student's t-test.

Secondary efficacy measures will consist of changes in the following from baseline through Day 14 (±1 day) and through Day 28 (±1 day):

- PAGI-SYM (Section 6.9, Appendix 2) subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores
- Gastric emptying as measured by the GEBT (Section 6.10)

The primary and secondary measures will be summarized by treatment group at each visit as well as changes from baseline using summary statistics (number of patients, mean, standard deviation, median, and range) including 95% confidence intervals for changes from baseline. Additional analyses may be conducted, and details will be provided in the statistical analysis plan (SAP).

9.6 Safety Analysis

Safety will be assessed in the Safety population. The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and treatment group. Severity of AEs and SAEs will be summarized similarly. Those AEs leading to premature discontinuation from the study drug and the serious TEAEs will be presented in a table or a listing. Clinical laboratory and HbA1c test results and vital signs will be summarized at each visit as will changes from baseline for each treatment group. A frequency distribution of abnormal physical examination results will be provided. Additional details will be provided in the SAP.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Table 1 summarizes the administrative structure for this study.

Table 1: Administrative Structure for GAS-001 Study

Contract Research Organization	InClin, Inc. 2655 Campus Drive, Suite 100 San Mateo, CA, 94403 Phone: [redacted]

10.2 Institutional Review Board Approval

The Investigator will submit this protocol, any protocol modifications, and the patient consent form to be utilized in this study, to the appropriate IRB for review and approval. This committee must operate in accordance with the ICH GCP. Documentation of approval of the protocol and the informed consent document must be forwarded to Censa Pharmaceuticals (or designee) prior to initiation of this study.

The Investigator is responsible for assuring continuing review and approval of the clinical study. The Investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to his/her IRB. The Investigator will not make any changes in the protocol without IRB approval except as necessary to eliminate apparent immediate hazards to the patients. The Investigator will provide progress reports to the IRB as required by the IRB. If the study remains in progress for >1 year, the Investigator must obtain annual renewal and re-approval from the IRB. Documentation of renewal must be submitted to Censa Pharmaceuticals (or designee). The Investigator will provide notice to the IRB of completion of participation in the study.

10.3 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol; GCPs, including ICH Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; applicable regional regulatory requirements (i.e., ICH E6); and in accordance with the ethical principles of the Declaration of Helsinki.

10.4 Patient Information and Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion in understandable terms of the purposes, procedures, risks and possible benefits of participation, and rights of study patients will be conducted with patients, and, as appropriate, their legally authorized representatives (LARs; henceforth in the discussion of informed consent, study patient means "patient and/or LAR") and family members. The study patients should have

the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Study patients will be asked to carefully review the ICF approved by Censa Pharmaceuticals (or designee) and the IRB. After any needed discussion and consideration of study participation and before undergoing any procedures specifically for the study, the patient will sign the ICF. The ICF will be retained in the study patient's study records, and a copy of the ICF will be given to the study patient.

Patients may decline to participate in the study and withdraw consent at any time or for any reason throughout the course of the study without AEs on the quality of their medical care.

10.5 Confidentiality

The Investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. This extends to testing of biological samples and genetic tests in addition to the clinical information relating to participants. Only an identification code (i.e., not names) should be recorded on any form or document submitted to Censa Pharmaceuticals, the Contract Research Organization (CRO), or the IRB. The Investigator must keep logs on screened and enrolled patients. In addition, the Investigator must have a list where the identity of all treated patients can be found.

The Investigator agrees that all information received from Censa Pharmaceuticals, including, but not limited to, the Investigator's Brochure, this protocol, CRFs, and any other information related to the protocol-specified treatment of the study, remain the sole and exclusive property of Censa Pharmaceuticals during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Censa Pharmaceuticals. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

The study monitor, other authorized representatives of Censa Pharmaceuticals, and representatives of the IRB may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, and hospital) and pharmacy records for the participants in this study. The clinical study site's research staff will permit access to such records.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

10.6 Study Monitoring

A clinical monitor authorized to represent Censa Pharmaceuticals will conduct site visits to inspect study data, patient's medical records, and eCRFs in accordance with ICH guidelines GCP, and applicable regulations and guidelines. The clinical monitor will also monitor ongoing drug accountability and adherence to protocol procedures. Details of clinical site monitoring are specified in a Clinical Monitoring Plan.

Independent audits may be conducted to ensure that monitoring practices are performed consistently across all participating sites and that monitors are following the Clinical Monitoring Plan.

The Investigator will allow representatives of the Censa Pharmaceuticals and regulatory authorities to inspect facilities and records relevant to this study.

10.7 Case Report Forms and Study Records

The eCRFs will be supplied by Censa Pharmaceuticals or designee for the recording of all information and study data as specified by this protocol. Original eCRF data should be handled in accordance with instructions from Censa Pharmaceuticals or designee. All eCRFs must be completed by the clinical study site's research staff authorized to do so by the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data reported in the eCRF derived from source documents should be consistent with the source documents. Source documents are defined as records of documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or patient-specific email correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by Censa Pharmaceuticals or designee and by regulatory authorities. The original ICF for each participating patient shall be filed with records kept by the Investigator, and copies shall be given to the patient.

Once all data queries and issues have been resolved for each patient the Investigator will electronically sign each patient's eCRF. This signature will indicate that the data have been thoroughly inspected and will thereby certify the contents of the eCRF.

Clinical data will be entered into a 21 Code of Federal Regulations (CFR) Part 11-compliant electronic data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered by the clinical study site's research staff directly from the source documents.

10.8 Protocol Violations/Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly. This is consistent with the following sections in ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1

- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

10.9 Access to Source Documentation

The Investigator agrees by his/her participation that the results of this study may be used for submission for national or international registration. If required, national or international authorities will be provided with the name of the Investigator and his or her address, full disclosure of his or her qualifications, any potential conflicts of interests, payments, and extent of involvement.

During site visits, the clinical monitor will review original patient records, drug accountability records, and additional documents as needed. During the course of the study, Censa Pharmaceutical's (or designee's) Quality Assurance personnel may conduct an on-site audit visit. The Investigator will provide direct access to and allow verification and copying of all trial-related documents (e.g., source data) for trial-related monitoring, audits, IRB reviews, and regulatory inspections.

10.10 Data Generation and Analysis

Some or all of the obligations of implementing or conducting this study may be transferred from Censa Pharmaceuticals to the CRO.

A case report, comprised of individual eCRFs, will be completed for every patient who signs an ICF and is enrolled into the study.

All original source documentation (laboratory results, treatment records, audit query responses, etc.) will be retained by the Investigator or institution unless specified otherwise by the protocol. The results as they become available will be entered on the appropriate eCRFs. Legible reproductions of the original laboratory reports for selected tests or variables will be submitted to Censa Pharmaceuticals or CRO as requested.

The eCRFs will be reviewed by a clinical monitor who will evaluate the completeness and accuracy of the data. Queries will be generated for omissions, corrections, and clarifications. Data may also be reviewed in-house by a clinical auditor and data management or other personnel.

Data analyses will be performed after database lock, when all queries have been resolved.

10.11 Retention of Data

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Censa Pharmaceuticals, if

applicable. It is the responsibility of Censa Pharmaceuticals to inform the Investigator when these documents no longer need to be retained.

10.12 Financial Disclosure

Each Investigator must submit to Censa Pharmaceuticals (or designee) financial disclosure information according to national law and/or local regulations.

10.13 Publication and Disclosure Policy

The data generated in this clinical study are the exclusive property of Censa Pharmaceuticals and are confidential. Authorship on any publication of the results from this study will be based on contributions to study design, patient enrollment, data analysis, interpretation of results, and drafting and editing of any publication in accordance with published authorship ethical guidelines for publication of research studies. Independent analysis and/or publication of these data by the Investigator(s) or any member of their staff is not permitted without the prior, written consent of Censa Pharmaceuticals.

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APPENDIX 1 SCHEDULE OF EVENTS

	Screening Period		Treatment Period		Follow-up Period			
					EOT		EOS	Telephone Follow-up
Evaluation	-28 to -1	Day 1 (Predose)	Day 1 Through Day 13	Day 14[a]	Day 14[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					X	X	
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 patient 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 patients 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). Patients will fast overnight before blood sample collections.

[g] Patients 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 patient 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 patient 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), patients 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 patient 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 patient vomits after taking a dose of study drug, the patient 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] Patients 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 patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day).

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; 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 2 GCSI AND PAGI-SYM ASSESSMENT INSTRUMENTS

Gastroparesis Cardinal Symptom Index Questionnaire (English Version):

GCSI

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please *circle the number* that best describes how *severe* the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5

Khoury V, Dubois, D. GCSI Gastroparesis Cardinal Symptom Index information booklet. 2nd ed. Lyon, France: Mapi Research Trust; 2015. p 30.

Gastroparesis Cardinal Symptom Index Questionnaire (United States Spanish Version):

Este cuestionario le pregunta acerca de la gravedad de los síntomas que usted pueda haber tenido relacionados con sus problemas de estómago. No hay respuestas correctas ni incorrectas. Por favor conteste cada pregunta lo más precisamente posible.

Para cada síntoma, por favor marque con un círculo el número que mejor describa qué tan grave ha sido el síntoma durante las últimas 2 semanas. Si usted no ha tenido este síntoma, marque con un círculo el 0. Si el síntoma ha sido muy leve, marque con un círculo el 1. Si el síntoma ha sido leve, marque con un círculo el 2. Si ha sido moderado, marque con un círculo el 3. Si ha sido grave, marque con un círculo el 4. Si ha sido muy grave, marque con un círculo el 5. Por favor, asegúrese de contestar cada pregunta.

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
1.	Náuseas (sentirse enfermo(a) del estómago como si fuera a vomitar)	0	1	2	3	4	5
2.	Arcadas/Ganas de vomitar (como si fuera a vomitar pero no sale nada)	0	1	2	3	4	5
3.	Vómitos	0	1	2	3	4	5
4.	Sensación de estómago lleno	0	1	2	3	4	5
5.	No poder terminar una comida de porción normal	0	1	2	3	4	5
6.	Sentirse excesivamente lleno(a) después de las comidas	0	1	2	3	4	5
7.	Pérdida del apetito	0	1	2	3	4	5
8.	Hinchado(a) de comer (sentir que necesita aflojar su ropa)	0	1	2	3	4	5
9.	Estómago o barriga visiblemente más grande	0	1	2	3	4	5

GCSI – USA / US Spanish – Final version – MAPI Research Institute
Spanish (USA)_ Versión 1.0 _Standard

Updated_cbe

Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (United States EnglishVersion)

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please circle the number that best describes how severe the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5
10. upper abdominal (above the navel) pain	0	1	2	3	4	5
11. upper abdominal (above the navel) discomfort	0	1	2	3	4	5
12. lower abdominal (below the navel) pain	0	1	2	3	4	5

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
13. lower abdominal (below the navel) discomfort	0	1	2	3	4	5
14. heartburn (burning pain rising in your chest or throat) during the day	0	1	2	3	4	5
15. heartburn (burning pain rising in your chest or throat) when lying down	0	1	2	3	4	5
16. feeling of discomfort inside your chest during the day	0	1	2	3	4	5
17. feeling of discomfort inside your chest at night (during sleep time)	0	1	2	3	4	5
18. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	0	1	2	3	4	5
19. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	0	1	2	3	4	5
20. bitter, acid or sour taste in your mouth	0	1	2	3	4	5

PAGI-SYM (Standard) - United States/English - Original version - Mapi
PAGI_SYM_AU2.1_standard_eng-USori doc

Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (United States Spanish Version)

Este cuestionario le pregunta acerca de la gravedad de los síntomas que usted pueda haber tenido relacionados con sus problemas de estómago. No hay respuestas correctas ni incorrectas. Por favor conteste cada pregunta lo más precisamente posible.

Para cada síntoma, por favor marque con un círculo el número que mejor describa qué tan grave ha sido el síntoma durante las últimas 2 semanas. Si usted no ha tenido este síntoma, marque con un círculo el 0. Si el síntoma ha sido muy leve, marque con un círculo el 1. Si el síntoma ha sido leve, marque con un círculo el 2. Si ha sido moderado, marque con un círculo el 3. Si ha sido grave, marque con un círculo el 4. Si ha sido muy grave, marque con un círculo el 5. Por favor, asegúrese de contestar cada pregunta.

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
1.	Náuseas (sentirse enfermo(a) del estómago como si fuera a vomitar)	0	1	2	3	4	5
2.	Arcadas/Ganas de vomitar (como si fuera a vomitar pero no sale nada)	0	1	2	3	4	5
3.	Vómitos	0	1	2	3	4	5
4.	Sensación de estómago lleno	0	1	2	3	4	5
5.	No poder terminar una comida de porción normal	0	1	2	3	4	5
6.	Sentirse excesivamente lleno(a) después de las comidas	0	1	2	3	4	5
7.	Pérdida del apetito	0	1	2	3	4	5
8.	Hinchado(a) de comer (sentir que necesita aflojar su ropa)	0	1	2	3	4	5
9.	Estómago o barriga visiblemente más grande	0	1	2	3	4	5
10.	Dolor abdominal superior (arriba del ombligo)	0	1	2	3	4	5
11.	Malestar abdominal superior (arriba del ombligo)	0	1	2	3	4	5

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
12.	Dolor abdominal inferior (abajo del ombligo)	0	1	2	3	4	5
13.	Malestar abdominal inferior (abajo del ombligo)	0	1	2	3	4	5
14.	Acidez (dolor ardiente que sube en su pecho o garganta) durante el día	0	1	2	3	4	5
15.	Acidez (dolor ardiente que sube en su pecho o garganta) cuando está recostado(a)	0	1	2	3	4	5
16.	Sentir malestar en el pecho durante el día	0	1	2	3	4	5
17.	Sentir malestar en el pecho durante la noche	0	1	2	3	4	5
18.	Regurgitación o reflujo (fluido o líquido que sube de su estómago hasta la garganta) durante el día	0	1	2	3	4	5
19.	Regurgitación o reflujo (fluido o líquido que sube de su estómago hasta la garganta) cuando está recostado(a)	0	1	2	3	4	5
20.	Sabor agrio, ácido o amargo en la boca	0	1	2	3	4	5

PAGI-SYM (Standard) - United States/Spanish - Version of 09 Nov 07 - Mapi.
ID4237/PAGI_SYM_AU2.1_standard_spa-US doc

CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Study Phase:	2 Pilot
Product Name:	CNSA-001 (sepiapterin)
Dosage Form:	Oral powder for suspension
Indication:	Treatment of women with moderate to severe diabetic gastroparesis
Investigators:	Multicenter study
Sponsor:	Censa Pharmaceuticals 65 William Street Wellesley, MA 02481
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	06 September 2018
Amendment 1:	09 October 2018
Amendment 2:	12 November 2018
Amendment 3:	21 February 2019

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

SPONSOR SIGNATURES

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Final Date:	06 September 2018
Amendment 1:	09 October 2018
Amendment 2:	12 November 2018
Amendment 3:	21 February 2019

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed [redacted] Date: 21 FEB 2019

[redacted]
Censa Pharmaceuticals, Inc.

[redacted] Date: 21 FEB 2019

[redacted]
Censa Pharmaceuticals

INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Pilot Study of CNSA-001 in Women With Moderate to Severe Diabetic Gastroparesis
Study Number:	GAS-001
Final Date:	06 September 2018
Amendment 1:	09 October 2018
Amendment 2:	12 November 2018
Amendment 3:	21 February 2019

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signature

Date (DD Month YYYY)

Printed Name, Credentials

Affiliation

Address

Phone Number

PROTOCOL AMENDMENT 3 (FEBRUARY 21, 2019)

Protocol GAS-001 is amended primarily for the following reasons:

1. Modified Inclusion Criterion #2 to increase the upper age limit from 65 to 75 years.
2. Modified Inclusion Criterion #4 to extend the evidence of gastric emptying to 2 years prior to enrollment and to offer the possibility of retesting during screening with either the GES or the GEBT for patients that have historical GES or GEBT greater than 2 years prior to enrollment. Consistent with FDA draft guidance, either GES or GEBT may be used to confirm delayed gastric emptying.
3. Modified Exclusion Criterion #9 to state the method of QT correction required. Fridericia's correction is being applied to ensure consistency across Censa sponsored clinical studies.

Major changes to the protocol are as follows:

Synopsis, Section 4.2 and Appendix 1: Modified exclusion criteria #2 and #4 to increase the upper age limit from 65 to 75 and to permit testing for gastric emptying with either the GES or the GEBT during screening, respectively.

Synopsis and Section 4.3: Modified exclusion criterion #9 to clarify that QTc will be reported using Fridericia's correction.

PROTOCOL AMENDMENT 2 (NOVEMBER 12, 2018)

Protocol GAS-001 is amended primarily for the following reasons:

1. Modified Exclusion Criterion #9 to exclude patients with a marked baseline prolongation of QT/QTc interval of ≥470 msec (based on triplicate measurements taken at screening).
2. Removed reference to Quality of Life measurements using the PAGI-SYM.
3. Corrected wording of secondary endpoints to more accurately reference change resulting from CNSA-001 treatment.
4. Corrected the methods of administration of the nutrient satiety test to 150mL of Ensure every 5 minutes.

Major changes to the protocol are as follows:

Synopsis and Section 4.3: Modified exclusion criterion #9 to QTc ≥470 msec.

Synopsis and Section 2.2: Corrected wording of secondary endpoints to reflect an effect of CNSA-001 treatment. Corrected the usage of PAGI-SYM as a symptom scale versus a quality of life scale.

Section 6.7: Corrected the methods for administering the nutrient satiety test.

PROTOCOL AMENDMENT 1 (OCTOBER 9, 2018)

Protocol GAS-001 is amended primarily for the following reasons:

1. Added Exclusion Criterion to exclude patients with baseline cardiovascular instability.
2. Added Exclusion Criterion to exclude patients with PKU or hyperphenylalaninemia.
3. Updated the discontinuation criteria related to AEs in Section 6.14.1.
4. Updated the study stopping criteria to include specific examples of adverse event criteria for temporarily or permanently stopping the study.

Major changes to the protocol are as follows:

Synopsis and Section 4.3: Added two additional exclusion criteria for patients with baseline cardiovascular instability and for patients with PKU or hyperphenylalaninemia.

Section 6.14.1: Added drug class adverse events to individual discontinuation criteria, specifically, hypersensitivity reactions, anaphylaxis, and gastritis.

Section 6.14.3: Added examples of study stopping criteria associated with adverse event criteria of severity, frequency, and relatedness.

SYNOPSIS

Sponsor:
Censa Pharmaceuticals

Name of Finished Product:
CNSA-001

Name of Active Ingredient:
Sepiapterin

Name of Inactive Ingredients:
Microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid

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

Study Number:
GAS-001

Study Phase: Phase 2 pilot

Primary Objective:

- 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:

In women with moderate to severe diabetic gastroparesis:

- To evaluate the effect of CNSA-001 on improvement of gastroparesis symptoms as measured by the change from baseline in the global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]) (Section 6.8, Appendix 2)
- To evaluate the effect of CNSA-001 on patient-reported symptoms as measured by the change from baseline in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) (Section 6.9, Appendix 2)
- 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

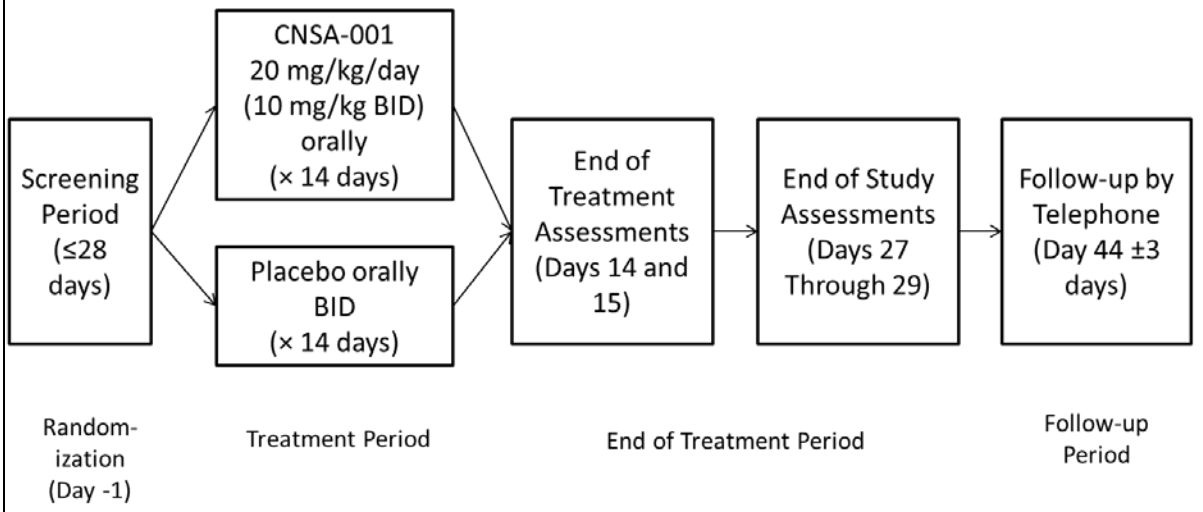
Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled pilot study of multiple doses of CNSA-001 (sepiapterin) powder for suspension administered orally in women with moderate to severe diabetic gastroparesis. Patients will be randomized in a ratio of 1:1 to receive CNSA-001 20 mg/kg/day or placebo, each dosed twice a day (BID); each group will consist of 10 patients. All patients will receive the standard of care for diabetic gastroparesis. Approximately 6 centers will participate in this study. The study design is summarized in the study schema below. A schedule of study events is provided in Appendix 1.

All study clinic visits will be outpatient visits.

Patients will continue their usual diet without modification throughout the study. Patients are required to have been fasting overnight for the following assessments:

- Clinical laboratory, including glycosylated hemoglobin A1c (HbA1c), tests
- The nutrient satiety test
- The GEBT



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, patients will undergo Screening procedures to determine study eligibility, as indicated in Appendix 1. Patients 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 patients will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Patients will undergo procedures during the Treatment Period as indicated in Appendix 1.

End of Treatment Period (Day 14 Through Day 15 Evaluations)
Patients will undergo End of Treatment (EOT) evaluations on Day 14 and Day 15 as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 14. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) 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)
Patients will undergo End of Study evaluations on Day 28 (±1 day) as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test on Day 28. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) 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])
Patients will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix 1.

Number of Patients:
Up to 20 women ≥18 and ≤75 years of age will be enrolled in this study and randomized in a ratio of 1:1 to receive CNSA-001 or placebo.

Main Criteria for Inclusion and Exclusion:
Patients are eligible to participate if they meet all the following inclusion criteria:

1. Informed consent
2. Females ≥18 and ≤75 years of age
3. Diagnosis of diabetes mellitus
4. Documentation of delayed gastric emptying by either
    - gastric emptying scintigraphy (GES) (within 2 years of enrollment), or
    - gastric emptying breath test (GEBT) (within 2 years of enrollment)

    If historical documentation is >2 years, either the GES or the GEBT may be conducted at screening to confirm diagnosis.
5. Symptoms of gastroparesis for at least 6 months with GCSI (Section 6.8, Appendix 2) score >21 indicating moderate to severe symptoms
6. Gastric accommodation, as measured by nutrient satiety testing, of ≤600 mL
7. Negative upper endoscopy or upper gastrointestinal (GI) series within 3 years of enrollment (no evidence of mechanical obstruction or peptic ulcer disease)
8. Either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following:
    - Hormonal contraception (stable dose for 3 months)
    - Intrauterine device/Intrauterine Hormone-releasing System
    - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

    Patients who are abstinent will not be required to use a contraceptive method unless they become sexually active.
9. If on analgesics, including narcotics; promotility agents, including metoclopramide, or neuromodulators, including tricyclic antidepressants, gabapentin, and pregabalin, doses are stable for >30 days before randomization and the patient is not expected to require dose changes during the study through the EOT
10. Have not used tobacco (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks prior to Day 1 and willingness to abstain from these products during the study through the EOT

Patients are not eligible to participate if they meet any of the following exclusion criteria:

1. Male gender
2. Normal gastric emptying
3. Gastroparesis from postsurgical etiologies
4. Another active disorder that could, in the opinion of the Investigator, explain symptoms
5. Weight >100 kg
6. Alanine aminotransferase > 2× upper limit of normal (ULN)
7. Pregnant, breastfeeding, or considering pregnancy
8. Clinically significant cardiac arrhythmia at Screening
9. QT interval corrected for heart rate (QTc) ≥470 msec using Fridericia's correction (based on triplicate measurements taken at Screening)
10. Resting heart rate ≤40 or ≥110 bpm or resting blood pressure <90/40 mmHg or >150/90 mmHg at Screening or prior to the first administration of study drug.

11. Recent clinically GI significant bleeding
12. Taking levodopa or domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT
13. Taking erythromycin within 30 days before randomization or expected to require erythromycin within 30 days before randomization or expected to require erythromycin during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization
14. Taking any fundic-relaxing agents including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT
15. Taking any systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)
16. Pulmonary dysfunction (e.g., chronic obstructive pulmonary disease)
17. Surgery for placement of a gastric stimulator within the past 6 months (patients postoperative >6 months with persistent symptoms and delayed gastric emptying are eligible)
18. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, small bowel malabsorption) that could affect the absorption of study drug or contraindicate undergoing the GEBT
19. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
20. History of allergies or adverse reactions to tetrahydrobiopterin or related compounds, to any excipients in the study drug formulation, or to egg, wheat, or algae (Spirulina)
21. Inability to tolerate oral medication
22. Current participation in any other investigational drug study or use of any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening
23. Any clinically significant laboratory abnormality; in general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range unless deemed not clinically significant by the Investigator
24. Major surgery within the previous 90 days
25. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study
26. History of alcohol or drug abuse within 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
27. Episodes of ketoacidosis or hypoglycemia that are frequent as defined by the Investigator
28. History of phenylketonuria (PKU) or hyperphenylalaninemia.
29. Any other conditions, including diabetic comorbidities, that, in the opinion of the Investigator or Sponsor, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

Test Product, Dose, and Mode of Administration:

The test product is CNSA-001 (sepiapterin) oral powder for suspension. CNSA-001 will be suspended in Medisca® Oral Mix prior to dispensing to the patient. Patients randomized to receive CNSA-001 will receive CNSA-001 20 mg/kg/day (i.e., 10 mg/kg BID) for 14 days.
Reference Therapy; Dose; and Mode of Administration: The reference product is placebo. The placebo is a ready-made suspension containing microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, ascorbic acid, and colorant (Yellow No. 6) that is suspended in Medisca® Oral Mix.
Duration of Treatment: Patients will be treated for a total of 14 days.
Criteria for Evaluation: **Safety:** Safety and tolerability of CNSA-001 as measured by severity and number of treatment-emergent adverse events (TEAEs), including assessment of severity of TEAEs, and changes in clinical laboratory and HbA1c tests, vital signs, and physical examinations **Efficacy:** The primary efficacy measure will be the change in maximal tolerated volume consumed during the nutrient satiety test from Day 1 to Day 14 and Day 1 to Day 28. Secondary efficacy measures will consist of changes in the following from baseline to Day 14 and baseline to Day 28 (±1 day): • GCSI (Section 6.8, Appendix 2) PAGI-SYM (Section 6.9, Appendix 2) subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores • Gastric emptying as measured by the GEBT
Statistical Methods: The following study populations will be analyzed: • Safety population: all patients who were randomized and received any amount of study drug (CNSA-001 or placebo) • Efficacy population: all patients who were randomized, received any amount of study drug (CNSA-001 or placebo), and had available Day 1 and Day 14 nutrient satiety test maximum tolerated volume results Safety will be assessed in the Safety population. Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and treatment group. Severity of AEs and serious adverse events (SAEs) will be summarized similarly. Those AEs leading to premature discontinuation from the study drug and the serious TEAEs will be presented in a table or a listing. Clinical laboratory and HbA1c test results and vital signs will be summarized at each visit as will changes from baseline for each treatment group. A frequency distribution of abnormal physical examination results will be provided. Efficacy will be assessed in the Efficacy population. The changes from Day 1 to Day 14 and from Day 1 to Day 28 in maximal tolerated volume consumed during the nutrient satiety test will be compared between treatment groups using a student's t-test. Results from the nutrient satiety test through Day 14 and Day 28, the GEBT through Day 15 and Day 27 or Day 29, and the GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) through Day 14 (+1) and through Day 28 (±1) will be summarized using summary statistics (number of patients, mean, standard deviation, median, and range) at each visit as well as changes from baseline within each treatment group. The 95% confidence intervals for the changes from baseline will be provided. Additional analyses may be conducted, and details will be provided in the statistical analysis plan.

Date of Original Protocol: 06 September 2018
Date of Amendment 1: 09 October 2018
Date of Amendment 2: 12 November 2018
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALB	Albumin
ALT	Alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT])
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
$AUC_{0\text{-last}}$	Area under the concentration time curve from 0 to the last measurement
BH4	Tetrahydrobiopterin
BID	Twice a day
BUN	Blood urea nitrogen
^{13}C	Carbon-13
Ca	Calcium
CFR	Code of Federal Regulations
Cl	Chloride
C_{max}	Maximum concentration
CO_2	Carbon dioxide
$^{12}CO_2$	Carbon-12 dioxide
$^{13}CO_2$	Carbon-13 dioxide
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GCSI	Gastroparesis Cardinal Symptom Index

GEBT	Gastric Emptying Breath Test
GES	Gastric Emptying Scintigraphy
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HbA1c	Glycosylated hemoglobin A1c
HCG	Human chorionic gonadotropin
HCT	Hematocrit
HEENT	Head, eyes, ears, nose, and throat
HGB	Hemoglobin
ICF	Informed consent form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
K	Potassium
kPCD	the Gastric Emptying Breath Test metric; “k” is a multiplier of 1000, and “PCD” is an acronym for percent carbon-13 dose excreted (as carbon-13 dioxide)
LAR	legally authorized representative
LDH	Lactate dehydrogenase
MedDRA®	Medical Dictionary for Regulatory Activities
Na	Sodium
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
PAGI-QOL	Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity
PRO	Patient-reported outcome
QTc	QT interval corrected for heart rate
RBC	Red blood cell

SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell

1 INTRODUCTION

1.1 Diabetic Gastroparesis

Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction; symptoms are chronic with episodic symptom exacerbation (Parkman et al, 2004). Gastroparesis affects women 4 times more than men (Soykan, et al, 1998). Idiopathic gastroparesis accounts for most cases, but gastroparesis is frequently associated with diabetes (diabetic gastroparesis) (Soykan, et al, 1998; Karamanolis et al, 2007). Several cross-sectional studies have found delayed gastric emptying of solids and/or liquids in 30% to 50% of patients with Type 1 or Type 2 diabetes (Horowitz et al, 2002). Patients with diabetes mellitus commonly experience gastric and intestinal dysfunction (Feldman and Schiller, 1983).

The actual mechanism of diabetic gastroparesis is not well known. Vagal nerve dysfunction and/or damage, interstitial cells of Cajal loss, and smooth muscle and enteric neuron dysfunction have all been implicated in the pathogenesis of diabetic gastroparesis (Stacher, 2001; Parkman et al, 2004). In addition, acute hyperglycemia has the potential to slow gastric emptying (Camilleri et al, 2013).

At a molecular level, attention has been devoted to the potential role of altered nitrergic signaling in the enteric nervous system. Gastric motility is regulated in large part by neurons of the enteric nervous system located in the muscle wall (Wood et al, 1999). These neurons are either excitatory (releasing acetylcholine) or inhibitory (releasing nitric oxide [NO] and vasoactive intestinal peptide). Nerves throughout the luminal gastrointestinal (GI) tract express neuronal nitric oxide synthase (nNOS), which generates NO, a key neurotransmitter in the regulation of GI motility (Takahashi, 2003); it is the principal nonadrenergic noncholinergic inhibitory neurotransmitter in the GI tract. In diabetic rats, which serve as a model for type 1 diabetes, nNOS expression was found to be impaired. This impairment in nNOS messenger RNA expression was associated with impaired smooth muscle relaxation in response to electrical stimulation of circular muscle fibers obtained from the proximal stomach of these rats (Takahashi et al, 1997). It has been demonstrated that female diabetic rats had slower gastric emptying than age matched diabetic male rats, female control rats had greater nitrergic relaxation of circular antral muscle strips compared to male controls, and nitrergic relaxation was impaired in diabetic female rats but not matched diabetic male rats (Gangula et al, 2007).

The core signs and symptoms of gastroparesis by incidence are nausea (92% to 96%), vomiting (68% to 88%), postprandial fullness (54% to 77%), early satiety (42% to 60%), and upper abdominal pain (36% to 85%) (Soykan et al, 1998; Hoogerwerf et al, 1999; Anaparthy et al, 2009). Patients may experience any combination of signs and symptoms with varying degrees of severity. Pain is less prevalent in diabetic gastroparesis than idiopathic gastroparesis. Patients with diabetic gastroparesis may experience further derangement of glucose control because of unpredictable gastric emptying and altered absorption of orally administered hypoglycemic drugs, which may, in turn, affect measurement of core signs and symptoms. Severe signs and symptoms may cause complications such as malnutrition,

esophagitis, and Mallory-Weiss tears. Gastroparesis adversely affects the lives of patients with the disease, resulting in decreased social interaction, poor work functionality, and development of anxiety or depression (Soykan et al, 1998; Parkman et al, 2004).

1.2 Impaired Gastric Accommodation in Gastroparesis

Patients with diabetic gastroparesis have also been shown to have gastric hypersensitivity, especially in the postprandial state, and impairment of the postprandial accommodation response. (Kumar et al, 2008). The stomach functions as 2 separate regions: the fundus acts as a reservoir accommodating a meal without a significant increase in intragastric pressure, and the distal stomach/antrum triturates gastric contents. Receptive relaxation or accommodation is vagally mediated resulting in the release of NO and activation of nitrergic myenteric neurons. Nitrergic signaling is responsible for gastric accommodation and pyloric relaxation in response to a meal (Ishiguchi et al, 2001).

Impaired accommodation has been associated with symptoms of early satiety and weight loss in patients with idiopathic gastroparesis (Karamanolis et al, 2007). A study of patients with diabetic gastroparesis found that 90% of patients had impaired gastric accommodation to a nutrient meal (Kumar et al, 2008). In the distal stomach, NO is required for the propulsive contractions that triturate gastric contents and control of pyloric closure; lack of NO can lead to delayed gastric emptying and impaired gastric accommodation (Gangula et al, 2007).

Several co-factors are known to be important for nNOS activity, including nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), calcium, and tetrahydrobiopterin (BH4) (Werner et al, 2003). The homodimeric conformation of all 3 isoforms of nitric oxide synthase (NOS) is regulated by BH4 (Werner et al, 2003). In the absence of BH4, uncoupling of NO production occurs and leads to super oxide production, resulting in further impaired nNOS bioactivity.

1.3 Current Treatment of Diabetic Gastroparesis

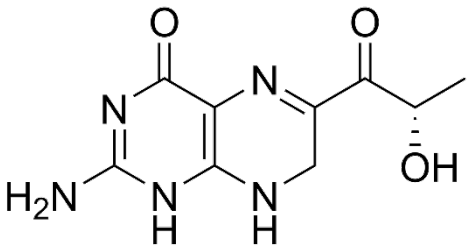
Therapies for gastroparesis have been targeted at accelerating gastric emptying or controlling symptoms. Available therapies for accelerating gastric emptying are limited in number and efficacy. These include metoclopramide (Snape et al, 1982), erythromycin (Arts et al, 2005), and domperidone (not available in the United States [US]) (Prakash and Wagstaff, 1998). There is also poor correlation between gastric emptying and baseline symptom severity (Karamanolis et al, 2007; Talley et al, 2001) and in response to therapeutic intervention. In part, as a result of lack of understanding of the underlying pathogenesis that leads to alterations in GI motility and sensation, medical therapies have not been targeted at the underlying pathophysiology of gastroparesis.

The first-line medical therapy for patients with diabetic gastroparesis is generally a combination of an antiemetic agent in addition to the promotility drug. Unfortunately, many patients with diabetic gastroparesis will not experience adequate symptom relief despite first-line therapy. For patients with refractory disease, options include combination prokinetic therapy, psychotropic medications, pyloric botulinum toxin injection, and gastric electric stimulation (Fass, 2010; Camilleri et al, 2013).

1.4 CNSA-001 (Sepiapterin)

Sepiapterin is 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$.

The chemical structure of sepiapterin is:



Sepiapterin serves as a substrate for BH4 synthesis via the pterin salvage pathway (Mayer and Werner, 1995). Oral administration of sepiapterin was shown to be more potent (>2 fold) than oral administration of BH4 in increasing intracellular BH4 in normal mice (Sawabe et al, 2002). Translation of this finding to humans has been confirmed in a Phase 1 study, PKU-001, conducted by Censa Pharmaceuticals.

1.5 Rationale for Study

BH4 biosynthesis is impaired in chronic diabetes. The mechanism of impairment is not well understood but is thought to be a result of hyperglycemia-induced proteasome-mediated degradation of GTP-cyclohydrolase, the rate-limiting enzyme in the synthesis pathway for BH4 (Xu et al, 2007).

CNSA-001 is the first viable formulation of sepiapterin, shown to increase intracellular BH4 (Section 1.4), intended for the treatment of female patients with diabetic gastroparesis. CNSA-001 was studied in a single and multiple ascending-dose study in healthy volunteers, the Phase 1 study, Study PKU-001. Part A of this study assessed the safety and pharmacokinetics of CNSA-001 at 6 dose levels inclusive of an assessment of food effect (i.e., 2.5 mg/kg, 7.5 mg/kg, 20 mg/kg, 40 mg/kg, 80 mg/kg, and 10 mg/kg [to assess food effect]). Additionally, Kuvan® (sapropterin dihydrochloride), a synthetic BH4 commercially available product, was administered at equivalent doses for the first 3 dose levels (2.5 mg/kg, 7.5 mg/kg, and 20 mg/kg). Dose-dependent correlations between CNSA-001 and plasma BH4 concentrations were observed with each successive dose level. Dose proportionality was observed between the top 2 dose levels (40 mg/kg and 80 mg/kg) and resultant BH4 concentrations. Administration with a standard high-fat (approximately 50 percent of total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) meal resulted in approximately 80% higher plasma BH4 concentrations (area under the concentration time curve from 0 to the last measurement [$AUC_{0\text{-last}}$] and maximum concentration [C_{max}]) than in subjects who had fasted before receipt of CNSA-001. Treatment-emergent adverse events (TEAEs) in Part A of Study PKU-001 were reported in 26 subjects (44.1%, 26/59). The TEAEs for CNSA-001 were generally mild and consistent with reported adverse events (AEs) for Kuvan® and placebo. The frequency of TEAEs did

not appear to increase with increasing dose. The TEAEs that were judged to be related to study treatment were reported in 17 subjects: 11 subjects (26.2%, 11/42) who received CNSA-001, 4 subjects (44.4%, 4/9) who received Kuvan®, and 2 subjects (25.0%, 2/8) who received placebo. No TEAEs were severe or serious or led to discontinuation of study drug. Headache and dizziness were the most common TEAEs , but these TEAEs occurred at a similar frequency as with placebo.

Part B of Study PKU-001 assessed multiple ascending doses CNSA-001 in healthy volunteers. Data indicate CNSA-001 was well tolerated following daily doses of 5, 20, and 60 mg/kg/day for 7 days and that TEAEs were reported in 14 subjects (58.3%, 14/24). The TEAEs in subjects who received CNSA 001 were mild or moderate and consistent with the TEAEs in subjects who received placebo: TEAEs were experienced by 10 subjects (55.6%, 10/18) who received CNSA-001 at doses from 5 mg/kg to 60 mg/kg daily for 7 days and by 4 subjects (66.7%, 4/6) who received placebo. No TEAEs were severe, serious, or led to discontinuation. Of the 10 TEAEs reported in subjects who received CNSA-001, only 4 were judged to be related to study drug, and, of the 4 TEAEs reported in subjects who received placebo, only 1 was judged to be related to study drug. Somnolence, fatigue, headache, and procedural pain (secondary to performance of 2 sequential lumbar punctures 7 days apart) were the most common TEAEs reported, and they occurred at a similar frequency when compared with placebo with the exception of fatigue and headache, which were each reported in 2 subjects who received CNSA-001 (11.1%, 2/18).

This Phase 2 pilot study will assess CNSA-001 doses of 20 mg/kg/day administered as 10 mg/kg twice a day (BID) in comparison to placebo administered BID in female patients with diabetic gastroparesis. This study will help support the design of future Phase 2/3 studies in patients with diabetic gastroparesis.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the impact of CNSA-001 on gastric accommodation, as measured by nutrient satiety testing (Section 6.7), in women with moderate to severe diabetic gastroparesis.

2.2 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 as measured by the change from baseline in the global assessment of symptoms and symptom severity (Gastroparesis Cardinal Symptom Index [GCSI]) (Section 6.8, Appendix 2)
- To evaluate the effect of CNSA-001 on patient-reported symptoms as measured by the change from baseline in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) (Section 6.9, Appendix 2)
- 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) (Section 6.10)
- To assess the safety and tolerability of CNSA-001 20 mg/kg/day

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Study GAS-001 is a Phase 2, randomized, double-blind, placebo-controlled pilot study of multiple doses of CNSA-001 (sepiapterin) powder for suspension administered orally in women with moderate to severe diabetic gastroparesis. This is an outpatient study in which up to 20 patients will be enrolled at approximately 6 centers.

The Schedule of Events is provided in Appendix 1. The study schema is displayed in Figure 1.

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, patients will undergo Screening procedures to determine study eligibility, as indicated in Appendix 1. Patients 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 patients will take their first dose of study drug (CNSA-001 or placebo) on Day 1 while in the clinic. Patients will undergo procedures during the Treatment Period as indicated in Appendix 1.

Study drug may be prematurely discontinued for safety reasons, as described in Section 6.14.1. Patients may also withdraw from the study for any reason, as described in Section 6.14.2. 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) (Section 7.5, Appendix 1). 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 (Section 7.5, Appendix 1). 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 (Section 7.6, Appendix 1).

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

Patients will undergo EOT evaluations on Day 14 and Day 15 as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test (Section 6.7) on Day 14. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) will also be administered on Day 14 (+1 day), and the GEBT (Section 6.10) will be conducted on Day 15.

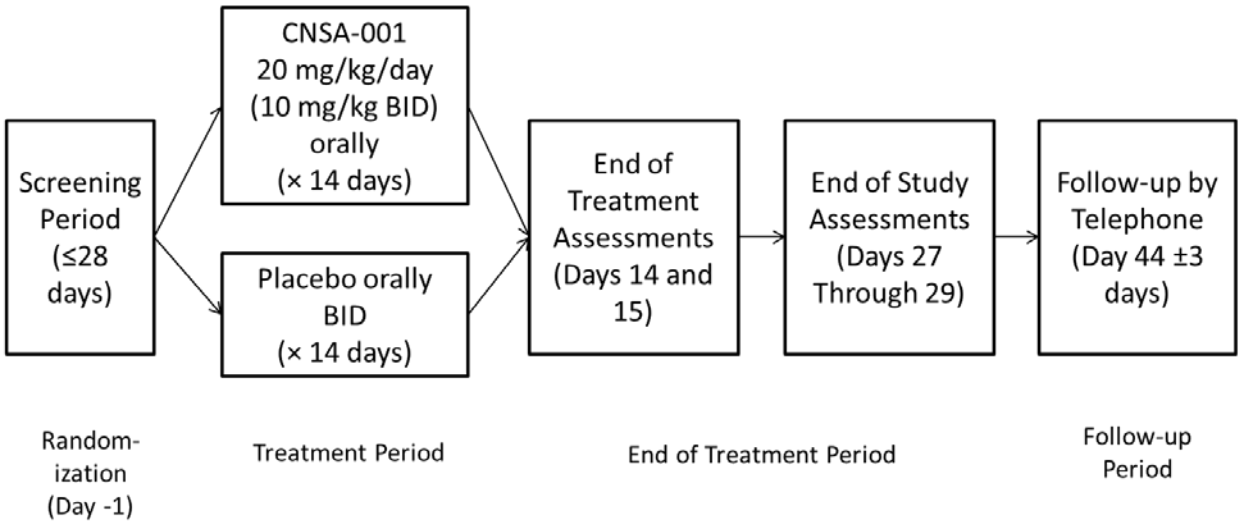
End of Study Period (Day 15 After Evaluations Through Day 28 [±1 Day] Evaluations)

Patients will undergo EOS evaluations on Day 28 (±1 day) as indicated in Appendix 1. Preliminary efficacy will be assessed by the changes from Day 1 in the nutrient satiety test (Section 6.7) on Day 28. The GCSI (Section 6.8, Appendix 2) and PAGI-SYM (Section 6.9, Appendix 2) will also be administered on Day 28 ±1, and the GEBT (Section 6.10) will be conducted on Day 27 or Day 29.

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

Patients will undergo telephone Follow-up on Day 44 ±3 days as indicated in Appendix 1.

Figure 1: Study Schema



Abbreviations: BID = twice a day.

3.2 Rationale for Study Design and Control Group

CNSA-001 (sepiapterin) is a new chemical entity that is an endogenous, naturally occurring precursor of BH4 via the pterin salvage pathway. Animal studies and data from a Phase 1 single and multiple ascending-dose study in healthy volunteers conducted by Censa Pharmaceuticals indicate rapid intracellular conversion of sepiapterin to BH4. It is expected that oral administration of CNSA-001 to women with diabetic gastroparesis will result in increases in both intracellular and circulating BH4 concentrations. In chronic diabetes, BH4 biosynthesis is impaired (Xu et al, 2007).

CNSA-001 was studied in two 14-day Good Laboratory Practice (GLP) toxicity studies, as described in Section 5.3, and in a single and multiple ascending-dose study in healthy volunteers, Study PKU-001, as described in Section 1.5.

Because all patients will receive the standard of care for diabetic gastroparesis in addition to their assigned study drug, the study design of a randomized study of CNSA-001 versus

placebo in female patients with diabetic gastroparesis will not expose patients to the risk of no treatment.

This study has a double-blind design intended to reduce bias.

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).

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 6 study centers will enroll up to 20 women with moderate to severe diabetic gastroparesis this study.

4.2 Inclusion Criteria

Patients are eligible to participate in this study if they meet all the following inclusion criteria:

1. Informed consent
2. Females ≥18 and ≤75 years of age
3. Diagnosis of diabetes mellitus
4. Documentation of delayed gastric emptying by either
   - gastric emptying scintigraphy (GES) (within 2 years of enrollment), or
   - gastric emptying breath test (GEBT) (within 2 years of enrollment)

   If historical documentation is >2 years, either the GES or the GEBT may be conducted at screening to confirm diagnosis.
5. Symptoms of gastroparesis for at least 6 months with GCSI (Section 6.8, Appendix 2) score >21 indicating moderate to severe symptoms
6. Gastric accommodation, as measured by nutrient satiety testing, of ≤600 mL
7. Negative upper endoscopy or upper GI series within 3 years of enrollment (no evidence of mechanical obstruction or peptic ulcer disease)
8. Either postmenopausal for ≥1 year or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception throughout the study such as 1 of the following:

   - Hormonal contraception (stable dose for 3 months)
   - Intrauterine device/Intrauterine Hormone-releasing System
   - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

   Patients who are abstinent will not be required to use a contraceptive method unless they become sexually active

9. If on analgesics (including narcotics), promotility agents (including metoclopramide), or neuromodulators (including tricyclic antidepressants, gabapentin, and pregabalin), doses are stable for >30 days before randomization and the patient is not expected to require dose changes during the study through the EOT

10. Have not used tobacco (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks prior to Day 1 and willingness to abstain from these products during the study through the EOT

4.3 Exclusion Criteria

Patients are not eligible to participate in this study if they meet any of the following exclusion criteria:

1. Male gender
2. Normal gastric emptying
3. Gastroparesis from postsurgical etiologies
4. Another active disorder that could, in the opinion of the Investigator, explain symptoms
5. Weight >100 kg
6. Alanine aminotransferase > 2× upper limit of normal (ULN)
7. Pregnant, breastfeeding, or considering pregnancy
8. Clinically significant cardiac arrhythmia at Screening
9. QT interval corrected for heart rate (QTc) ≥470 msec using Fridericia's correction (based on triplicate measurements taken at Screening)
10. Resting heart rate ≤40 or ≥110 bpm or resting blood pressure <90/40 mmHg or >150/90 mmHg at Screening or prior to the first administration of study drug.
11. Recent clinically significant GI bleeding
12. Taking levodopa or domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT
13. Taking erythromycin within 30 days before randomization or expected to require erythromycin within 30 days before randomization or expected to require erythromycin during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization
14. Taking any fundic-relaxing agents including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT
15. Taking any systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)
16. Pulmonary dysfunction (e.g., chronic obstructive pulmonary disease)

17. Surgery for placement of a gastric stimulator within the past 6 months (patients postoperative >6 months with persistent symptoms and delayed gastric emptying are eligible)
18. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, small bowel malabsorption) that could affect the absorption of study drug or contraindicate undergoing the GEBT (Section 6.10)
19. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
20. History of allergies or adverse reactions to BH4 or related compounds, to any excipients in the study drug formulation, or to egg, wheat, or algae (Spirulina)
21. Inability to tolerate oral medication
22. Current participation in any other investigational drug study or use of any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening
23. Any clinically significant laboratory abnormality; in general, each laboratory value from Screening and baseline chemistry and hematology panels should fall within the limits of the normal laboratory reference range unless deemed not clinically significant by the Investigator
24. Major surgery within the previous 90 days
25. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study
26. History of alcohol or drug abuse within 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
27. Episodes of ketoacidosis or hypoglycemia that are frequent as defined by the Investigator
28. History of phenylketonuria (PKU) or hyperphenylalaninemia.
29. Any other conditions, including diabetic comorbidities, that, in the opinion of the Investigator or Sponsor, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Test Product

The test product is CNSA-001 (sepiapterin) oral powder for suspension. CNSA-001 contains the new chemical entity, sepiapterin. Sepiapterin is 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$. Inactive ingredients in CNSA-001 include microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid. CNSA-001 will be suspended in Medisca® Oral Mix prior to dispensing it to the patient.

5.1.2 Placebo Control

The placebo is a ready-made suspension containing microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, ascorbic acid, and colorant (Yellow No. 6) that is suspended in Medisca® Oral Mix.

5.2 Treatments Administered

Patients will be randomized in a ratio of 1:1 to the following treatment groups:

- CNSA-001 20 mg/kg/day (10 mg/kg BID) for 14 days
- Placebo BID for 14 days

Dosing of CNSA-001 is based on the patient's weight. The weight obtained on Day -1 will be used to calculate the exact amount (mg) of CNSA-001 active ingredient (sepiapterin) required for each patient's daily dose.

The placebo is formulated as ready-made suspension. The placebo will be administered in the same manner (volume) as CNSA-001.

Details on preparation of study drug and dosing guidelines will be provided in a pharmacy manual for the site and an instruction guide for patients.

5.3 Selection and Timing of Dose for Each Patient

All patients will be randomly assigned in a ratio of 1:1 to receive CNSA-001 20 mg/kg/day (10 mg/kg BID) or placebo BID.

The CNSA-001 dose was selected following completion of two 14-day GLP toxicity studies in the rat and marmoset. The no observed adverse effect level from both studies was set at 1000 mg/kg/day, which represents a human equivalent dose of 161.3 mg/kg/day based on allometric scaling. Consequently, the proposed dose of 20 mg/kg/day represents an 8.1-fold safety margin.

Study drug will be dispensed on Day 1 (Section 6.11) with a dosing diary in which patients will record all doses taken and times they were taken (Section 5.8.1). The first dose on Day 1 will be taken in the clinic after patients undergo the nutrient satiety test (Section 6.7).

If a patient vomits after taking a dose of study drug, the patient 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.

5.4 Method of Assigning Patients to Treatment Groups

Patients 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. Patients who are randomized will be considered to be enrolled.

5.5 Blinding

This study has a double-blind design. The Investigator, study personnel, and patients will not make any effort to determine which study drug is being received. Unblinded pharmacy (or other qualified site) personnel will be utilized in this study to prepare the study drug.

Patients will be blinded to study drug assignment. Only in an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific patient, may the Investigator unblind a patient's study drug assignment. Copies of the randomization sequence and treatment codes will be kept in the pharmacy at the sites. If emergency unblinding is required, the Investigator will have immediate access to individual sealed codes containing treatment allocations. However, before any unblinding occurs, the Investigator is strongly advised to discuss options with the Sponsor's Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the patient's study drug assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to the unblinding. The Investigator will record in source documentation the date and reason for revealing the blinded study drug assignment for any patient and the names and roles of personnel unblinded.

5.6 Concomitant Therapy

Patients will be permitted to take:

- Analgesics, including narcotics, if the patient has been on a stable dose of the medication for >30 days before randomization; dose escalation is NOT permitted during the study through the EOT

- Promotility agents, including metoclopramide if the patient has been on a stable dose of the medication >30 days before randomization; dose changes are NOT permitted during the study through the EOT

- Neuromodulators, including any tricyclic antidepressant, gabapentin, and pregabalin, if the patient has been on a stable dose >30 days before randomization; dose changes are NOT permitted during the study through the EOT

- Rescue medications that patients would usually take, including ondansetron (Zofran®), promethazine (Phenergan®) or prochlorperazine (Compazine®) for nausea and tramadol (Ultram®), if symptoms related to gastroparesis require further treatment during the study through the EOT

All prescription and over-the-counter medications (including herbal medications) that the patient took within 30 days before Screening though the EOT should be recorded.

5.7 Restrictions

5.7.1 Prior Therapy and Concomitant Therapy

The following are prohibited:

- Any investigational agent, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before Screening

- Domperidone within 30 days before randomization or expected to require domperidone during the study through the EOT

- Dose escalation of analgesic or promotility agents or neuromodulators within 30 days before randomization or during the study through the EOT

- Erythromycin within 30 days before randomization or during the study through the EOT; if a patient is taking erythromycin and is otherwise eligible to participate in the study, following signing the ICF, the patient may go through an erythromycin washout period of 30 days before randomization

- Systemic antifolates, including, but not limited to, methotrexate, pemetrexed, and trimetrexate or expected to require any systemic antifolates during the study through the EOT (topical antifolates [e.g., cream, ointment, gel] or eye drops with antifolates are allowed)

- Fundic-relaxing agents, including, but not limited to, buspirone, clonidine, nitrates, phosphodiesterase inhibitors (i.e., sildenafil citrate [Viagra®]) and triptan-containing medications, within 30 days before randomization or expected to require any of these agents during the study through the EOT

- Medications that can alter GI sensation or accommodation or gastric emptying overnight before the nutrient satiety test (Section 6.7)

5.7.2 Food Intake

Patients will continue their usual diet without modification throughout the study. Patients are required to have been fasting overnight for the following assessments:

- Clinical laboratory, including glycosylated hemoglobin A1c (HbA1c), tests
- The nutrient satiety test (Section 6.7), which requires the consumption of Ensure™ (Abbott Laboratories, Abbott Park, IL, USA)
- The GEBT (Section 6.10), which requires consumption of a standardized 230 kCal meal, consisting of a standardized carbon-13 (^{13}C)-labeled egg component and 6 saltine crackers, with 6 ounces of water

5.7.3 Total Blood Volume

The total volume of blood obtained from an individual study patient is expected to be approximately 40 mL, for clinical laboratory tests inclusive of the HbA1c test.

5.7.4 Patient Activity and Tobacco Restrictions

Patients will not be confined during the study and will not require any activity restrictions. Patients must abstain from tobacco use (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco, nicotine replacement) for 2 weeks before Day 1 and during the study through the EOT.

5.8 Treatment Compliance

Patients will be instructed to return all used (empty containers) and unused study drug on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day). Compliance with the dosing regimen will be assessed by reconciliation of used and unused study drug. The quantities dispensed, returned, used, and lost will be recorded on the dispensing log provided for the study.

5.8.1 Dosing Diary

Patients will be provided with a dosing diary on Day 1 along with instructions for recording all doses of study drug and times they were taken. The dosing diary will be collected on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15 or Day 28 (±1 day), and the Investigator (or designee) will transcribe all entries into the electronic case report form (eCRF).

5.9 Packaging and Labeling

CNSA-001 Oral Powder for Suspension is packaged in 10 mL amber glass vials with black child proof caps. Each glass vial contains 175 mg of sepiapterin.

Each vial of CNSA-001 Oral Powder for Suspension will contain the product name, strength, content, expiry/retest date, and company name. Each vial label will contain the words, "Caution: Investigational medicine for clinical trial use only."

CNSA-001 PLACEBO suspension is packaged in 500 mL bottles. Each bottle of CNSA-001 PLACEBO suspension will contain the content and company name as well as "CNSA-001 PLACEBO" on its label.

The suspending vehicle, Medisca® Oral Mix, is commercially available and will be provided separately.

5.10 Storage and Accountability

All drug product required for completion of this study will be provided by Censa Pharmaceuticals. It is the responsibility of the pharmacy staff or study staff to ensure that a current record of drug inventory and drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the study monitor and are open to inspection at any time by applicable regulatory authorities.

CNSA-001 Oral Powder for Suspension (non-reconstituted) may be stored frozen at -20°C or at refrigerated conditions (2 to 8°C). If not administered on the same day of suspending, CNSA-001 suspension should be stored at refrigerated conditions (2 to 8°C) until time of dosing. Once suspended, CNSA-001 is stable for 14 days.

CNSA-001 PLACEBO suspension may be stored refrigerated at 2 to 8°C.

5.11 Investigational Product Retention at Study Site

Upon completion of the study and once inventoried by the study site, all used (empty) containers of study drug will be destroyed. Any unused containers of study drug may be either destroyed or returned to the Sponsor following discussion with the Sponsor. If study drug is destroyed, a certificate of destruction will be provided to the Sponsor by the appropriate facility performing the destruction.

6 STUDY PROCEDURES

6.1 Informed Consent

Consent forms describing in detail the study drug, study procedures, and risks are given to the patient, and written documentation of informed consent is required prior to conducting study-related procedures. See Section 10.4 for more information on the informed consent process.

6.2 Medical History and Demographic Data

A detailed medical/surgical history will be obtained at Screening. The history will include specific information related to any prior or existing medical conditions or surgical procedures involving the following systems: dermatologic; head, eyes, ears, nose, and throat (HEENT); lymphatic; cardiovascular; respiratory; GI; musculoskeletal; and neurological. The medical history will be updated on Day 1 before the start of study drug.

Demographic data obtained at Screening will include age, gender, and self-reported race/ethnicity.

6.3 Vital Signs, Weight, and Height

Vital signs, including blood pressure, pulse, respiratory rate, and temperature, will be measured at Screening, Day 1 (predose and 2 hours postdose), and at the EOT and EOS visits. Vital signs will be measured prior to collection of laboratory samples and after patients have rested for 5 minutes in the supine position. For timepoints other than Day 1, vital signs will be taken at any time during the visit after resting and laboratory sample collection.

Weight will only be collected at Screening as necessary to determine the response to Exclusion Criterion #5 (Section 4.3) and on Day -1. Height will only be collected at Screening.

6.4 Physical Examination

A complete physical examination will be performed at Screening, on Day 1 before start of study drug and at the EOT and EOS visits. The examination will assess general appearance, as well as dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters.

6.5 Clinical Laboratory Tests and Glycosylated Hemoglobin A1c

Clinical laboratory tests will be performed by qualified local laboratories. Blood and urine samples for clinical chemistry, hematology, and urinalysis will be collected at Screening, Day 1 (predose), and at the EOT and EOS visits. Patients should fast overnight prior to collection of blood samples (minimum of 8 hours before blood sample collection). Blood samples for HbA1c will be collected at Screening and at the EOT and EOS visits. Clinically significant laboratory abnormalities should be followed to a satisfactory resolution, as determined by the Investigator.

The following clinical laboratory and other laboratory parameters will be assessed:

Hematology:	**Serum Chemistry:**
Hematocrit (HCT)	Albumin (ALB)
Hemoglobin (HGB)	Alkaline phosphatase (AP)
Platelet count	Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT])
Red blood cell (RBC) count	Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT])
White blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)	Blood urea nitrogen (BUN)
Urinalysis:	Calcium (Ca)
Bilirubin	Carbon dioxide (CO_2)
Glucose	Chloride (Cl)
Ketones	Creatinine
Occult blood	Gamma glutamyl transferase (GGT)
pH	Glucose
Protein	Lactate dehydrogenase (LDH)
Specific gravity	Phosphorus
Urobilinogen	Potassium (K)
Microscopy:	Sodium (Na)
WBCs	Total bilirubin
RBCs	Direct bilirubin
Epithelial cells	Total cholesterol
Pregnancy Testing: [a]	Total protein
Serum human chorionic gonadotropin (HCG) at Screening	Uric acid
Urine HCG Day 1 (predose) and Day 14 (±1 day)	**Other:**
	Glycosylated hemoglobin A1(HbA1c)

[a] Required for all women who are of childbearing potential. Any positive urine pregnancy test should be confirmed by a serum pregnancy test.

6.6 Electrocardiogram

At Screening, 12-lead electrocardiograms (ECGs) will be obtained in triplicate, with 1 minute separating the first and second recordings and 1 minute separating second and third recordings. The following ECG parameters will be collected and recorded in the eCRF: RR, PR, QRS, QT, and QTc intervals. In addition, the ECG tracing should be reported as normal,

abnormal clinically significant, or abnormal not clinically significant. If abnormalities are noted on the ECG, these should be recorded in the eCRF.

6.7 Nutrient Satiety Test

For the nutrient satiety test, patients consume 150 mL of Ensure™ every 5 minutes. At 5-minute intervals, patients 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). Patients 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 patients 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. The sum of the four 100-mm visual analogue scales provides an aggregate symptom score (Park, 2011).

The nutrient satiety test will be administered in the clinic 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. A nutrient satiety test volume of ≤600 mL at Screening is required for patients to participate in this study.

6.8 Gastroparesis Cardinal Symptom Index

The GCSI (Appendix 2) consisting of a subset of items from the PAGI-SYM instrument (Section 6.9, Appendix 2), will be administered in the clinic at Screening and on Day 1 (predose), Day 14 (+1 day), and Day 28 (±1 day). A GCSI score >21 at Screening, indicating moderate to severe symptoms, is required for patients to participate in this study.

6.9 Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity

The PAGI-SYM (Appendix 2) is a 20-item upper GI symptom severity instrument with 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. It will be administered in the clinic on Day 1 (predose) and on Day 14 (+1 day), and Day 28 (±1 day).

6.10 Gastric Emptying Breath Test

The GEBT, which is a nonradioactive noninvasive test, will be administered in the clinic on Day -1, Day 15, and Day 27 or Day 29 after the patient 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 patient provides baseline (premeal) breath samples and then consumes 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. The meal is to be consumed within 10 minutes. Single postmeal breath samples are collected in capped glass tubes at 45, 90, 120, 150, 180, and 240 minutes after the meal is consumed and sent to the specified local laboratory for

analysis by Gas Isotope Ratio Mass Spectrometry. By adding ^{13}C to the test meal, the GEBT can determine how fast the stomach empties the meal by measuring the rate of carbon-13 dioxide ($^{13}CO_2$) excretion arising from the digested test meal. The rate of $^{13}CO_2$ excretion found in the patient's breath is proportional to the patient's rate of gastric emptying. The patient's $^{13}CO_2$ excretion rate at each breath collection time is reported using the GEBT metric "kPCD." The "k" is a multiplier of 1000, and "PCD" is an acronym for percent ^{13}C dose excreted (as $^{13}CO_2$). The test should not be administered to patients with a known allergy to egg, wheat, or algae (Spirulina) (Cairn Diagnostics™; Sutton et al, 2015; GEBT package insert, 2015; United States Food and Drug Administration, 2015).

6.11 Dispensing Study Drug

Study drug will be dispensed on Day 1 along with a dosing diary to record all doses taken and times they were taken. A sufficient supply of study drug will be dispensed for dosing through Day 14. Details on the preparation of study drug, dosing guidelines, and storage will be provided in a pharmacy manual for the site and an instruction guide for patients.

6.12 Adverse Events Assessments

An AE is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

The occurrence of an AE or serious adverse event (SAE) (Section 6.12.6) may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes, but is not limited to, the event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. Action taken regarding study medication (e.g., drug withdrawn, interrupted) will also be collected in the eCRF. All AEs that start during the study must be documented appropriately regardless of relationship. All treatment-related AEs or AEs leading to discontinuation will be followed to an adequate resolution, as determined by the Investigator.

Any medical condition that is present at the time that the patient is screened will be considered as medical history and not reported as an AE. However, if the patient's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. The AEs characterized as intermittent require documentation of onset and duration of each episode.

6.12.1 Reporting Timelines

The Investigator will record all reportable events with start dates occurring any time after informed consent and continue through clinical study completion or, in the case of withdrawal, until the outcome is determined. The AEs will be assessed at each visit and/or

through telephone contact with the patient. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

All SAEs should be reported after the patient signs the informed consent and followed until resolution, stabilization, or until the Investigator provides sufficient evidence that no further information can be obtained.

All SAEs and pregnancies (in a patient or partner of a male patient) occurring while the patient is on the study or within 30 (±3) days after the patient received the last dose of study drug must be reported within 24 hours of the knowledge of the event by study personnel whether or not considered to be related to study drug.

Deaths that occur ≥30 (±3) days after the patient's last study dose must be reported within 24 hours of knowledge of the event, if deemed related to study drug by the Investigator.

Although pregnancy is not considered an AE or SAE by regulatory definition, for this study pregnancies must be processed following SAE timelines (e.g., within 24 hours of knowledge of the pregnancy) for data transmission purposes. In the event that a pregnancy complication occurs, or elective termination of a pregnancy is required for medical reasons, then the complication will be recorded as an AE or SAE, as appropriate.

While elective and uncomplicated induced abortion not required for medical reasons does not constitute an AE or SAE (even if the patient or patient's partner is hospitalized to undergo abortion), spontaneous abortion is considered a fatal event and must be reported as an AE and SAE, as appropriate.

Any pregnancy and/or suspected pregnancy that occurs during the study in a female patient should be reported using Pregnancy Reporting Form within 24 hours of knowledge of the event by study personnel. Any pregnancy and/or suspected pregnancy will be followed for outcome.

If the patient has received the investigational drug prior to becoming pregnant, the patient will continue the efficacy assessment and Follow-up periods and measures of safety and efficacy will be obtained.

The patient will be followed until the outcome of the pregnancy is determined. It is the responsibility of the Investigator to obtain and document pregnancy information on the most recent Pregnancy Report Form. Furthermore, any SAE occurring as an outcome of the pregnancy must be reported according to the procedures outlined for SAE reporting.

6.12.2 Severity

The intensity of each AE will be graded as follows:

Mild:	Events require minimal or no treatment and do not interfere with the patient's daily activities.
Moderate:	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe:	Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but may not be considered an SAE. Alternatively, a stroke that results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE.

6.12.3 Relationship

The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. For purposes of consistency, guidelines for assessing causality are provided below:

Not Related	The AE is completely independent of study drug 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. No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state.
Unlikely to be 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 chemicals or underlying disease provides plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).
Possibly Related	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
Probably Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
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 response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to study drug administration, then an alternative explanation should be provided, if available.

6.12.4 Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigators' Brochure or is not listed at the specificity or severity that has been observed;

or, if an Investigators' Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the protocol.

The drug safety medical reviewer will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent (e.g., Investigators' Brochure).

6.12.5 Clinical Laboratory Adverse Events

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms or require medical intervention, as determined by the Investigator. However, each laboratory abnormality (e.g., clinically significant changes detected in hematology, serum chemistry panel, urinalysis, urine microscopic, and HbA1c evaluations) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to study drug interruption or discontinuation, must be recorded as an AE, or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (e.g., vital signs) performed that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described below.

6.12.6 Serious Adverse Events

6.12.6.1 Definition

An SAE is defined as an AE or suspected adverse reaction occurring at any dose that results in any of the following outcomes: death, life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

An AE or suspected adverse reaction is considered ''life-threatening'' if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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, or the development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in these other situations.

6.12.6.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Sponsor must submit a safety report for any suspected adverse reaction to study treatment that is both serious and unexpected. Before submitting a safety report, the Sponsor needs to ensure that the event meets all 3 of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the AE does not meet all 3 of the definitions, it should not be submitted as a safety report.

6.12.6.3 Reporting Serious Adverse Events

The Investigator will report all SAEs to the designated drug safety team within 24 hours of knowledge of the event whether or not considered to be related to study drug using the SAE Report Form provided.

Although not all information required for a complete SAE Report Form may be readily available at the time of the event, the Investigator must include sufficient information on the SAE Report Form to allow for a complete medical assessment. This should include at a minimum the patient number, site number, detailed description of the event, seriousness criteria, causality/relationship to study drug, and Investigator signature.

The designated drug safety team will acknowledge the receipt of the SAE via email to the clinical site. After submission of the initial report, the Investigator will provide follow-up information to the drug safety team as requested (e.g., concomitant medications, hospital discharge summary) to further evaluate the event and assure that all appropriate information is received. Once all information is received and the SAE has been deemed appropriate for closure, the SAE Report Form must be signed and dated by the Investigator.

The Investigator is responsible for informing the Institutional Review Board (IRB) of the SAE in accordance with institutional policies and procedures including relevant initial and follow-up information about the SAE.

Treatment-related SAEs or events leading to discontinuation of study drug will be followed for outcome information until resolution or stabilization. Other supporting documentation of the event may be requested by Censa Pharmaceuticals (or designee) and should be provided as soon as possible. The Medical Monitor should be contacted when the Investigator considers an SAE to be treatment-related.

6.12.7 Treatment-Emergent Adverse Events

Those AEs that start at the time of or after the first dose of study drug are TEAEs. Those AEs that worsen at or after the time of first dose of study drug are also considered treatment-emergent. All AEs that occur on or after the ICF has been signed, including all TEAEs, through Day 29 will be recorded in the eCRF.

All SAEs through Day 44 ±3 days [30 ±3 days after the patient received last dose of study drug] will be recorded in the eCRF and reported as described in Section 6.12.6.3.

6.13 Prior and Concomitant Medication Assessments

All prescription and over-the-counter medications (including herbal medications) taken by a patient starting from the 30-day period before Screening through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations will be recorded. Any concomitant medications added or discontinued during the study will be recorded at each visit.

6.14 Removal of Patients From the Trial or Study Drug

6.14.1 Early Discontinuation From Study Drug Administration

Premature discontinuation of study drug administration is defined as the discontinuation of study drug for an individual patient before the required full course of study drug is completed. Reasons for premature discontinuation from study drug administration should be recorded on the appropriate page(s) of the eCRF and may include, but are not limited to the following:

- Occurrence of an AE, SAE, or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from study drug administration
- In the judgment of the Investigator, the patient experiences a general or specific change(s) that renders the patient unsuitable for continued study drug administration
- There is a need for concomitant medication that makes the patient ineligible for further study drug administration
- Pregnancy
- Specific reasons related to adverse events that have been observed in pre- and post-marketing treatment with the same drug class of CNSA-001 (i.e., sapropterin):
    - Hypersensitivity reactions including anaphylaxis
    - Gastritis
    - Abnormal liver function tests in patients with liver impairment
    - Unexplained hyperactivity

Given the requirement for pregnancy testing in women of childbearing potential at Screening and the requirement for highly effective methods of contraception during the study, it is unlikely that pregnancies will occur during study conduct. However, study drug will be discontinued should suspected or confirmed pregnancy or nursing during the study drug administration period occur.

Patients who prematurely discontinue study drug due to any of the above reasons will complete the EOT assessments within 24 hours of withdrawal.

6.14.2 Withdrawal From the Study

Patients may withdraw from the study for any reason or be withdrawn at the request of the Investigator or Sponsor. The reason for a patient's withdrawal must be recorded on the appropriate page(s) of the eCRF. Reasons for withdrawal from the study may include, but are not limited to:

- Withdrawal of consent
- AEs or SAEs
- Significant patient noncompliance, defined as refusal or inability to adhere to the protocol requirements
- The Investigator determines that it is in the best interest of the patient to withdraw from study participation, due to a reason other than safety

Each patient who withdraws from the study after receipt of any amount of study drug will be asked to undergo EOT assessments. However, patients may withdraw consent to participate in this study at any time without penalty. Withdrawn patients who receive any amount of study drug, will not be replaced. Withdrawn patients who do not receive any study drug will be replaced.

6.14.3 Study Stopping Criteria

The study may be terminated if significant violations of Good Clinical Practice (GCP) that compromise the ability to achieve the study objectives or compromise patient safety are observed at any time during the study. With regard to safety, the study may be temporarily suspended or terminated should the Investigator, Sponsor, or IRB determine that the safety of patients is significantly jeopardized. The decision for a temporary or permanent study hold will depend on the nature, frequency, and severity of AEs that were observed in all enrolled patients to date. For example, the study will be temporarily or permanently halted should either of the following occur:

- The presence of the same system organ class (e,g., gastrointestinal, cardiac, etc.) severe AE for which no other alternative etiology can be identified, considered related to study drug, in 2 or more patients (Severity defined in Section 6.12.2).
- The presence of life-threatening AE or AE requiring urgent intervention in 1 or more patients.
- Death related to Adverse Event.

In a temporary study hold, no additional patients will be enrolled into the study or dosed with study drug until the study team members (including the Investigator and the Medical Monitor) decide it is safe to proceed with the study.

6.15 Appropriateness of Measurements

Safety will be measured by AEs (including SAEs), vital signs, physical examinations, and clinical laboratory and HbA1c tests.

Because treatment with BH4 is hypothesized to restore nNOS function in the control of gastric accommodation, the nutrient satiety test (Section 6.7) was chosen for the primary endpoint for this study. Gastric accommodation has been measured using ultrasonography (Undeland et al, 1998), single-photon emission computed tomography (Bredenoord et al, 2003), and barostat testing (Coulie et al, 1998; Sarnelli et al, 2001). Barostat studies have been shown to be reproducible (Sarnelli et al, 2001) but are invasive and not widely available. Satiety testing using a nutrient liquid has been shown to be reproducible (Kindt et al, 2008) and correlate with impairment in gastric accommodation but not gastric emptying or visceral sensitivity (Tack et al, 2003).

The GEBT is nonradioactive, noninvasive test of gastric emptying rate that has been validated against the reference method of gastric scintigraphy. It has been accepted by the United States Food and Drug Administration (FDA) for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastroparesis. The GEBT can determine how fast the stomach empties a standardized meal with a ^{13}C-labeled egg component by measuring the ratio of $^{13}CO_2$ to carbon-12 dioxide ($^{12}CO_2$) collected in breath samples at multiple time points after the meal is consumed compared to baseline. The breath samples are collected in capped glass tubes and sent to a specified local laboratory for analysis. By measuring the change in the ratio of $^{13}CO_2$ to $^{12}CO_2$ over time in comparison to the premeal value, the rate of $^{13}CO_2$ excretion can be calculated and the gastric emptying rate determined. The GEBT does not require administration by specially trained health care professionals or special precautions related to radiation-emitting compounds (Section 6.10).

The GCSI (Section 6.8, Appendix 2), consisting of a subset of items from the PAGI-SYM instrument (Section 6.9, Appendix 2) (described below), is based on reviews of the medical literature and results from clinician interviews and patient focus groups. Its reliability and validity were examined in 169 gastroparesis patients from 7 clinical centers in the US. Patients completed the GCSI, SF-36 Health Survey, and disability day questions at baseline and again at 8 weeks. Clinicians independently rated the severity of the patients' symptoms, and both clinicians and patients rated the changes in gastroparesis-related symptoms over the 8weeks. For the GCSI total score, the internal consistency reliability was 0.84, and the test-re-test reliability was 0.76. Significant relationships were observed between the clinician-assessed symptom severity and the GCSI total score, and significant associations were found between the GCSI scores and SF-36 physical and mental component summary scores and restricted activity and bed disability days. Patients with greater symptom severity, as rated by

clinicians, reported greater symptom severity on the GCSI. The GCSI total scores were responsive to changes in overall gastroparesis symptoms as assessed by clinicians ($p = 0.0002$) and patients ($p = 0.002$) (Revicki et al, 2003).

The PAGI-SYM (Section 6.9, Appendix 2) is a 20-item upper GI symptom severity instrument with 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. To develop the instrument, patients with GERD ($n = 810$), dyspepsia ($n = 767$), or gastroparesis ($n = 169$) from the US, France, Germany, Italy, the Netherlands, and Poland completed the PAGI-SYM, the SF-36 Health Survey, a disease-specific health-related quality of life measure (Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life [PAGI-QOL]), and disability day questions. Two-week reproducibility was evaluated in 277 stable patients. Construct validity was evaluated by correlating subscale scores with SF-36, PAGI-QOL and global symptom severity scores and disability days. Internal consistency reliability ranged from 0.79 to 0.91, and test-retest reliability ranged from 0.60 to 0.82 for the PAGI-SYM subscales. The PAGI-SYM subscale scores correlated significantly with SF-36 scores (all $p < 0.0001$), PAGI-QOL scores (all $p < 0.0001$), disability days ($p < 0.0001$), and global symptom severity ($p < 0.0001$). Mean PAGI-SYM scores varied significantly in groups defined by disability days (all $p < 0.0001$), in which greater symptom severity was associated with more disability days (Rentz et al, 2004; Revicki et al, 2004).

7 STUDY ACTIVITIES

7.1 Screening Procedures (Day –28 to Day -1)

The following will be performed/collected during the Screening Period from Day -28 to Day -1 after obtaining informed consent with a properly signed ICF (Section 10.4):

- Obtain demographic data (age, gender, self-reported race/ethnicity)
- Obtain medical/surgical history, including specific information related to any prior or existing medical conditions or surgical procedures involving the dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological systems (Section 6.2)
- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) prior to collection of any laboratory samples and after patients have rested for 5 minutes in a supine position; obtain the patient's weight (as necessary to determine the response to Exclusion Criterion #5 [Section 4.3] and on Day -1) and height (Section 6.3)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4)
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5)
- Perform a serum pregnancy test for all women who are of childbearing potential
- Obtain 12-lead ECGs in triplicate, with 1 minute separating the first and second recordings and 1 minute separating second and third recordings (Section 6.6)
- Administer the GCSI (Section 6.8, Appendix 2)
- Record all prescription and over-the-counter medications (including herbal medications) taken within 30 days before the Screening
- Assess/record AEs from the time of informed consent
- Administer the nutrient satiety test (Section 6.76.10) after the patient has fasted overnight and after any medications that can alter GI sensation or accommodation or gastric emptying have been held overnight
- Confirm patient meets inclusion criteria and no exclusion criteria (Section 4.2 and Section 4.3, respectively)
- Administer the GEBT (Section 6.10) on Day -1 after the patient 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)

- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations (Section 6.5) and the nutrient satiety test (Section 6.7) is administered on Day 1 predose
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the days of the nutrient satiety test (Section 6.7)
- Randomize patient on Day -1

7.2 Day 1 Predose

The following will be performed/collected on Day 1 in the clinic before the patient receives study drug:

- Obtain medical/surgical history since Screening, including specific information related to any prior or existing medical conditions or surgical procedures involving the dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological systems (Section 6.2)
- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine position (Section 6.3)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4)
- Collect blood samples for clinical chemistry, and hematology after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5)
- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test
- Record all prior prescription and over-the-counter medications (including herbal medications) taken since Screening
- Assess/record AEs since Screening
- Administer:
  - Nutrient satiety test (Section 6.76.10)
  - GCSI (Section 6.8, Appendix 2)
  - PAGI-SYM (Section 6.9, Appendix 2)

7.3 Day 1 After Baseline Evaluations Through Day 13

7.3.1 Day 1

- Administer first dose of study drug in the clinic

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature) 2 hours postdose after patients have rested 5 minutes in a supine position (Section 6.3)
- Dispense study drug and instruct the patient on its preparation and administration BID starting with the second dose on Day 1 and continuing through Day 14 (Section 5.2 and Section 6.11)
- Dispense dosing diary and instruct the patient on its completion (Section 5.8.1)
- Instruct the patient not to take any Day 14 doses of study drug before the Day 14 clinic visit, and to bring the dosing diary and all study drug supplies to the Day 14 visit
- Record all medications the patient received since the predose assessment
- Assess/record AEs since the predose assessment
- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations, the nutrient satiety test (Section 6.7), and the GEBT (Section 6.10) on Day 14 and/or on Day 15
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the Day 14 visit (for the nutrient satiety test)

7.4 Early Termination Procedures

If a patient discontinues study drug early (Section 6.14.1), the patient should return to the study site within 24 hours of withdrawal and complete all of the procedures outlined for the EOT (Section 7.5). If a patient withdraws early from the study (Section 6.14.2), 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 (Section 7.5). All study drug and supplies and the dosing diary will be collected.

7.5 End of Treatment Visits (Day 14 and Day 15)

Patients will complete EOT visit(s) at early termination (Section 7.4) or on Day 14 and Day 15. During the EOT visits, the following will be completed:

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature), prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine (Section 6.3) on Day 14 or Day 15
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4) on Day 14 or Day 15
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5) on Day 14 or Day 15

- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test on Day 14 or Day 15
- Administer:
  - Nutrient satiety test (Section 6.76.10) on Day 14
  - GCSI (Section 6.8, Appendix 2) on Day 14 or Day 15
  - PAGI-SYM (Section 6.9, Appendix 2) on Day 14 or Day 15
  - GEBT (Section 6.10) on Day 15
- Administer first Day 14 dose of study drug on Day 14; administer the second Day 14 dose of study drug on Day 14 or instruct patient to take second Day 14 dose of study drug on Day 14 after the patient leaves the clinic
- Record all prescription and over-the-counter medications (including herbal medications) taken since the Day 1 visit through Day 15 before the patient leaves the clinic
- Assess/record AEs since last visit through Day 15 before the patient leaves the clinic
- Collect study drug, dosing diary, and assess study drug compliance on Day 14 if the patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient takes the last dose of study drug on Day 14 after leaving the clinic, on Day 15
- Instruct the patient regarding fasting overnight before blood is drawn for the clinical laboratory evaluations on Day 28 (±1 day), the nutrient satiety test (Section 6.7) on Day 28, and the GEBT (Section 6.10) on Day 27 or Day 29
- Instruct the patient regarding not taking any medications that can alter GI sensation or accommodation or gastric emptying overnight before the Day 28 visit (for the nutrient satiety test)

7.6 End of Study (Day 28 ±1 Day)

Patients will complete the EOS assessments on Days 27 through Day 29. The following EOS assessments will be completed:

- Obtain vital signs (blood pressure, pulse, respiratory rate, and temperature), prior to collection of any laboratory samples and after patients have rested 5 minutes in a supine position (Section 6.3) on Day 28 (±1 day)
- Conduct a complete physical examination, including assessments of general appearance, dermatologic, HEENT, lymphatic, cardiovascular, respiratory, GI, musculoskeletal, and neurological parameters (Section 6.4) on Day 28 (±1 day)
- Collect blood samples for clinical chemistry, hematology, and HbA1c after the patient has fasted overnight (a minimum of 8 hours before blood sample collection) and a urine sample for urinalysis (Section 6.5) on Day 28 (±1 day)

- Perform a urine pregnancy test for all women who are of childbearing potential; confirm any positive urine pregnancy test by performing a serum pregnancy test on Day 28 (±1 day)
- Administer:
  - Nutrient satiety test (Section 6.76.10) on Day 28
  - GCSI (Section 6.8, Appendix 2) on Day 28 (±1 day)
  - PAGI-SYM (Section 6.9, Appendix 2) on Day 28 (±1 day)
  - GEBT (Section 6.10) on Day 27 or Day 29
- Collect study drug, dosing diary, and assess study drug compliance on Day 28 (±1 day) (if not done on Day 14 or Day 15)
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations
- Assess/record AEs since last visit through Day 28 (±1 day) before the patient leaves the clinic after completion of all EOS evaluations

7.7 Telephone Follow-up Day 44 (±3 Days) (30 ±3 Days After Last Dose)

During telephone Follow-up on Day 44 (±3 days), the following will be completed:

- Call the patient to see if any SAEs were experienced during the 30 ±3 days after the last dose of study drug
- Record SAEs in the eCRF, if applicable
- Report SAEs following SAE reporting timelines per Section 6.12.1

8 QUALITY CONTROL AND ASSURANCE

Regular monitoring and an independent audit, if conducted, must be performed according to International Council on Harmonisation (ICH)-GCP (Section 10.6).

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., GLPs, Good Manufacturing Practices).

The investigational site will provide direct access to all trial-related sites, source data/documents (including patient diaries), and reports for the purpose of monitoring and auditing by Censa Pharmaceuticals (or designee), and inspection by local and regulatory authorities.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Descriptive statistics, including numbers and percentages for categorical variables, and numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Exploratory analyses may also be performed. Listings of individual patient data will be produced. Additional details can be found in the statistical analysis plan.

9.2 Determination of 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 (Section 6.7), in women with moderate to severe diabetic gastroparesis. A total of 10 patients 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.

9.3 Analysis Populations

Two study populations will be analyzed:

- Safety population: all patients who were randomized and received any amount of study drug (CNSA-001 or placebo)
- Efficacy population: all patients who were randomized, received any amount of study drug (CNSA-001 or placebo), and had available Day 1 predose and Day 14 nutrient satiety test (Section 6.7) maximum tolerated volume results

9.4 Demographics, Baseline Characteristics, Enrollment, Protocol Deviations, and Patient Disposition

Enrollment, protocol deviations, demographics (age, sex, race/ethnicity), prior and concomitant medications, and medical history will be summarized by treatment group using descriptive statistics. Discontinuations from study drug and the study will be summarized by treatment group as well and the reasons for discontinuation will be listed.

9.5 Statistical Analysis of Efficacy Variables

Efficacy will be assessed in the Efficacy population.

The primary efficacy measure will be the changes in maximal tolerated volume consumed during the nutrient satiety test (Section 6.7) from Day 1 to Day 14 and Day 28. The changes from Day 1 to Day 14 and from Day 1 to Day 28 in maximal tolerated volume consumed

during the nutrient satiety test will be compared between treatment groups using a student's t-test.

Secondary efficacy measures will consist of changes in the following from baseline through Day 14 (±1 day) and through Day 28 (±1 day):

- PAGI-SYM (Section 6.9, Appendix 2) subscale (heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain) scores
- Gastric emptying as measured by the GEBT (Section 6.10)

The primary and secondary measures will be summarized by treatment group at each visit as well as changes from baseline using summary statistics (number of patients, mean, standard deviation, median, and range) including 95% confidence intervals for changes from baseline. Additional analyses may be conducted, and details will be provided in the statistical analysis plan (SAP).

9.6 Safety Analysis

Safety will be assessed in the Safety population. The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class, preferred term, and treatment group. Severity of AEs and SAEs will be summarized similarly. Those AEs leading to premature discontinuation from the study drug and the serious TEAEs will be presented in a table or a listing. Clinical laboratory and HbA1c test results and vital signs will be summarized at each visit as will changes from baseline for each treatment group. A frequency distribution of abnormal physical examination results will be provided. Additional details will be provided in the SAP.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Table 1 summarizes the administrative structure for this study.

Table 1: Administrative Structure for GAS-001 Study

Contract Research Organization	InClin, Inc. 2655 Campus Drive, Suite 100 San Mateo, CA, 94403 Phone: [redacted]

10.2 Institutional Review Board Approval

The Investigator will submit this protocol, any protocol modifications, and the patient consent form to be utilized in this study, to the appropriate IRB for review and approval. This committee must operate in accordance with the ICH GCP. Documentation of approval of the protocol and the informed consent document must be forwarded to Censa Pharmaceuticals (or designee) prior to initiation of this study.

The Investigator is responsible for assuring continuing review and approval of the clinical study. The Investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to his/her IRB. The Investigator will not make any changes in the protocol without IRB approval except as necessary to eliminate apparent immediate hazards to the patients. The Investigator will provide progress reports to the IRB as required by the IRB. If the study remains in progress for >1 year, the Investigator must obtain annual renewal and re-approval from the IRB. Documentation of renewal must be submitted to Censa Pharmaceuticals (or designee). The Investigator will provide notice to the IRB of completion of participation in the study.

10.3 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol; GCPs, including ICH Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; applicable regional regulatory requirements (i.e., ICH E6); and in accordance with the ethical principles of the Declaration of Helsinki.

10.4 Patient Information and Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion in understandable terms of the purposes, procedures, risks and possible benefits of participation, and rights of study patients will be conducted with patients, and, as appropriate, their legally authorized representatives (LARs; henceforth in the discussion of informed consent, study patient means "patient and/or LAR") and family members. The study patients should have

the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Study patients will be asked to carefully review the ICF approved by Censa Pharmaceuticals (or designee) and the IRB. After any needed discussion and consideration of study participation and before undergoing any procedures specifically for the study, the patient will sign the ICF. The ICF will be retained in the study patient's study records, and a copy of the ICF will be given to the study patient.

Patients may decline to participate in the study and withdraw consent at any time or for any reason throughout the course of the study without AEs on the quality of their medical care.

10.5 Confidentiality

The Investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. This extends to testing of biological samples and genetic tests in addition to the clinical information relating to participants. Only an identification code (i.e., not names) should be recorded on any form or document submitted to Censa Pharmaceuticals, the Contract Research Organization (CRO), or the IRB. The Investigator must keep logs on screened and enrolled patients. In addition, the Investigator must have a list where the identity of all treated patients can be found.

The Investigator agrees that all information received from Censa Pharmaceuticals, including, but not limited to, the Investigator's Brochure, this protocol, CRFs, and any other information related to the protocol-specified treatment of the study, remain the sole and exclusive property of Censa Pharmaceuticals during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Censa Pharmaceuticals. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

The study monitor, other authorized representatives of Censa Pharmaceuticals, and representatives of the IRB may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, and hospital) and pharmacy records for the participants in this study. The clinical study site's research staff will permit access to such records.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

10.6 Study Monitoring

A clinical monitor authorized to represent Censa Pharmaceuticals will conduct site visits to inspect study data, patient's medical records, and eCRFs in accordance with ICH guidelines GCP, and applicable regulations and guidelines. The clinical monitor will also monitor ongoing drug accountability and adherence to protocol procedures. Details of clinical site monitoring are specified in a Clinical Monitoring Plan.

Independent audits may be conducted to ensure that monitoring practices are performed consistently across all participating sites and that monitors are following the Clinical Monitoring Plan.

The Investigator will allow representatives of the Censa Pharmaceuticals and regulatory authorities to inspect facilities and records relevant to this study.

10.7 Case Report Forms and Study Records

The eCRFs will be supplied by Censa Pharmaceuticals or designee for the recording of all information and study data as specified by this protocol. Original eCRF data should be handled in accordance with instructions from Censa Pharmaceuticals or designee. All eCRFs must be completed by the clinical study site's research staff authorized to do so by the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data reported in the eCRF derived from source documents should be consistent with the source documents. Source documents are defined as records of documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or patient-specific email correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by Censa Pharmaceuticals or designee and by regulatory authorities. The original ICF for each participating patient shall be filed with records kept by the Investigator, and copies shall be given to the patient.

Once all data queries and issues have been resolved for each patient the Investigator will electronically sign each patient's eCRF. This signature will indicate that the data have been thoroughly inspected and will thereby certify the contents of the eCRF.

Clinical data will be entered into a 21 Code of Federal Regulations (CFR) Part 11-compliant electronic data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered by the clinical study site's research staff directly from the source documents.

10.8 Protocol Violations/Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly. This is consistent with the following sections in ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1

- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

10.9 Access to Source Documentation

The Investigator agrees by his/her participation that the results of this study may be used for submission for national or international registration. If required, national or international authorities will be provided with the name of the Investigator and his or her address, full disclosure of his or her qualifications, any potential conflicts of interests, payments, and extent of involvement.

During site visits, the clinical monitor will review original patient records, drug accountability records, and additional documents as needed. During the course of the study, Censa Pharmaceutical's (or designee's) Quality Assurance personnel may conduct an on-site audit visit. The Investigator will provide direct access to and allow verification and copying of all trial-related documents (e.g., source data) for trial-related monitoring, audits, IRB reviews, and regulatory inspections.

10.10 Data Generation and Analysis

Some or all of the obligations of implementing or conducting this study may be transferred from Censa Pharmaceuticals to the CRO.

A case report, comprised of individual eCRFs, will be completed for every patient who signs an ICF and is enrolled into the study.

All original source documentation (laboratory results, treatment records, audit query responses, etc.) will be retained by the Investigator or institution unless specified otherwise by the protocol. The results as they become available will be entered on the appropriate eCRFs. Legible reproductions of the original laboratory reports for selected tests or variables will be submitted to Censa Pharmaceuticals or CRO as requested.

The eCRFs will be reviewed by a clinical monitor who will evaluate the completeness and accuracy of the data. Queries will be generated for omissions, corrections, and clarifications. Data may also be reviewed in-house by a clinical auditor and data management or other personnel.

Data analyses will be performed after database lock, when all queries have been resolved.

10.11 Retention of Data

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Censa Pharmaceuticals, if

applicable. It is the responsibility of Censa Pharmaceuticals to inform the Investigator when these documents no longer need to be retained.

10.12 Financial Disclosure

Each Investigator must submit to Censa Pharmaceuticals (or designee) financial disclosure information according to national law and/or local regulations.

10.13 Publication and Disclosure Policy

The data generated in this clinical study are the exclusive property of Censa Pharmaceuticals and are confidential. Authorship on any publication of the results from this study will be based on contributions to study design, patient enrollment, data analysis, interpretation of results, and drafting and editing of any publication in accordance with published authorship ethical guidelines for publication of research studies. Independent analysis and/or publication of these data by the Investigator(s) or any member of their staff is not permitted without the prior, written consent of Censa Pharmaceuticals.

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APPENDIX 1 SCHEDULE OF EVENTS

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 14[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 patient 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 patients 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). Patients will fast overnight before blood sample collections.

[g] Patients 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 patient 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 patient 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), patients 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 patient 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 patient vomits after taking a dose of study drug, the patient 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] Patients 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 patient takes the last dose of study drug on Day 14 while in the clinic or, if the patient 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 2 GCSI AND PAGI-SYM ASSESSMENT INSTRUMENTS

Gastroparesis Cardinal Symptom Index Questionnaire (English Version):

GCSI

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please *circle the number* that best describes how *severe* the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5

Khoury V, Dubois, D. GCSI Gastroparesis Cardinal Symptom Index information booklet. 2nd ed. Lyon, France: Mapi Research Trust; 2015. p 30.

Gastroparesis Cardinal Symptom Index Questionnaire (United States Spanish Version):

Este cuestionario le pregunta acerca de la gravedad de los síntomas que usted pueda haber tenido relacionados con sus problemas de estómago. No hay respuestas correctas ni incorrectas. Por favor conteste cada pregunta lo más precisamente posible.

Para cada síntoma, por favor marque con un círculo el número que mejor describa qué tan grave ha sido el síntoma durante las últimas 2 semanas. Si usted no ha tenido este síntoma, marque con un círculo el 0. Si el síntoma ha sido muy leve, marque con un círculo el 1. Si el síntoma ha sido leve, marque con un círculo el 2. Si ha sido moderado, marque con un círculo el 3. Si ha sido grave, marque con un círculo el 4. Si ha sido muy grave, marque con un círculo el 5. Por favor, asegúrese de contestar cada pregunta.

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
1.	Náuseas (sentirse enfermo(a) del estómago como si fuera a vomitar)	0	1	2	3	4	5
2.	Arcadas/Ganas de vomitar (como si fuera a vomitar pero no sale nada)	0	1	2	3	4	5
3.	Vómitos	0	1	2	3	4	5
4.	Sensación de estómago lleno	0	1	2	3	4	5
5.	No poder terminar una comida de porción normal	0	1	2	3	4	5
6.	Sentirse excesivamente lleno(a) después de las comidas	0	1	2	3	4	5
7.	Pérdida del apetito	0	1	2	3	4	5
8.	Hinchado(a) de comer (sentir que necesita aflojar su ropa)	0	1	2	3	4	5
9.	Estómago o barriga visiblemente más grande	0	1	2	3	4	5

GCSI – USA / US Spanish – Final version – MAPI Research Institute
Spanish (USA)_ Versión 1.0 _Standard

Updated_cbe

Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (United States EnglishVersion)

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please circle the number that best describes how severe the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5
10. upper abdominal (above the navel) pain	0	1	2	3	4	5
11. upper abdominal (above the navel) discomfort	0	1	2	3	4	5
12. lower abdominal (below the navel) pain	0	1	2	3	4	5

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
13. lower abdominal (below the navel) discomfort	0	1	2	3	4	5
14. heartburn (burning pain rising in your chest or throat) during the day	0	1	2	3	4	5
15. heartburn (burning pain rising in your chest or throat) when lying down	0	1	2	3	4	5
16. feeling of discomfort inside your chest during the day	0	1	2	3	4	5
17. feeling of discomfort inside your chest at night (during sleep time)	0	1	2	3	4	5
18. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	0	1	2	3	4	5
19. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	0	1	2	3	4	5
20. bitter, acid or sour taste in your mouth	0	1	2	3	4	5

PAGI-SYM (Standard) - United States/English - Original version - Mapi
PAGI_SYM_AU2.1_standard_eng-USori doc

Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (United States Spanish Version)

Este cuestionario le pregunta acerca de la gravedad de los síntomas que usted pueda haber tenido relacionados con sus problemas de estómago. No hay respuestas correctas ni incorrectas. Por favor conteste cada pregunta lo más precisamente posible.

Para cada síntoma, por favor marque con un círculo el número que mejor describa qué tan grave ha sido el síntoma durante las últimas 2 semanas. Si usted no ha tenido este síntoma, marque con un círculo el 0. Si el síntoma ha sido muy leve, marque con un círculo el 1. Si el síntoma ha sido leve, marque con un círculo el 2. Si ha sido moderado, marque con un círculo el 3. Si ha sido grave, marque con un círculo el 4. Si ha sido muy grave, marque con un círculo el 5. Por favor, asegúrese de contestar cada pregunta.

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
1.	Náuseas (sentirse enfermo(a) del estómago como si fuera a vomitar)	0	1	2	3	4	5
2.	Arcadas/Ganas de vomitar (como si fuera a vomitar pero no sale nada)	0	1	2	3	4	5
3.	Vómitos	0	1	2	3	4	5
4.	Sensación de estómago lleno	0	1	2	3	4	5
5.	No poder terminar una comida de porción normal	0	1	2	3	4	5
6.	Sentirse excesivamente lleno(a) después de las comidas	0	1	2	3	4	5
7.	Pérdida del apetito	0	1	2	3	4	5
8.	Hinchado(a) de comer (sentir que necesita aflojar su ropa)	0	1	2	3	4	5
9.	Estómago o barriga visiblemente más grande	0	1	2	3	4	5
10.	Dolor abdominal superior (arriba del ombligo)	0	1	2	3	4	5
11.	Malestar abdominal superior (arriba del ombligo)	0	1	2	3	4	5

Por favor, evalúe la gravedad de los siguientes síntomas durante las últimas 2 semanas.

		Ninguno	Muy leve	Leve	Moderado	Grave	Muy grave
12.	Dolor abdominal inferior (abajo del ombligo)	0	1	2	3	4	5
13.	Malestar abdominal inferior (abajo del ombligo)	0	1	2	3	4	5
14.	Acidez (dolor ardiente que sube en su pecho o garganta) durante el día	0	1	2	3	4	5
15.	Acidez (dolor ardiente que sube en su pecho o garganta) cuando está recostado(a)	0	1	2	3	4	5
16.	Sentir malestar en el pecho durante el día	0	1	2	3	4	5
17.	Sentir malestar en el pecho durante la noche	0	1	2	3	4	5
18.	Regurgitación o reflujo (fluido o líquido que sube de su estómago hasta la garganta) durante el día	0	1	2	3	4	5
19.	Regurgitación o reflujo (fluido o líquido que sube de su estómago hasta la garganta) cuando está recostado(a)	0	1	2	3	4	5
20.	Sabor agrio, ácido o amargo en la boca	0	1	2	3	4	5

PAGI-SYM (Standard) - United States/Spanish - Version of 09 Nov 07 - Mapi.
ID4237/PAGI_SYM_AU2.1_standard_spa-US doc