CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind Placebo-Controlled Scintigraphy Study to Investigate the Effect of CIN-102 on Gastric Emptying and Antral Contractility in Adults with Diabetic Gastroparesis

Investigational Product: CIN-102

Protocol Number: CIN-102-122

Sponsor:

CinDome Pharma, Inc.

5375 Medpace Way

Cincinnati, OH 45227

United States

[redacted]

Version Number: 1.0

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Confidentiality Statement

SIGNATURE PAGE

STUDY TITLE: A Randomized, Double-Blind, Placebo-controlled Scintigraphy Study to Investigate the Effect of Oral CIN-102 on Gastric Emptying and Antral Contractility in Adults with Diabetic Gastroparesis

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

[redacted]

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by CinDome Pharma, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to CinDome Pharma, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by CinDome Pharma, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Randomized, Double-Blind, Placebo-Controlled Scintigraphy Study to Investigate the Effect of Oral CIN-102 on Gastric Emptying and Antral Contractility in Adults with Diabetic Gastroparesis

PROTOCOL NUMBER: CIN-102-122

INVESTIGATIONAL PRODUCT: CIN-102

PHASE: 2a

INDICATION(S): Treatment and relief of symptoms associated with acute and recurrent gastroparesis

OBJECTIVES:

The objectives of this study are the following:

- To evaluate the change from baseline in gastric percentage retention of a radiolabeled meal after dosing CIN-102 in patients with diabetic gastroparesis.
- To evaluate the safety and tolerability of CIN-102 in patients with diabetic gastroparesis.
- To assess the effect of CIN-102 on antral contractility as measured by Dynamic Antral Scintigraphy (DAS).
- To assess the effect of CIN-102 on gastric accommodation.
- To assess the effect of CIN-102 on symptom severity as measured by patient/investigator-reported outcomes.

POPULATION:

The population for this study is adult patients 18 to 70 years old with Type 1 or Type 2 diabetes mellitus, according to the American Diabetes Association criteria, and a diagnosis of diabetic gastroparesis defined by upper gastrointestinal symptoms felt to be consistent with gastroparesis AND previously documented delayed gastric emptying within the past 3 years by scintigraphy.

SELECTION AND WITHDRAWAL OF PATIENTS:

Inclusion Criteria:

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male and female patients 18 to 70 years old, inclusive.
2. Has Type 1 or Type 2 diabetes mellitus, according to the American Diabetes Association criteria.
3. Current diagnosis of diabetic gastroparesis as defined by the following:

- Upper gastrointestinal (GI) symptoms felt to be consistent with gastroparesis (eg, postprandial nausea/vomiting, postprandial fullness, early satiety, anorexia, bloating, epigastric or abdominal pain) within the 6 months prior to Screening; AND
- Delayed gastric emptying (DGE) within the past 3 years as defined by > [redacted]% gastric retention at 4 hours based on scintigraphy.

4. Has a body mass index (BMI) between 18 and 40 kg/m^2, inclusive.
5. Glycosylated hemoglobin level ≤11%.
6. Male patients with female partners of child-bearing potential must agree to use 2 medically accepted, highly effective methods of birth control from Day 1 through 60 days following the final dose of study drug.

   Medically accepted, highly effective methods of birth control for male patients with female partners of child-bearing potential include the following: latex condom with spermicide, diaphragm with intravaginal spermicide, cervical cap with spermicide, indwelling intrauterine device (hormonal or nonhormonal), implanted contraceptives, and oral contraceptives.
7. Male patients must agree to abstain from sperm donation from Day 1 through 60 days following the final dose of study drug.
8. Female patients with male partners must be surgically sterile (hysterectomy and/or bilateral oophorectomy), postmenopausal for at least 1 year (with confirmed follicle-stimulating hormone in postmenopausal range at the Screening Visit), or agree to use 2 medically accepted, highly effective methods of birth control from Day -14 until 60 days following the final dose of study drug.

   Medically accepted, highly effective methods of birth control for female patients with male partners include the following: latex condom with spermicide, diaphragm with intravaginal spermicide, cervical cap with spermicide, and nonhormonal indwelling intrauterine device.
9. Negative alcohol and drug screen at Screening and Randomization Visits.

   NOTE: Patients who utilize medical marijuana or Tetrahydrocannabinol (THC)-containing products may be considered for this study if they are able to discontinue within 14 days prior to baseline scintigraphy until the end of the study.
10. Willing to abstain from tobacco or nicotine-containing product use after midnight on the day of the DAS test and throughout the time that gastric emptying is being imaged.

[redacted]

13. Able to understand and willing to comply with all study visits, procedures, restrictions, discontinuation of medications, including those to treat gastroparesis (as specified in the protocol), and provide written informed consent according to institutional and regulatory guidelines.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. History of, or current, clinically significant arrhythmias as judged by the Investigator, including ventricular tachycardia, ventricular fibrillation, atrial fibrillation, and Torsades de Pointes. Patients with minor forms of ectopy (eg, premature atrial contractions) are not necessarily excluded.
2. Clinically significant bradycardia with a resting heart rate under 50 beats per minute, sinus node dysfunction, or heart block.
3. Prolonged heart rate-corrected QT interval using Fridericia's formula (QTcF) (QTcF >450 msec for males or QTcF >470 msec for females) based on the average of triplicate ECGs.
4. A personal or family history of long QT syndrome, Torsades de pointes, or other complex ventricular arrhythmias or family history of sudden death;
5. Evidence (based on Screening or Baseline assessments) or history of clinically significant immunologic, hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies); surgical conditions; cancer (with the exception of basal or squamous cell carcinoma of the skin and cancer that resolved or has been in remission for >5 years prior to the Screening Visit); or any condition that, in the Investigator's opinion, might significantly interfere with the absorption, distribution, metabolism, or excretion of the study drug.

   Note: Cholecystectomy and appendectomy are allowed.
6. History of prolactin-releasing pituitary tumor (ie, prolactinoma).
7. Serum prolactin greater than the upper limit of normal.

   Note: Patients who are on domperidone with an elevated prolactin at the time of Screening may be considered for this study, provided prolactin is within normal limits at time of randomization.
8. Known or suspected hypogonadism, current clinically significant menstrual abnormalities (eg, oligomenorrhea or amenorrhea), gynecomastia, galactorrhea, or other clinical features that in the Investigator's opinion may be consistent with hyperprolactinemia.
9. Pyloric injection of botulinum toxin within 6 months of Screening and during the course of the study.
10. Has a serum creatinine level greater than 1.5 × the upper limit of normal or has an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at Screening.

11. Has bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) levels greater than 2 × the upper limit of normal or has a Child-Pugh classification grade of B or C.
12. Has a hemoglobin level <10 g/dL at Screening.
13. Thyroid-stimulating hormone (TSH) levels that are abnormal at Screening, as judged by the Investigator.
14. Allergic to egg or intolerant to gluten
15. Use of investigational, prescription, or over-the-counter medications as follows:
    - Actively participating in an experimental therapy study; received experimental therapy with a small molecule within 30 days of Day -1, or 5 half-lives, whichever is longer; or received experimental therapy with a large molecule within 90 days of Day -1, or 5 half-lives, whichever is longer.
    - [redacted]
16. History of alcoholism or drug abuse within 2 years prior to dosing as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.
17. Typical consumption of ≥14 alcoholic drinks weekly.
18. History or evidence of illicit drug use within 2 years prior to dosing.
19. Positive for human immunodeficiency virus (HIV), Hepatitis C virus (HCV) by RNA, or Hepatitis B surface antigen (HBsAg) at the Screening Visit.
20. Donated blood or blood products within 30 days prior to dosing.
21. Currently undergoing treatment with weight loss medication or prior weight loss surgery (eg, gastric bypass surgery).
22. Pregnant, breastfeeding, or planning to become pregnant during the course of study.
23. Inability to swallow medication.
24. Currently receiving parenteral feeding or presence of a nasogastric or other enteral tube (eg, percutaneous endoscopic gastrostomy tube [PEG]) for feeding or decompression.

25. Known or suspected gastric outlet obstruction (eg, peptic stricture) or other gastrointestinal mechanical obstruction.
26. Known history or current diagnosis of intestinal malabsorption or pancreatic exocrine disease.
27. History of gastric surgery such as fundoplication, gastrectomy, gastric pacemaker placement, vagotomy, pyloroplasty, or bariatric procedure.

    Note: A history of diagnostic endoscopy is not exclusionary. Cholecystectomy and appendectomy are allowed.
28. History or presence of any medical condition or psychiatric disease, which, in the opinion of the Investigator, could interfere with the conduct of the study or would put the patient at unacceptable risk.
29. Known hypersensitivity to domperidone or any of the excipients in the CIN-102 formulation.
30. Judged by the Investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluation, to be unsuitable for any other reason that may either place the patient at increased risk during participation or interfere with the interpretation of the study outcomes.

Randomization Criteria

In addition to the inclusion/exclusion criteria, in order to be randomized into the study, patients must meet the following criteria at the Randomization Visit:

- Continues to satisfy all Inclusion/Exclusion criteria.
- Has been off all motility agents and antiemetics for at least 14 days and is willing to remain off such medications (except for protocol-specified antiemetic rescue medication) during the course of the clinical trial.
- Demonstrates evidence of delayed GE as demonstrated by gastric retention [redacted]% at 2 hours or [redacted]% at 4 hours by DAS.

STUDY DESIGN AND DURATION:

This is a randomized, double-blind, placebo-controlled study to investigate the effect of oral CIN-102 on gastric emptying in adults with diabetic gastroparesis. The safety, tolerability and pharmacodynamics (PD) of multiple doses of CIN-102 will also be assessed in this population.

The study will begin by randomizing patients in Cohort 1 to either CIN-102 [redacted] BID or placebo BID in a ratio such that approximately 10 patients receive CIN-102 and 5 patients receive placebo. After approximately 12 patients in Cohort 1 complete the study, the safety and efficacy data from Cohort 1 will be reviewed by a Data Review Committee (DRC). The DRC will determine if it is safe and appropriate to escalate to the planned dose level for Cohort 2 of [redacted] BID, with 10 patients receiving the study drug and 5 patients receiving placebo or if the planned regimen for cohort should be modified. Emerging information from other ongoing studies will be taken into consideration in the decision to escalate as well. The highest dose will not exceed [redacted] BID without a protocol amendment. Further details regarding the role, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

The dosing regimens for this study have been chosen based upon the safety, tolerability, PD, and PK profile established in healthy subjects in single-ascending and multiple-ascending dose studies.

At the Screening Visit, all patients will sign informed consent prior to any study procedures being performed. Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for study participation.

Patients will be evaluated as follows:

- Days -28 to Day -6: Screening procedures will be performed. [redacted]
- Day -5 to Day -1: Scintigraphic gastric emptying and Dynamic Antral Scintigraphy (DAS) will be performed on a single day within this window for baseline determination. [redacted]. Patients may be randomized at any point during the baseline period once all procedures have been performed and all eligibility criteria are met.
- Days 1 to 14: Study drug will be administered (CIN-102 or placebo BID for 14 [+1 day]) and safety assessments, prolactin, and PK, will be completed.
    - Day 14 (+1 day): The patient will present after an overnight (≥8-hour) fast. [redacted] Study drug will be administered and the patient will consume the radiolabeled meal 30 minutes after study drug administration. The radiolabeled meal should be consumed by the patient in ≤10-minutes. Scintigraphic gastric emptying and DAS will be administered following completion of the radiolabeled meal. [redacted] Blood glucose will be measured by glucometer prior to the meal and at the 2 hour and 4 hour timepoints.
- Day 20 (±1 day): Patients will have a follow up phone call 5 to 7 days following the last dose of study drug to assess adverse events and changes to concomitant medications (including use of rescue medication).

On days of the scintigraphy, patients will present after an overnight (≥8-hour) fast and should take regular medications, including any treatment for diabetes, with the exception of any prohibited concomitant medication. Patients should be instructed to bring in their medication. Patients on insulin should self-administer their usual morning insulin injection, (calculated considering their fasting status). Fasting blood glucose will be assessed before study drug administration and gastric emptying assessments to ensure a blood glucose of ≤275 mg/dL. Additional insulin may be given to ensure a blood glucose of ≤275 mg/dL prior to the gastric emptying procedure.

Patients will be given a meal consisting of 120 cc of egg beaters labeled with Technetium (Tc-99m) sulfur colloid at a dosage of 2 millicurie (mCi [74 Megabecquerel (MBq)]) and 2 pieces of bread toast, 30 g of strawberry jam and 120 mL of water as a standardized meal recommended by a Joint Consensus of the Society of Nuclear Medicine and American Neurogastroenterology and Motility Society for GES. On Day 14, the meal will be taken one hour after study drug administration. Patients should consume the meal within ≤10-minutes.

During the period of time from immediately prior to the meal to 4 hours after the meal, patients will be asked about symptoms [redacted]. Additionally, finger stick blood glucose will be monitored over this period.

For the baseline scintigraphy, patients who ingest <50% of the meal or who vomit before the 2 hour scintigraphy data point may be excluded. Patients who have demonstrated delayed gastric emptying at the 2 hour data point but vomit before the 4 hour data point may continue to randomization.

Safety will be evaluated through assessments of adverse events, vital signs, physical examinations, clinical laboratory evaluations, and electrocardiogram (ECG) findings. Time-matched PK samples will be collected with each ECG.

Patients will have a final follow-up phone call 5 to 7 days after the final dose of study drug to assess adverse events and changes to concomitant medications (including use of rescue medications), unscheduled visits and/or additional follow-up may be required at the discretion of the Investigator. For example, patients with clinically significant abnormal laboratory findings, unresolved treatment-emergent adverse events, serious adverse events that require follow-up laboratories and review, and clinically significant adverse events may necessitate further assessments.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

All patients will take a dose of blinded study drug (CIN-102 or placebo capsules) orally at [redacted] AM and [redacted] PM [redacted] On Day 14 [+1 day] patients will fast for a minimum of 8 hours before the morning dose of study drug and for a minimum of 4 hours following completion of the radiolabeled meal. [redacted] Patients will be provided study drug for self-administration for doses not administered at the site.

RESCUE MEDICATIONS

[redacted] Patients who require further treatment with prohibited medications may be discontinued from study treatment (at discretion of Principal Investigator [PI] and in consult with the sponsor's medical monitor) and undergo follow-up study procedures.

EFFICACY VARIABLES:

The efficacy variables are as follows:

- The change from baseline in gastric percentage retention of a radiolabeled meal at 2 and 4 hours after dosing CIN-102 in patients with diabetic gastroparesis.
- The change from baseline in antral contractility as measured by Dynamic Antral Scintigraphy at Day 14.
- The change from baseline in gastric accommodation at Day 14.
- [redacted]

SAFETY VARIABLES:

Safety of CIN-102 will be assessed by physical examinations, ECGs, vital sign assessments, clinical laboratory evaluations, and adverse events.

STATISTICAL ANALYSES:

The Intent-to-Treat (ITT) Population: All patients who are randomized.

Modified ITT (MITT) Population: All patients in the ITT Population who received any amount of study drug and have a baseline DAS and a post-baseline DAS.

The primary analysis population will be the MITT Population.

The Safety Population will consist of all randomized patients who receive any study drug.

The PK Population will consist of all randomized patients who have at least one quantifiable plasma concentration following administration of CIN-102.

[redacted]

[redacted]

Symptom scores at various time points will be compared to baseline using paired t tests and significance determined. The change from baseline in the [redacted] scores will be compared between the CIN-102-treated and placebo groups.

If the data permit, an attempt may be made to correlate plasma concentrations with select safety measures, prolactin data, and/or measures of gastric emptying time and symptoms of gastroparesis.

Safety data, including physical examinations, ECGs, vital sign assessments, clinical laboratory evaluations (including prolactin), and adverse events, will be summarized by treatment group (placebo patients from all dose levels will be pooled) and time of collection, when appropriate. Individual and mean time course of absolute prolactin values and change from baseline prolactin by treatment may also be generated.

Descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum) will be calculated for quantitative safety data, as well as for the difference from baseline, when appropriate. Absolute and change from baseline values in QT and QTc (using Fridericia's correction factor) will be presented.

Shift tables describing out-of-normal range shifts will be provided for clinical laboratory results.

SAMPLE SIZE DETERMINATION:

A total of approximately 30 patients (approximately 10 patients per group) will be randomized to CIN-102 [redacted] BID or CIN-102 [redacted] BID or placebo BID. The sample size is considered adequate to provide the necessary data to evaluate the objectives of the study. No formal statistical assessment for sample size determination has been performed. Additional cohorts or expansion cohorts may be added at the discretion of the Sponsor and DRC, but no more than 30 additional patients will be added without a protocol amendment.

SITES: 1-2 sites in the United States

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
[redacted]	[redacted]
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma-Time Curve
AV	Atrioventricular
BID	Twice Daily
BMI	Body Mass Index
BPM	Beats Per Minute
C	Carbon
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CO2	Carbon Dioxide
[redacted]	[redacted]
CRA	Clinical Research Associate
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DAS	Dynamic Antral Scintigraphy
DGE	Delayed Gastric Emptying
dL	Deciliter(s)
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EIU	Exposure In Utero
FDA	Food and Drug Administration
g	Gram(s)
GCP	Good Clinical Practice
GI	Gastrointestinal
[redacted]	[redacted]
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus

Abbreviation	Definition
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
keV	Kiloelectron Volt(s)
kPCD	Percent Dose Excreted * 1000
LBBB	Left Bundle Branch Block
MAD	Multiple Ascending Dose
MBQ	Megabecquerel(s)
MCI	Millicurie(s)
mg	Milligram(s)
mITT	Modified Intent-to-Treat
mL	Milliliter(s)
mm	Millimeter(s)
mREM	Millirem(s)
MSEC	Millisecond(s)
mSv	Millisievert(s)
MTT	Mean Transit Time
ng	Nanogram(s)
[redacted]	[redacted]
PD	Pharmacodynamics(s)
PEG	Percutaneous Endoscopic Gastrostomy
PI	Principal Investigator
PK	Pharmacokinetic(s)
POC	Point-of-Care
QTcF	Heart rate-corrected QT interval using Fridericia's formula
ROI	Region(s) of Interest
SAD	Single Ascending Dose
SAE	Serious Adverse Event
[redacted]	[redacted]
SVT	Supraventricular Tachycardia
$T_{1/2}$	Terminal Phase Elimination Half-Life
TAC	Time-Activity Curve(s)
Tc-99	Technetium-99
TEAE	Treatment-Emergent Adverse Event
THC	Tetrahydrocannabinol
TSH	Thyroid-Stimulating Hormone
TWA	Time-Weighted Average

Abbreviation	Definition
ULN	Upper Limit(s) of Normal
USA	United States of America

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Indication and Treatment Options

Gastroparesis is defined as impaired gastric emptying in the absence of physical gastric outlet obstruction. Symptoms include early satiety, postprandial fullness, nausea, vomiting, and abdominal pain.[1] The disease is often associated with diabetes or may occur after gastric surgery; it may also be idiopathic from unknown etiologies.[2] Gastroparesis affects the patient's nutritional state, especially in diabetics, and severe symptoms of gastroparesis can lead to other complications such as malnutrition, esophagitis, and Mallory-Weiss tears.[3,4] Gastroparesis negatively impacts a patient's quality of life, causing decreased social interaction, poor work functionality, and development of anxiety or depression.[3]

The first-line treatment for gastroparesis involves nutritional management and support, including fluid and electrolyte replacement. Pharmacologic therapy is directed at increasing gastric emptying and accelerating intestinal transit time. Currently, metoclopramide, a dopamine D2 receptor antagonist, is the only United States Food and Drug Administration (FDA)-approved agent for the treatment of gastroparesis. While effective, this agent readily crosses the blood-brain barrier resulting in central nervous system (CNS) side effects in up to 40% of patients.[5] Common CNS effects associated with metoclopramide treatment include restlessness, drowsiness, fatigue, and lassitude; however, the major safety concern with metoclopramide treatment is the development of tardive dyskinesia. Tardive dyskinesia is a disorder characterized by involuntary movements of the face, tongue, or extremities and is often irreversible. Increased risk of developing tardive dyskinesia correlates to treatment duration; therefore, it is recommended that therapy with metoclopramide not exceed 12 weeks.[6]

Domperidone is a peripheral dopamine D2 receptor antagonist that acts as an antiemetic and a prokinetic agent through its effects on the chemoreceptor trigger zone in the area postrema and the motor function in the stomach and small intestine.[7,8] Domperidone has been available worldwide outside of the United States since 1978 as a treatment for gastroparesis as well as a general antiemetic. It is currently available in 58 countries, including Canada. In those countries where domperidone is approved, the current recommended daily dose is up to 30 mg/day (10 mg administered orally 3 times a day) for nausea and vomiting. While available in many countries worldwide, domperidone is only available to patients in the United States through a physician-initiated Investigational New Drug application at doses up to 120 mg/day (30 mg administered orally 4 times per day) for the treatment of gastroparesis and any condition causing chronic nausea and vomiting.[8] Current treatment guidelines recommend the use of domperidone for patients unable to use metoclopramide.[9]

Unlike metoclopramide, domperidone does not cross the blood-brain barrier and seldom causes extrapyramidal side effects. Similar to other dopamine D2 receptor antagonists, domperidone has been shown to raise prolactin levels with chronic administration, but prolactin levels return to normal upon discontinuation of the drug.[7,10] Use of domperidone has also been associated with QT prolongation. Due to reports of cardiac arrest with the use of intravenous (IV) domperidone, the IV dose form was removed from the market. Given the low oral bioavailability of domperidone (approximately 13% to 17% of the administered dose),[8] oral doses in excess of 1000 mg/day would correlate with the IV doses administered to patients at the time when the cardiac issues were

reported.[11] When QT prolongation has been reported with oral domperidone, it has primarily been in patients over 60 years of age, in patients taking more than 30 mg/day, in patients with cardiac predispositions, or in patients who were also receiving other QT-prolonging drugs or potent cytochrome P450 (CYP) 3A4 inhibitors, such as ketoconazole. However, there have been reports of cases of QT prolongation among patients taking domperidone with none of these additional risk factors.[12,13] The potential for QT prolongation is believed to be related to increased plasma concentrations of domperidone. It is suggested that the mean effect on QT of 10 msec (the definition of QT prolongation) may occur when the domperidone plasma concentration reaches approximately 65 ng/mL.[14,15] Therefore, limiting the maximum plasma concentration (C_{max}) of domperidone to approximately 60 ng/mL may significantly lower the risk of QT prolongation.

1.2 CIN-102

CinDome Pharma, Inc. is currently developing CIN-102, a deuterated form of domperidone. A new process was developed to synthesize a deuterated version of domperidone [redacted] Given that the pharmacological properties of CIN-102 are similar to those of domperidone, CIN-102 is intended to provide an alternative for the treatment and relief of symptoms associated with acute and recurrent gastroparesis that may have less potential for QT prolongation.

Two clinical studies of CIN-102 in healthy subjects have completed to date: a single-ascending dose (SAD) study (Study CIN-102-111) and a multiple-ascending dose (MAD) study (Study CIN-102-112). [redacted]

[redacted]

A Phase 2 study to evaluate the effect of CIN-102 in diabetic patients with gastroparesis is ongoing (Protocol CIN-102-121). The CIN-102-121 protocol will enroll patients in a similar manner as this current protocol CIN-102-122 and will start at the same [redacted] BID starting dose. Instead of utilizing scintigraphy as in this current protocol, the CIN-102-121 protocol will evaluate the patient's gastric emptying via the Gastric Emptying Breath Test, a nonradioactive stable isotope breath test, in which the ratio of exhaled $^{13}CO2/^{12}CO2$ is used to determine the rate of gastric emptying after consumption of a standardized, ^{13}C-enriched meal. Data from the CIN-102-121 protocol will be shared with the investigators in the CIN-102-122 protocol as available, and vice versa.

1.3 Study Rationale

To date, the PK, pharmacodynamics (PD; based on increases in prolactin), and safety of CIN-102 have been evaluated in a SAD study and a MAD study in healthy subjects. The current study is the second study to commence in patients with gastroparesis. As such, this study is intended to evaluate the effect of CIN-102 on gastric emptying in patients with diabetic gastroparesis over a range of doses. The safety, PD, and effect of CIN-102 on symptoms of gastroparesis in these patients will also be assessed in this study. The results of this study will be used to support dose selection for future studies.

1.4 Risk/Benefit

Side effects that have been reported by 1% of patients treated in clinical trials with traditional domperidone with a median total daily dose of 80 mg include the following: depression, anxiety, loss of libido, headache, somnolence, akathisia, diarrhea, rash, pruritus, gynecomastia, breast tenderness, galactorrhea, amenorrhea, breast pain, irregular menstruation, lactation disorders, and asthenia.[7]

Less frequently reported adverse events that occurred in <1% of treated patients include hypersensitivity, urticaria, breast discharge, and breast swelling.[7] Rare or very rare adverse reactions that have been estimated from spontaneous reporting include anaphylactic reactions, agitations, nervousness, extrapyramidal disorders, convulsions, sudden cardiac death, ventricular arrhythmias, angioedema, urinary retention, abnormal liver tests, and increased blood prolactin.[7]

As noted previously, domperidone has been associated with prolongation of the QT interval on electrocardiograms (ECGs).[16] During postmarketing surveillance, there have been very rare cases (<1/10,000 cases) of QT prolongation and QT prolongation-induced Torsades de Pointes in patients taking oral domperidone.[16,17] These reports included patients with confounding risk factors,

electrolyte abnormalities, and concomitant treatment, which may have been contributing factors.[17] Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death.[16] A higher risk was observed with IV administration and following oral administration in patients older than 60 years, patients taking total daily oral doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.[11,12] However, there have been reports of cases of QT prolongation in patients taking domperidone with none of these additional risk factors.[12,13] From a review of the literature, including an assessment of the thorough QT and case-controlled studies with respect to the incidence of QT prolongation and sudden cardiac death, the data appear to indicate that the risk of QT prolongation is related to the increased plasma levels of domperidone.[11,14,18] Additionally, the FDA Expanded Access to Investigational Drugs program website for requesting domperidone indicates that the serious risks associated with domperidone are related to domperidone levels in the blood, and higher domperidone blood levels are associated with higher risk of these events.[19]

Other study-related risks include those associated with blood draws, such as discomfort, bruising, infection, bleeding, pain, redness at the puncture site, and/or lightheadedness, as well as temporary discomfort, redness, or rash at the site of ECG electrode placement, and dizziness, headache, stomach discomfort, or fainting due to fasting.

Dynamic antral scintigraphy (DAS), a non-invasive technique for the assessment of post-prandial gastric contractions, will be used to evaluate antral motility. DAS exposes patients to more radioactivity than routine gastric emptying scintigraphy. The estimated effective dose to be delivered by DAS is 1.7 millisieverts (mSv [170 millirem(mrem)]).[20] A routine screening mammogram delivers a dose 4 times less than DAS, and 7 times less than a CT of the abdomen and pelvis.[21] The annual average effective dose the US population receives from natural and artificial sources is almost 4 times more than a DAS.[22] The rationale to 2 mCi is that the usual gastric emptying dose of 0.5 mCi would not provide adequate image fidelity because too few counts would be collected in each 0.5-second dynamic image, resulting in suboptimal processing. Urbain et al (study referenced on this protocol) used 2 mCi in 1995. In a prior study that he also authored, he used 3 mCi. The dose proposed on this protocol is within the recommended range by the American College of Radiology Practice Guidelines.[23] This practice of increasing doses is common knowledge when acquisitions are very short.

The doses of CIN-102 planned for inclusion in this study were chosen based upon the safety, tolerability, and PK profile established in the Phase 1 SAD and MAD studies. [redacted] Given the association of QT prolongation and domperidone, patients participating in this study will be monitored closely for adverse events, including those that have been reported with domperidone, and 12-lead ECGs will be collected at each visit to the clinic. As such, ECGs are being collected following the initial dose, during the climb to steady-state and at steady-state. The timing of ECGs at the visits is intended to occur within the range of observed times at which peak plasma concentrations are achieved. Corresponding plasma concentration measurements will be obtained with each ECG.

A goal of this study is to assess the effect of CIN-102 on gastric emptying in patients with diabetic gastroparesis. Given the known antiemetic and prokinetic effects of domperidone, it is possible that patients may experience improvement in their symptoms during the course of this study.

2 STUDY OBJECTIVES

2.1 Objectives

The objectives of this study are to evaluate the following:

- To evaluate the change from baseline in gastric percentage retention of a radiolabeled meal after dosing CIN-102 in patients with diabetic gastroparesis.
- To evaluate the safety and tolerability of CIN-102 in patients with diabetic gastroparesis.
- To assess the effect of CIN-102 on antral contractility as measured by Dynamic Antral Scintigraphy.
- To assess the effect of CIN-102 on gastric accommodation.
- To assess the effect of CIN-102 on symptom severity as measured by patient/investigator-reported outcomes.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled study to investigate the effect of oral CIN-102 on gastric emptying in adults with diabetic gastroparesis. The safety, tolerability and pharmacodynamics (PD) of multiple doses of CIN-102 will also be assessed in this population.

The study will begin by randomizing patients in Cohort 1 to either CIN-102 [redacted] BID or placebo BID in a ratio such that approximately 10 patients receive CIN-102 and 5 patients receive placebo. The Data Review Committee (DRC) will review emerging safety and/or efficacy data throughout the study. After approximately 12 patients in Cohort 1 complete the study, the data from Cohort 1 will be reviewed by the DRC to determine if it is safe and appropriate to continue the study with the currently planned dose levels or if further refinement of the proposed dose levels is warranted. Currently planned dose level for Cohort 2 is [redacted] BID, with 10 patients receiving the study drug and 5 patients receiving placebo. However, this dosing cohort may be modified based on emerging information from the prior cohort as well as other ongoing studies. The highest dose will not exceed [redacted] BID without a protocol amendment. Further details regarding the role, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

The dosing regimens for this study have been chosen based upon the safety, tolerability, and PK profile established in healthy subjects in single-ascending and multiple-ascending dose studies as well as modelling and simulation.

At the Screening Visit, all patients will sign informed consent prior to any study procedures being performed. Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for study participation.

Patients will be evaluated as follows:

- Days -28 to Day -6: Screening procedures will be performed. [redacted]
- Day -5 to Day -1: Scintigraphic gastric emptying and Dynamic Antral Scintigraphy (DAS) will be performed on a single day within this window for baseline determination. [redacted] Patients may be randomized at any point during the baseline period once all procedures have been performed and all eligibility criteria are met.
- Days 1 to 14: Study drug will be administered (CIN-102 or placebo BID for 14 [+1 day]) and safety assessments and PK, will be completed. [redacted]
    - Day 14 (+1 day): The patient will present after an overnight (≥8-hour) fast. [redacted] Study drug will be administered and the patient will consume the radiolabeled meal 30 minutes after study drug administration. The

radiolabeled meal should be consumed by the patient in ≤10-minutes. Scintigraphic gastric emptying and DAS will be administered following completion of the radiolabeled meal. [redacted] Blood glucose will be measured by glucometer prior to the meal and at the 2 hour and 4 hour timepoints.

- Day 20 (±1 day): Patients will have a follow up phone call 5 to 7 days following the last dose of study drug to assess adverse events and changes to concomitant medications (including use of rescue medication).

On days of the scintigraphy, patients will present after an overnight (≥8-hour) fast and should take regular medications, including any treatment for diabetes, with the exception of any prohibited concomitant medication. Patients should be instructed to bring in their medication. Patients should self-administer their usual morning insulin injection, (calculated considering their fasting status). Fasting blood glucose will be assessed before study drug administration and gastric emptying assessments to ensure a blood glucose of ≤275 mg/dL. Additional insulin may be given to ensure a blood glucose of ≤275 mg/dL prior to the gastric emptying procedure.

Patients will be given a meal consisting of 120 cc of egg beaters labeled with Tc-99m sulfur colloid at a dosage of 2 mCi (74 MBq) and 2 pieces of white wheat bread toast, 30 g of strawberry jam and 120 mL of water as a standardized meal recommended by a Joint Consensus of the Society of Nuclear Medicine and American Neurogastroenterology and Motility Society for GES. On Day 14, the meal will be taken 30 minutes after study drug administration and should be consumed in ≤10-minutes.

During the period of time from immediately prior to the meal to 4 hours after the meal, patients will be asked about symptoms [redacted]. Additionally, finger stick blood sugars will be monitored over this period.

For the baseline scintigraphy, patients who ingest <50% of the meal or who vomit before the 2 hour scintigraphy data point may be excluded. Patients who have demonstrated delayed gastric emptying at the 2 hour data point but vomit before the 4 hour data point may continue to randomization.

Safety will be evaluated through assessments of adverse events, vital signs, physical examinations, clinical laboratory evaluations, and electrocardiogram (ECG) findings.

Patients will have a final follow-up phone call 5 to 7 days after the final dose of study drug to assess adverse events and changes to concomitant medications (including use of rescue medications), unscheduled visits and/or additional follow-up may be required at the discretion of the Investigator. For example, patients with clinically significant abnormal laboratory findings, unresolved treatment-emergent adverse events, serious adverse events that require follow-up laboratories and review, and clinically significant adverse events may necessitate further assessments.

3.2 Study Indication

CIN-102 is being developed for the treatment and relief of symptoms associated with acute and recurrent gastroparesis.

3.3 Dose Escalation and Review Committee

A DRC consisting of at least three members, including a cardiologist, a clinical pharmacologist, and an independent clinician experienced in the treatment of patients with diabetic gastroparesis

will be formed to review emerging safety and efficacy data in a blinded manner to determine if it is safe and appropriate to continue the study with the currently planned dose level of [redacted] BID or if further refinement of the proposed dose level is warranted.

Upon each DRC review, the following may occur:

- Proceed to the next protocol-specified dose level, or
- Proceed to alternate dosing regimen(s) not to exceed the next protocol-specified dose level

Further detail on DRC conduct will be described in the DRC Charter.

3.3.1 Criteria for Temporary Suspension of Dosing

Dosing within a cohort or between cohorts will be temporarily suspended until a full cumulative data review is completed if any of the following occur:

- Any study drug-related SAE grade 3 or higher based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- Any single subject whose ECG (average triplicate ECGs as interpreted by central read) demonstrates a heart-rate corrected QTcF interval (QTcF) >500 msec or in whom there is an increase in QTcF >60 msec from baseline (confirmed by repeat ECG).
- Any new ECG abnormality deemed clinically significant by the investigator.
- Any study drug-related cardiac adverse event. In the event that a patient experiences a vasovagal or near-syncopal episode, dosing within a cohort or subsequent cohort may proceed as planned unless the episode is associated with ECG abnormality or the event is deemed to be severe in intensity (severity) by the Investigator.
- A study drug-related adverse event from a single System Organ Class deemed to be of moderate intensity (severity) in 4 or more patients.
- Any of the following laboratory abnormalities that are thought to be study drug-related or in which an alternative explanation is not reasonable:
    - ALT or AST >8 × the upper limit of normal (ULN), or
    - ALT or AST >5 × ULN and persist for more than 2 weeks, or
    - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio >1.5, or
    - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Any single patient who develops serious study drug-related electrolyte abnormalities due to vomiting and/or inability to maintain adequate oral hydration that impacts cardiac stability.
- Other conditions as deemed medically appropriate based on the Investigator's judgement.

The Sponsor and/or DRC may also suspend dosing for any other reason based on emerging data from this or other ongoing studies. Should dosing be temporarily suspended, the DRC can review and discuss all available safety and PK data from all patients participating in the study up until the time of the event. The DRC will decide whether knowledge of the treatment

assignment of any patient(s) is(are) necessary to make an appropriate decision about continuation of the study. If so, a request to unblind will be made and relevant data will be reviewed in an unblinded manner. All unblinding Standard Operating Procedures will be followed and documented as appropriate.

Upon completion of the cumulative data review (whether fully blinded or partially unblinded), the DRC may elect to terminate the study or to resume study conduct. If study conduct is resumed, the DRC may elect to do one of the following:

- Continue dosing in the current cohort with the same number of patients originally planned.
- Expand the current cohort with additional patients to obtain more information at that dose level.
- Escalate to a higher dose level.
- Increase the frequency of dosing at the current dose level (if the protocol-specified number of subjects at the current dose level have already completed).
- De-escalate to a lower dose level.
- Decrease the frequency of dosing at the current dose level.

If additional cohorts or expansion cohorts are added at the discretion of the Sponsor and DRC, no more than 30 additional patients (ie, a study total of 60 patients) will be added without a protocol amendment.

3.3.2 Criteria to Cease Dose Escalation

Dosing within a cohort or between cohorts will cease if either of the following occurs:

- Any two grade 3 or 1 grade 4 or higher study drug-related SAE based on CTCAE Version 5.0.
- Any 2 patients with an ECG (average of triplicate ECGs as determined by central read) demonstrating QTcF >500 msec or a change in QTcF >60 msec from baseline (confirmed by repeat ECG with central read).

Should one of the above occur, consideration may still be given to continued study of an alternate dose level or frequency (either expansion of a previously studied cohort or addition of a lower dose level).

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male and female patients 18 to 70 years old, inclusive.
2. Has Type 1 or Type 2 diabetes mellitus, according to the American Diabetes Association criteria.
3. Current diagnosis of diabetic gastroparesis as defined by the following:
    - Upper gastrointestinal (GI) symptoms felt to be consistent with gastroparesis (eg, postprandial nausea/vomiting, postprandial fullness, early satiety, anorexia, bloating, epigastric or abdominal pain) within the 6 months prior to screening; AND
    - Delayed gastric emptying (DGE) within the past 3 years as defined by > [redacted] gastric retention at 4 hours based on scintigraphy.
4. Has a body mass index (BMI) between 18 and 40 kg/m^2, inclusive.
5. Glycosylated hemoglobin level ≤11%.
6. Male patients with female partners of child-bearing potential must agree to use 2 medically accepted, highly effective methods of birth control from Day 1 through 60 days following the final dose of study drug.

   Medically accepted, highly effective methods of birth control for male patients with female partners of child-bearing potential include the following: latex condom with spermicide, diaphragm with intravaginal spermicide, cervical cap with spermicide, indwelling intrauterine device (hormonal or nonhormonal), implanted contraceptives, and oral contraceptives.
7. Male patients must agree to abstain from sperm donation from Day 1 through 60 days following the final dose of study drug.
8. Female patients with male partners must be surgically sterile (hysterectomy and/or bilateral oophorectomy), postmenopausal for at least 1 year (with confirmed follicle-stimulating hormone in postmenopausal range at the Screening Visit), or agree to use 2 medically accepted, highly effective methods of birth control from Day -14 until 60 days following the final dose of study drug.

   Medically accepted, highly effective methods of birth control for female patients with male partners include the following: latex condom with spermicide, diaphragm with intravaginal spermicide, cervical cap with spermicide, and nonhormonal indwelling intrauterine device.
9. Negative alcohol and drug screen at Screening and Randomization Visits.

   NOTE: Patients who utilize medical marijuana or THC-containing products may be considered for this study if they are able to discontinue within 14 days prior to baseline scintigraphy until the end of the study.
10. Willing to abstain from tobacco or nicotine-containing products use after midnight on the day of the DAS test and throughout the time that gastric emptying is being imaged.
11. [redacted]

12. [redacted]

13. Able to understand and willing to comply with all study visits, procedures, restrictions, discontinuation of medications, including those to treat gastroparesis (as specified in the protocol), and provide written informed consent according to institutional and regulatory guidelines.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. History of, or current, clinically significant arrhythmias as judged by the Investigator, including ventricular tachycardia, ventricular fibrillation, and Torsades de Pointes. Patients with minor forms of ectopy (eg, premature atrial contractions) are not necessarily excluded.
2. Clinically significant bradycardia with a resting heart rate under 50 beats per minute, sinus node dysfunction, or heart block.
3. Prolonged heart rate-corrected QT interval using Fridericia's formula (QTcF) (QTcF >450 msec for males or QTcF >470 msec for females) based on the average of triplicate ECGs.
4. A personal or family history of long QT syndrome, Torsades de pointes, or other complex ventricular arrhythmias or family history of sudden death;
5. Evidence (based on screening or baseline assessments) or history of clinically significant immunologic, hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies); surgical conditions; cancer (with the exception of basal or squamous cell carcinoma of the skin and cancer that resolved or has been in remission for >5 years prior to the Screening Visit); or any condition that, in the Investigator's opinion, might significantly interfere with the absorption, distribution, metabolism, or excretion of the study drug.

   Note: Cholecystectomy and appendectomy are allowed.
6. History of prolactin-releasing pituitary tumor (ie, prolactinoma).
7. Serum prolactin greater than the upper limit of normal.

   Note: Patients who are on domperidone with an elevated prolactin at the time of Screening may be considered for this study, provided prolactin is within normal limits at time of randomization.
8. Known or suspected hypogonadism, current clinically significant menstrual abnormalities (eg, oligomenorrhea or amenorrhea), gynecomastia, galactorrhea, or other clinical features that in the Investigator's opinion may be consistent with hyperprolactinemia.
9. Pyloric injection of botulinum toxin within 6 months of Screening and during the course of the study.
10. Creatinine levels greater than 1.5 × the upper limit of normal at Screening, or has an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at Screening.

11. Has bilirubin, alkaline phosphatase, aspartate aminotransferase or alanine transaminase greater than 2 × the upper limit of normal at Screening or has a Child-Pugh classification grade of B or C.
12. Has a hemoglobin level <10 g/dL at Screening.
13. Thyroid-stimulating hormone (TSH) levels that are abnormal at Screening, as judged by the Investigator.
14. Allergic to egg or intolerant to gluten.
15. Use of investigational, prescription, or over-the-counter medications as follows:
    - Actively participating in an experimental therapy study; received experimental therapy with a small molecule within 30 days of Day -1, or 5 half-lives, whichever is longer; or received experimental therapy with a large molecule within 90 days of Day -1, or 5 half-lives, whichever is longer.
    - [redacted]
16. History of alcoholism or drug abuse within 2 years prior to dosing as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.
17. Typical consumption of ≥14 alcoholic drinks weekly.
18. History or evidence of illicit drug use within the past two years.
19. Positive for human immunodeficiency virus (HIV), Hepatitis C virus (HCV) by RNA, or Hepatitis B surface antigen (HBsAg) at the Screening Visit.
20. Donated blood or blood products within 30 days prior to dosing.
21. Currently undergoing treatment with weight loss medication or prior weight loss surgery (eg, gastric bypass surgery).
22. Pregnant, breastfeeding, or planning to become pregnant during the course of study.
23. Inability to swallow medication.
24. Currently receiving parenteral feeding or presence of a nasogastric or other enteral tube (eg, percutaneous endoscopic gastrostomy tube [PEG]) for feeding or decompression.
25. Known or suspected gastric outlet obstruction (eg, peptic stricture) or other gastrointestinal mechanical obstruction.
26. Known history or current diagnosis of intestinal malabsorption or pancreatic exocrine disease.

27. History of gastric surgery such as fundoplication, gastrectomy, gastric pacemaker placement, vagotomy, pyloroplasty, or bariatric procedure.

    Note: A history of diagnostic endoscopy is not exclusionary. Cholecystectomy and appendectomy are allowed.

28. History or presence of any medical condition or psychiatric disease, which, in the opinion of the Investigator, could interfere with the conduct of the study or would put the patient at unacceptable risk.

29. Known hypersensitivity to domperidone or any of the excipients in the CIN-102 formulation.

30. Judged by the Investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluation, to be unsuitable for any other reason that may either place the patient at increased risk during participation or interfere with the interpretation of the study outcomes.

4.3 Randomization Criteria

In addition to the inclusion/exclusion criteria listed in Sections 4.1 and 4.2, in order to be randomized into the study, patients must meet the following criteria at the Randomization Visit:

- Continues to satisfy all Inclusion/Exclusion criteria.
- Has been off all motility agents and antiemetics for at least 14 days and is willing to remain off such medications (except for protocol-specified antiemetic rescue medication) during the course of the clinical trial.
- Demonstrates evidence of delayed gastric emptying by gastric retention [redacted] at 2 hours or [redacted] at 4 hours by DAS.

4.4 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation from the study for any reason.
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject.
- Pregnancy.
- Requirement of prohibited concomitant medication.
- Subject failure to comply with protocol requirements or study-related procedures.
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

Study enrollment will continue until approximately 30 patients (approximately 10 patients per treatment) have completed the treatment period, unless the DRC and Sponsor have expanded a cohort or added a cohort. Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

This study is planned to include 3 treatment groups with approximately 10 patients each: CIN-102 [redacted] BID, CIN-102 [redacted] BID, or placebo BID.

At randomization, patients who meet all eligibility criteria (based on inclusion/exclusion and randomization criteria) will be randomized to in Cohort 1 to either CIN-102 [redacted] BID or placebo BID in a ratio such that approximately 10 patients receive CIN-102 and 5 patients receive placebo. After approximately 12 patients in Cohort 1 complete the study, the data from Cohort 1 will be reviewed by the DRC. The DRC will review emerging safety and/or efficacy data throughout the study to determine if it is safe and appropriate to continue the study with the currently planned dose levels or if further refinement of the proposed dose levels is warranted. Currently planned dose level for Cohort 2 is [redacted] BID, with 10 patients receiving the study drug and 5 patients receiving placebo. However, this dosing cohort may be modified based on emerging information from the prior cohort as well as other ongoing studies. The highest dose will not exceed [redacted] BID without a protocol amendment and no more than 30 additional patients (ie, a study total of 60 patients) will be enrolled without an amendment. Further details regarding the role, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

The duration of the double-blind treatment period will be 14 days (+1 day) of study drug administration.

5.2 Rationale for Dosing

The dosing regimens for this study have been chosen based upon the safety, tolerability, and PK profile established in healthy subjects in single-ascending and multiple-ascending dose studies.

Two clinical studies of CIN-102 in healthy subjects have commenced to date: a SAD study (study CIN-102-111) and a MAD study (study CIN-102-112). [redacted]

5.3 Randomization and Blinding

Patients who have completed the Screening Visit and meet all of the inclusion, none of the exclusion criteria, and all of the additional criteria based on randomization procedures, including safety laboratory tests (see Section 6.5), will be randomized into the study. Randomization will occur on Day 1. Randomization assignments will be provided by the [redacted]. Following randomization, study drug will be dispensed in a double-blind manner on Day 1. The Sponsor and all clinical personnel will be blinded to the treatment group for each patient. Patients will also be blinded to the treatment they receive.

Bioanalytical staff involved in analysis of PK samples will be unblinded to treatment either via receipt of the randomization code to allow for analysis of samples from patients receiving CIN-102 only (and possibly limited analysis of samples from patients receiving placebo), or by the nature of the results of sample analysis. The PK data will be de-identified before being provided to any other individuals, including those involved in calculating PK parameters and associated descriptive statistics, performing any modelling or simulations, and/or plotting PK data, in order to maintain blinding.

5.4 Breaking the Blind

Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of patient safety or as determined by the DRC or Sponsor. Unblinding at the site for any other reason will be considered a protocol deviation. The Investigator should contact the Medical Monitor before breaking the blind, if time permits. When the blind is broken, the reason must be fully documented. The Investigator will be informed of treatment assignment via blinding envelopes provided to the Investigator.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

[redacted]

5.5.2 Study Drug Preparation and Dispensing

CIN-102 and matching placebo capsules will be provided to the site by the Sponsor or designee.

5.5.3 Study Drug Administration

All patients will take a dose of blinded study drug (CIN-102 or placebo capsules) orally at [redacted] AM [redacted] hours) and [redacted] PM ([redacted] hours). A [redacted] interval will be maintained between each dose for

a given individual. On Day 14 [+1 day] patients will fast for a minim of 8 hours before the morning dose of study drug and for a minimum of 4 hours following completion of the radiolabeled meal. [redacted]. Patients will be provided study drug for self-administration for doses not administered at the site.

5.5.4 Treatment Compliance

Study drug will be administered at the site by site staff during patient confinement and at all outpatient visits. A hand and mouth check will be performed by site staff to ensure study drug compliance. Dosing compliance will be recorded by the Investigator or designee at the site. The date and time of study drug administration will be recorded.

For all protocol-specified doses when the patient is not at the site, patients will self-administer study drug and will record the date and time of study drug administration. Compliance to study drug will also be assessed by clinical site personnel via tablet counts of study drug and by questioning the patient, if necessary, upon return to the site on Days 3 [±1 day], 7 [±1 day], 10 [±1 day], and 14 [+1 day]. A patient who is not compliant (compliance being defined as having taken 75% of study drug) will be counseled at each visit on the importance of taking study drug as instructed.

If a patient withdraws from the study or does not comply with the study protocol procedures, the patient can cease participation in the study but will still be considered evaluable for safety purposes. If a patient withdraws from the study or does not comply with the protocol after receiving study drug but before Day 14 procedures have been performed, they will be requested to undergo the Early Termination procedure.

5.5.5 Storage and Accountability

Records will be maintained indicating the receipt and dispensation of all study drug supplies. At the conclusion of the study, any unused study drug will be returned to the Sponsor or designee for final drug accountability and destruction. A certificate of destruction will be provided. If no study drug remains, this will be indicated in the Drug Accountability Log.

[redacted]

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Use of the following investigational, prescription, or over-the-counter medications is not permitted during the study:

- [redacted]

[redacted]

- Experimental therapy with a small molecule within 30 days prior to randomization or 5 half-lives (whichever is longer); or experimental therapy with a large molecule within 90 days prior to randomization or 5 half-lives (whichever is longer).
- [redacted]
- Pyloric injection of botulinum toxin within 6 months of screening and during the course of the study.
- Weight loss medication or prior weight loss surgery (eg, gastric bypass surgery).
- Parenteral feeding or presence of a nasogastric or other enteral tube (eg, PEG tube) for feeding or decompression.

5.6.2 Restricted Medications and/or Procedures

[redacted]. Patients who require further treatment with prohibited medications may be discontinued from study treatment (at discretion of the Investigators and in consult with the Sponsor's Medical Monitor) and undergo follow-up study procedures.

5.6.3 Allowed Medications and/or Procedures

Other medications that are not explicitly and previously excluded are permitted (eg, rescue medications in accordance with Section 5.6.2) after approval from the Investigator.

On days of the scintigraphy, patients will present after an overnight (≥8-hours) fast and should take regular medications, including any treatment for diabetes, with the exception of any prohibited concomitant medication. Patients should be instructed to bring in their study medication. Patients should self-administer their usual morning insulin injection, (calculated

considering their fasting status). Fasting blood glucose will be assessed before study drug administration and gastric emptying assessments to ensure a blood glucose of ≤275 mg/dL. Additional insulin may be given to ensure a blood glucose of ≤275 mg/dL prior to the gastric emptying procedure.

5.6.4 Documentation of Prior and Concomitant Medication Use

Any medications administered 28 days prior to the first dose of study drug and/or during the study period must be recorded.

6 STUDY PROCEDURES

6.1 Informed Consent

Written informed consent for the study will be obtained from all patients before any study procedures are performed. See Section 11.3 for details on informed consent.

6.2 Screening Visit (Days -28 to -6)

Screening procedures, including vital sign assessments, may be repeated no more than 2 times for eligibility purposes. Patients who are screened but failed to meet inclusion/exclusion criteria (despite potentially having undergone repeated Screening assessments, if relevant) may be considered for rescreening with prior written sponsor approval.

For all patients, the Screening Visit will occur up to 28 days prior to randomization (between Days -28 and -6).

The screening prolactin should be performed at the local lab to determine eligibility.

The following procedures will be performed at the Screening Visit:

- Obtain informed consent.
- Assess eligibility based on inclusion/exclusion criteria.
- Record demographics and medical/surgical history.
- Record prior medications.
- Perform a complete physical examination (general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system).
- Measure height and weight and calculate BMI.
- Perform breath alcohol test.
- Collect urine samples for the following:
    - Urinalysis,
    - Urine drug screen.
- Obtain vital signs (including heart rate, blood pressure, respiration rate, and temperature) while patient is sitting after a minimum of 5-minute rest.
- Perform 12-lead ECG (in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10 minutes).

  Note: Screening 12-lead ECGs will be printed and will be interpreted as soon as possible by the Investigator or Sub-Investigator.
- Collect blood samples for the following:
    - Chemistry, hematology, coagulation, and prolactin,

- FSH (only for females who have been postmenopausal for at least 1 year and are not surgically sterile),
- TSH,
- Serum pregnancy test (only for females who are not surgically sterile or postmenopausal for at least 1 year [with confirmed FSH in postmenopausal range]),
- HIV, HBsAg, and HCV screen.

- [redacted].

6.3 Baseline Scintigraphy Test Visit (Days -5 to -1)

Baseline scintigraphy will be performed between Days -5 and -1 after a minimum 14-day washout from motility agents with the exception of the protocol-specified rescue medication.

The following procedures will be performed at the Baseline scintigraphy Visit (Days -5 to -1):

- [redacted]
- Record medical/surgical history.
- Record prior medications.
- Obtain vital signs (including heart rate, blood pressure, respiration rate, and temperature) while patient is sitting after a minimum of 5-minute rest.
- Assess fasting blood glucose before gastric emptying assessments to ensure a blood glucose of <275 mg/dL. Blood glucose will be measured at 2 hours (+/-15 min) and 4 hours (+/-15 min) after the start of the gastric emptying assessment.
- Collect blood sample for a serum pregnancy test (females).
- Patient will consume standardized meal after an ≥8-hour fast.
- Obtain scintigraphy following completion of standardized meal.

Note: patients should fast for 4 hours after the completion of the standardized meal. If the patient or Investigator determine that food should be consumed by the patient (ie, due to low blood glucose levels or symptoms of hypoglycemia), it is permissible to break the specified fast to ensure patient safety.

- [redacted].
- [redacted]

6.4 Treatment Period – Day 1 through Day 14 (+ 1 Day)

For outpatient visits, patients will report to the clinic before taking their morning dose of study drug.

6.4.1 Day 1 (Randomization)

Eligible patients will be randomized to receive CIN-102 or placebo. Randomization will occur on the morning of Day 1, although randomization procedures may also be performed at a separate outpatient visit 1 day prior to taking the morning dose of study drug (Day -1) to allow adequate turnaround time for test results if necessary. The safety laboratory tests (ie, chemistry, hematology, coagulation, and urinalysis) from Day -1 or Day 1 will be processed at local laboratories for verifying patient eligibility. Other than the Screening prolactin which should be performed at the local lab to determine eligibility, prolactin will be sent to the central laboratory for analysis to maintain the site blind. A point-of-care (POC) urine pregnancy test and urine drug screen will be used to assess eligibility for the purpose of randomization.

The following procedures will be performed:

- Assess eligibility based on inclusion/exclusion and randomization criteria.
- Record medical/surgical history.
- Measure weight and calculate BMI using height from Screening Visit.
- Perform limited physical examination (minimum of general appearance, skin, heart, lungs, and abdomen).
- Obtain vital signs (including heart rate, blood pressure, respiration rate, and temperature) while patient is sitting after a minimum 5-minute rest.
- Perform 12-lead ECGs [redacted] in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10-minutes.

  Note: 12-lead ECGs will be printed and will be interpreted as soon as possible by the Investigator. A digital recording of each ECG will be submitted to a central reviewer.
- Perform breath alcohol test.
- Record concomitant medications (prior to each dose).
- Collect blood samples for the following:
  - Chemistry, hematology, coagulation, prolactin. Sample to be collected predose.
  - PK analysis.

    Note: [redacted]
- Collect urine samples for the following:

- Urinalysis,
- Urine drug screen,
- POC urine drug screen.

- If the patient continues to meet all eligibility criteria, the patient will be randomized, treatment assigned, and study drug will be dispensed.
- Administer study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted] The evening dose will be self-administered by the patient.
- Record adverse events following fist dose of study drug.
- [redacted]

6.4.2 Day 2

The following procedures will be performed by the patient on Day 2:

- Patient will record concomitant medications and adverse events.
- [redacted]
- Patient will self-administer study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted]

6.4.3 Day 3 (± 1 Day)

The following procedures will be performed at Day 3:

- Record concomitant medications (prior to each dose) and adverse events.
- Obtain vital signs (including heart rate, blood pressure, respiration rate, and temperature) while patient is sitting after a minimum 5-minute rest.
- Perform 12-lead ECGs in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10-minutes.

  Note: 12-lead ECGs will be printed and will be interpreted as soon as possible by the Investigator. A digital recording of each ECG will be submitted to a central reviewer.
- Collect blood samples for the following:
  - Chemistry, hematology, coagulation, prolactin. Sample to be collected predose.

- PK analysis.

  Note: The PK samples will be collected within ±15 minutes of the corresponding ECG.

- Collect urine samples for urinalysis.
- Administer study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted] The evening dose will be self-administered by the patient.
- Perform study drug accountability. Verify that the patient has the necessary amount of study drug for self-administration for the remainder of the treatment period.
- [redacted]

6.4.4 Days 4, 5, 6

The following procedures will be performed by the patient on Days 4, 5, and 6 respectively:

- Patient will record concomitant medications and adverse events.
- [redacted]
- Patient will self-administer study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted]

6.4.5 Day 7 (± 1 Day)

The following procedures will be performed at Day 7:

- Record concomitant medications (prior to each dose) and adverse events
- Obtain vital signs (including heart rate, blood pressure, respiration rate, and temperature) while patient is sitting after a minimum 5-minute rest.
- Perform 12-lead ECGs in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10-minutes.

  Note: 12-lead ECGs will be printed and will be interpreted as soon as possible by the Investigator. A digital recording of each ECG will be submitted to a central reviewer.

- Collect blood samples for the following
  - Chemistry, hematology, coagulation, prolactin. Sample to be collected predose.
  - PK analysis.

Note: The PK samples will be collected within ±15 minutes of the corresponding ECG.

- Collect urine samples for urinalysis.
- Administer study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted] The evening dose will be self-administered by the patient.
- Perform study drug accountability. Verify that the patient has the necessary amount of study drug for self-administration for the remainder of the treatment period.
- [redacted]

6.4.6 Days 8 and 9

The following procedures will be performed by the patient on Days 8 and 9, respectively:

- Patient will record concomitant medications and adverse events.
- [redacted]
- Patient will self-administer study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted]

6.4.7 Day 10 (± 1 Day)

The following procedures will be performed at Day 10:

- Record concomitant medications (prior to each dose) and adverse events
- Obtain vital signs (including heart rate, blood pressure, respiration rate, and temperature) while patient is sitting after a minimum 5-minute rest.
- Perform 12-lead ECGs in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10-minutes.

  Note: 12-lead ECGs will be printed and will be interpreted as soon as possible by the Investigator. A digital recording of each ECG will be submitted to a central reviewer.
- Collect blood samples for the following
  - Chemistry, hematology, coagulation, prolactin. Sample to be collected predose.
  - PK analysis.

Note: The PK samples will be collected within ±15 minutes of the corresponding ECG.

- Collect urine samples for urinalysis.
- Administer study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted]
  The evening dose will be self-administered by the patient.
- Perform study drug accountability. Verify that the patient has the necessary amount of study drug for self-administration for the remainder of the treatment period.
- [redacted]

6.4.8 Days 11, 12, 13

The following procedures will be performed by the patient on Days 11, 12, and 13, respectively:

- Patient will record concomitant medications and adverse events.
- [redacted].
- Patient will self-administer study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted]

6.4.9 Day 14 (+ 1 Day)

The following procedures will be performed at Day 14:

- [redacted].
- Record concomitant medications (prior to each dose) and adverse events.
- Obtain vital signs (including heart rate, blood pressure, respiration rate, and temperature) while patient is sitting after a minimum 5-minute rest.
- Perform a complete physical examination (general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system).
- Perform 12-lead ECGs [redacted] in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10-minutes.

  Note: 12-lead ECGs will be printed and will be interpreted as soon as possible by the Investigator. A digital recording of each ECG will be submitted to a central reviewer.

- Collect blood samples for the following:
  - Chemistry, hematology, and coagulation, and prolactin. Sample collected predose.
  - PK analysis

    [redacted]
  - Serum pregnancy test (only for females who are not surgically sterile or postmenopausal for at least 1 year [with confirmed FSH in postmenopausal range]),
- Collect urine samples for the following:
  - Urinalysis,
  - Urine drug screen.
- Assess fasting blood glucose before gastric emptying assessments to ensure a blood glucose of <275 mg/dL. Blood glucose will be measured at 2 hours (+/-15 min) and 4 hours (+/-15 min) after the start of the gastric emptying assessment.
- Administer the final dose of study drug (all patients will take a dose of blinded study drug [CIN-102 or placebo capsules] orally at [redacted] AM [redacted] with approximately 240 mL of water. Patients will fast for a minimum of 8 hours before the morning dose and 4 hours after the completion of the standardized meal. If the patient or Investigator determine that food should be consumed by the patient (ie, due to low blood glucose levels or symptoms of hypoglycemia), it is permissible to break the specified fast to ensure patient safety.
- Obtain scintigraphy following completion of standardized meal.
- [redacted]
- [redacted]
- Perform study drug accountability and collect unused study drug.

6.5 Follow-up Visit (Day 20 ± 1 Day)

The following procedures will be performed via telephone call to the patient:

- Record concomitant medications and adverse events.

6.6 Early Termination Visit and Withdrawal Procedures

For patients who are withdrawn from the study prior to completion, an attempt should be made to perform the following procedures at the Early Termination Visit:

- Record concomitant medications and adverse events.

- [redacted]
- Perform a complete physical examination (general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system).
- Obtain vital signs (including heart rate, blood pressure, respiration rate, and temperature) while patient is sitting after a minimum 5-minute rest.
- Perform 12-lead ECGs in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10-minutes.

  Note: 12-lead ECGs will be printed and will be interpreted as soon as possible by the Investigator. A digital recording of each ECG will be submitted to a central reviewer.
- Collect blood samples for the following:
  - Chemistry, hematology, coagulation, prolactin. Sample to be collected predose if applicable.
  - PK analysis.

    Note: The PK samples will be collected within ±15 minutes of the corresponding ECG.
  - Serum pregnancy test (only for females who are not surgically sterile or postmenopausal for at least 1 year [with confirmed FSH in postmenopausal range])
- Collect urine samples for the following:
  - Urinalysis,
  - Urine drug screen.
- Patient will consume standardized meal after an ≥8-hour fast.
- Obtain scintigraphy following completion of standardized meal.
- [redacted]
- [redacted]
- Perform study drug accountability and collect unused study drug.

7 EFFICACY ASSESSMENTS

7.1 Efficacy Assessments

The efficacy variables are as follows:

- The change from baseline in gastric percentage retention of a radiolabeled meal at 2 and 4 hours after dosing CIN-102 in patients with diabetic gastroparesis.
- The change from baseline in antral contractility as measured by Dynamic Antral Scintigraphy at Day 14.
- The change from baseline in gastric accommodation at Day 14.
- [redacted]

[redacted]

[redacted]

[redacted].

Dynamic antral scintigraphy (DAS), a non-invasive technique for the assessment of post-prandial peristaltic gastric contraction frequency and contraction amplitude of the distal antrum will be used to evaluate antral motility at study timepoints that demonstrate a sufficient count rate (labeled food content). [redacted]

[redacted]

7.2 Pharmacokinetics

Blood samples for measurement of plasma concentrations of deuterated domperidone (and possibly metabolites) will be collected each time a triplicate ECG is obtained.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of first dose of study drug until participation is complete. Patients should be instructed to report any adverse event that they experience to the Investigator and/or relevant site staff whether or not they think the event is due to study treatment. Beginning at the time of first dose of study drug, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at the time of first dose of study drug should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at the time of first dose of study drug and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of all adverse events (serious and non-serious) and will be graded using the CTCAE Version 5.0 criteria as shown in Table 1. The Investigator will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

Table 1. CTCAE Severity Assessment of Adverse Events

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living*
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**
4	Life Threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to AE
*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.		
Ref: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf		

Causality assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug-

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and pharmacokinetics of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

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

- Requires hospitalization or prolongation of existing hospitalizations

Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of first dose of study drug until 30 days following the final dose of study drug must be reported to [redacted] within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to [redacted] or the Sponsor/designee. Of note, reporting of SAEs after the follow-up phone call 72 hours after discharge is dependent on spontaneous reporting by the patient. The Investigator is not required to have further contact to elicit this information after completion of the follow-up phone call but should instruct the patient to contact the site to report any such events.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to [redacted] at [redacted] or call the [redacted] SAE reporting line (phone number listed below), and fax/e-mail the completed paper SAE form to [redacted] (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: [redacted]

[redacted] reporting line – USA:

Telephone: [redacted]

Fax: [redacted]

E-mail: [redacted]

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to [redacted] via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an adverse event or SAE; however, it must be reported to [redacted] within 24 hours of knowledge of the event. [redacted] will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax or e-mail it back to [redacted].

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify [redacted] as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/e-mailed to [redacted]. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Clinical Laboratory Evaluations

Safety laboratory tests will include chemistry, hematology, coagulation, prolactin, and urinalysis. See Appendix B for a complete list of analytes.

Safety laboratory tests will be evaluated at the times indicated in the Schedule of Procedures table in Appendix A.

Abnormal Screening laboratory tests may be repeated no more than 2 times for eligibility purposes.

If, in the opinion of the Investigator, any patient has a clinically significant abnormal laboratory finding in comparison to the value at the time of randomization or unresolved treatment-emergent

adverse event(s) (TEAE), additional follow-up visits will be scheduled. Patients will be followed approximately once a week (or more frequently as deemed appropriate) until the Investigator determines that repeat laboratory findings are clinically unremarkable in comparison to baseline, or unresolved adverse events return to prestudy levels or clinically acceptable levels.

If a patient experiences an SAE for which follow-up laboratories and review are required, the Investigator will schedule additional postdose visits as necessary.

If, in the opinion of the Investigator, any patient has a clinically significant adverse event at the follow-up call, the Investigator will provide additional follow-up until the adverse event returns to clinically acceptable levels.

The safety laboratory sample collection times may be refined based on emerging data to ensure study objectives are met.

8.6 Vital Signs

Vital signs, including heart rate, blood pressure, respiration rate, and temperature, will be measured at the times indicated in the Schedule of Procedures table in Appendix A using the following standardized procedures:

- Prior to measuring vital signs, the patient should be sitting for a minimum of 5 minutes with his/her back supported, feet flat on the floor, and his/her measurement arm supported so that the midpoint of the manometer cuff is at heart level.
- An appropriately sized cuff should be used with the bladder centered over the brachial artery.
- The cuff size and arm used for the measurement should be recorded. Whenever possible, the same arm should be used for all vital sign assessments throughout the study.

8.7 Electrocardiograms

Twelve-lead ECGs will be performed at the times indicated in the Schedule of Procedures table in Appendix A.

Every effort will be made to eliminate any sources of physical (including any movement, eating, or drinking) or electrical interference. During these assessments, patients are not permitted to use cell phones, iPods, laptop computers, tablets, or any type of battery-operated or electrical device, and all of these devices must be turned off during the assessments.

All 12-lead ECGs will be performed in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10 minutes. The average QTcF will be used for eligibility and safety assessments. Twelve-lead ECGs will be printed and will be interpreted as soon as possible by an Investigator (or Subinvestigator for Screening Visit only). All ECGs collected at the time of randomization and throughout the treatment period must be evaluated for the presence of abnormalities by a qualified physician. A digital recording of all ECGs for randomized subjects will be submitted to a central reviewer. The central overread ECG data will be utilized for all safety assessments and analyses.

Standard ECG parameters will be measured, and the following ECG parameters will be recorded:

- QRS interval
- Heart rate
- RR interval
- QT interval
- QTc (QTcF)

Investigators should contact the Sponsor or designee if any clinically meaningful changes from baseline are noted on review. Please refer to Appendix C for ECG alert criteria guidance.

8.8 Physical Examinations

Complete physical examinations will be performed at the times indicated in the Schedule of Procedures table in Appendix A. A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system.

Brief limited physical examinations will be performed at the times indicated in the Schedule of Procedures table in Appendix A. A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen.

All complete and limited physical examination findings must be recorded.

8.9 Height and Weight

Height and weight will be measured at the times indicated in the Schedule of Procedures table in Appendix A and will be used to calculate BMI. Height will be measured with the patient's shoes off. Weight will be measured with the patient's shoes off and after the patient's bladder has been emptied.

9 STATISTICS

9.1 Analysis Populations

The Intent-to-Treat (ITT) Population: All patients who are randomized.

Modified ITT (MITT) Population: All patients in the ITT Population who received any amount of study drug and have a baseline DAS and a post-baseline DAS.

The primary analysis population will be the MITT Population.

The Safety Population will consist of all randomized patients who receive any study drug.

The PK Population will consist of all randomized patients who have at least one quantifiable plasma concentration following administration of CIN-102.

9.2 Statistical Methods

The data from placebo patients of all cohorts will be pooled for efficacy and safety analysis.

9.2.1 Analysis of Efficacy

[redacted]

9.2.2 Pharmacokinetic Analysis

Plasma concentrations of deuterated domperidone (and any measured metabolites) will be listed by individual.

9.2.3 Pharmacokinetic-Pharmacodynamic Analysis

If the data permit, an attempt may be made to correlate plasma concentrations with select safety measures, prolactin data, and/or measures of gastric emptying time and symptoms of gastroparesis.

9.2.4 Analysis of Safety

Safety data, including physical examinations, ECGs, vital sign assessments, clinical laboratory evaluations (including prolactin), and adverse events, will be summarized by treatment group (placebo patients from all dose levels will be pooled) and time of collection, when appropriate. Individual and mean time course of absolute prolactin values and change from baseline prolactin by treatment may also be generated.

Descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum) will be calculated for quantitative safety data, as well as for the difference from baseline, when appropriate. Absolute and change from baseline values in QT and QTc [using Fridericia's correction factor) will be plotted against time points by cohort, if applicable.

Shift tables describing out-of-normal range shifts will be provided for clinical laboratory results.

9.2.5 Sample Size Determination

A total of 30 patients (10 patients per group) will be randomized to CIN-102 [redacted] BID or CIN-102 [redacted] BID or placebo BID. The sample size is considered adequate to provide the necessary data to evaluate the objectives of the study. No formal statistical assessment for sample size determination has been performed.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and adverse events
- World Health Organization Drug Dictionary for prior and concomitant medications

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

On enrollment in the study, the subject will receive a subject card to be carried at all times. The subject card will state that the subject is participating in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to the Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records; eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

13 REFERENCES

1. Bielefeldt K. Gastroparesis: concepts, controversies, and challenges. *Scientifica (Cairo)*. 2012;2012:424802.
2. Parkman HP, Jacobs MR, Mishra A, et al. Domperidone treatment for gastroparesis: demographic and pharmacogenetic characterization of clinical efficacy and side-effects. *Dig Dis Sci*. 2011;56(1):115-124.
3. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Gastroparesis: clinical evaluation of drugs for treatment. Guidance for industry [draft guidance]. July 2015.
4. Camilleri M, Bharucha AE, Farrugia G. Epidemiology, mechanisms, and management of diabetic gastroparesis. *Clin Gastroenterol Hepatol*. 2011;9(1):5-12.
5. Ortiz A, Cooper CJ, Alvarez A, et al. Cardiovascular safety profile and clinical experience with high-dose domperidone therapy for nausea and vomiting. *Am J Med Sci*. 2015;349(5):421-424.
6. [redacted]
7. Motilium® (domperidone) [product information]. Macquarie Park, NSW, Australia. Janssen-Cilag Pty Ltd. 04 February 2019.
8. Reddymasu SC, Soykan I, McCallum RW. Domperidone: review of pharmacology and clinical applications in gastroenterology. *Am J Gastroenterol*. 2007;102(9):2036-2045.
9. Camilleri M, Parkman HP, Shafi MA, et al. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013;108(1):18-37.
10. Fitzgerald P, Dinan TG. Prolactin and dopamine: what is the connection? A review article. *J Psychopharmacol*. 2008;22(2 Suppl):12-19.
11. Buffery PJ, Strother RM. Domperidone safety: a mini-review of the science of QT prolongation and clinical implications of recent global regulatory recommendations. *N Z Med J.* 2015;128(1416):66-74.
12. European Medicines Agency, Pharmacovigilance Risk Assessment Committee (PRAC). Assessment report. Domperidone-containing medicinal products. March 2014.
13. FDA Briefing Document (Domperidone). Pharmacy Compounding Advisory Committee Meeting. October 2015.
14. Biewenga J, Keung C, Solanki B, et al. Absence of QTc prolongation with domperidone: a randomized, double-blind, placebo- and positive-controlled thorough QT/QTc study in healthy volunteers. *Clin Pharmacol Drug Dev*. 2015;4(1):41-48.
15. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Guidance for Industry. October 2005.
16. Motilium® (domperidone) [datasheet]. Auckland, New Zealand. Janssen-Cilag (New Zealand) Ltd. 02 May 2016.
17. Food and Drug Administration, Center for Drug Evaluation and Research. Pharmacy Compounding Advisory Committee (PCAC) Meeting transcript. 28 October 2015.

18. Boyce MJ, Baisley KJ, Warrington SJ. Pharmacokinetic interaction between domperidone and ketoconazole leads to QT prolongation in healthy volunteers: a randomized, placebo-controlled, double-blind, crossover study. *Br J Clin Pharmacol*. 2012;73(3):411-421.
19. US Food and Drug Administration. How to request domperidone for expanded access use. https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm368736.htm. Accessed 09 August 2018.
20. International Commission on Radiological Protection. Radiation Dose to Patients from Radiopharmaceuticals. ICRP Publication 53. *Ann. ICRP.* 1988: 18(1-4).
21. Mettler FA, Huda W, Yoshizumi TT, et al. Effective doses in radiology and diagnostic medicine: a catalog. *Radiology*. 2008;248(1):254-63.
22. National Council on Radiation Protection and Measurements. Ionizing radiation exposure of the population of the United States. National Council on Radiation Protection report no. 160. Bethesda, MD: National Council on Radiation Protection Measurements, 2009.
23. American College of Radiology. Practice Parameter for the Performance of Gastrointestinal Scintigraphy. http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/GI_Scintigraphy.pdf. 2015. Accessed 23 August 2019.

APPENDIX A: SCHEDULE OF PROCEDURES

	Screening	Baseline	Treatment Period					Follow Up Phone Call	Early Term
	D-28 to -6	D-5 to -1	D1	D3	D7	D10	D14	D20	
Visit window (± days)			± 0	± 1	± 1	± 1	+1	± 1	
Visit number	1	2	4	5	6	7	8	9	
Informed consent [1]	X								
Inclusion/exclusion [2]	X		X						
Demographics	X								
Medical/surgical history	X	X	X						
Prior and concomitant medications [3]	X	X	X	X	X	X	X	X	X
Adverse events [4]			X	X	X	X	X	X	X
[redacted]									
Complete physical exam [6]	X						X		X
Limited physical exam [6]			X						
Weight and Height [7]	X		X						
Vital Signs [8]	X	X	X	X	X	X	X		X
Urine drug screen [9]	X	X	X				X		X
Alcohol test	X		X						
12-lead ECG [10]	X		X	X	X	X	X		X
PK sample(s) [11]			X	X	X	X	X		X
HIV, HBsAG/HCV screen	X								
FSH [12]	X								
TSH	X								
Pregnancy test [13]	X	X					X		X
Chemistry, hematology and coagulation	X		X	X	X	X	X		X
Prolactin [14]	X		X		X		X		X
Urinalysis	X		X		X		X		X
Blood glucose (point of care fingerstick) [15]		X					X		X
Dynamic Antral Scintigraphy [16]		X					X		X

	Screening	Baseline	Treatment Period					Follow Up Phone Call	Early Term
	D-28 to -6	D-5 to -1	D1	D3	D7	D10	D14	D20	
Visit window (± days)			± 0	± 1	± 1	± 1	+1	± 1	
Visit number	1	2	4	5	6	7	8	9	
Randomization and Dispense Study Drug [17]			X						
Study drug administration [18]			X	X	X	X	X		
Study drug accountability and collection of unused study drug [19]				X	X	X	X		X

Note: All days will be reported as the next nominal day in sequential order (ie, if the outpatient visit Day 3 [±1 Day] takes place on the sequential Day 4, it will be recorded as Day 4. All following days will be recorded likewise).

1. Written informed consent for the study will be obtained from all patients before any study procedures are performed.
2. Screening procedures, including vital sign assessments, may be repeated no more than 2 times for eligibility purposes.
3. Any medications administered 28 days prior to the first dose of study drug and during the study period must be recorded. Starting on Day 1, concomitant medications will be recorded by the patient prior to each dose and recorded by the Investigator at each outpatient visit prior to each dose.
4. Adverse events will be monitored and documented by the patient and by the Investigator at each outpatient visit from the time of first dose of study drug until study participation is complete.
5. [redacted].
6. A complete physical examination will consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system. A limited physical examination will consist of a minimum of general appearance, skin, heart, lungs, and abdomen.
7. Height will be measured at the Screening Visit only. Body mass index will be calculated at the Screening Visit using height and weight collected at the Screening Visit. At the time of randomization (Day 1), BMI will be calculated using weight from the time of randomization (Day 1) and height from the Screening visit.
8. Vital signs include heart rate, blood pressure, respiration rate, and temperature and will be collected while the patient is sitting after a minimum 5-minute rest.
9. At the time of randomization (Day 1), a POC drug test will be performed for use in assessing eligibility.
10. All 12-lead ECGs will be performed in triplicate approximately 1 minute apart after the patient has been resting in the supine position for at least 10 minutes. Twelve-lead ECGs will be printed and will be interpreted as soon as possible by an Investigator (or Subinvestigator for Screening visit only). A digital recording of all ECGs from randomized patients will be submitted to a central reviewer. On Day 1 ECGs will be performed [redacted]. On Day 14 (+1 Day) ECGs will be performed [redacted]. See Appendix C for ECG review criteria guidance.
11. Blood samples for PK. On Day 1, samples will be collected [redacted]. On Day 14 (+1 day), samples will be collected [redacted]. All PK samples should be collected within ±15 minutes of the corresponding ECG.
12. Follicle stimulating hormone will only be measured for females who have been postmenopausal for at least 1 year and are not surgically sterile.
13. A pregnancy test will only be performed in females who are not surgically sterile (or postmenopausal for at least 1 year [with confirmed FSH in postmenopausal range at the Screening visit]). A serum pregnancy test will be performed by the local lab on Days -28 to -6, Days -5 to -1, and Day 14 (+1 Day).
14. Sample collected predose on visit Day 1, Day 7 (±1 Day), and Day 14 (+1 Day).

	Screening	Baseline	Treatment Period					Follow Up Phone Call	Early Term
	D-28 to -6	D-5 to -1	D1	D3	D7	D10	D14	D20	
Visit window (± days)			± 0	± 1	± 1	± 1	+1	± 1	
Visit number	1	2	4	5	6	7	8	9	

15. Fasting blood glucose will be measured before gastric emptying assessments to ensure a blood glucose of <275 mg/dL and blood glucose will be measured at 2 hours and 4 hours after the start of the gastric emptying assessment.
16. Scintigraphy will be obtained following the completion of a standardized meal. Patients will fast for ≥8 hours before and for 4 hours after completion of the standardized meal.
17. Randomization will occur on the morning of Day 1, although randomization procedures may also be performed at a separate outpatient visit 1 day prior to taking the morning dose of study drug (Day -1) to allow adequate turnaround time for test results if necessary. The safety laboratory tests (ie, chemistry, hematology, coagulation, and urinalysis) from Day -1 or Day 1 will be processed at local laboratories for verifying patient eligibility [see Section 6.4.1]. Study drug will be dispensed via randomized treatment assignment on Day 1.
18. All patients will take a dose of blinded study drug (CIN-102 or placebo capsules) orally at [redacted] AM [redacted] and [redacted] PM [redacted] with approximately 240 mL of water. [redacted]. Patients will fast for a minimum of 8 hours before the morning dose and 4 hours after the completion of the standardized meal on Day 14 [+1 Day]. [redacted]. During confinement and outpatient visits, study drug will be administered at the site by site staff. Patients will be provided study drug for self-administration for study days not at the site.
19. Study drug accountability will occur on Day 3 (±1 Day), Day 7 (±1 Day), Day 10 (±1 Day), and Day 14 (+1 Day) or on Early Termination if applicable. Unused study drug will be collected on Day 14 (+1 Day) or on Early Termination if applicable.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

Endocrinology

Follicle-stimulating hormone [1]	Prolactin
Thyroid-stimulating hormone	Glycosylated hemoglobin (HbA1c)

1. Follicle-stimulating hormone will only be assessed in females who have been postmenopausal for at least 1 year and are not surgically sterile.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy is performed only as needed based on positive dipstick test results.

Serology

Hepatitis B surface antigen	Hepatitis C virus antibody
Human immunodeficiency virus antibody	

Pregnancy Test

Serum and point-of-care pregnancy tests will only be performed in females who are not surgically sterile (or postmenopausal for at least 1 year [with confirmed FSH in postmenopausal range at the Screening Visit]).

Urine Drug Screen [1]

Amphetamines	Cocaine
Cotinine	Opiates
Phencyclidine	Tetrahydrocannabinol

1. Urine drug screen point-of-care drug test on randomization day.

Breath Alcohol Test

APPENDIX C: ELECTROCARDIOGRAM ALERT CRITERIA GUIDANCE

Investigators should contact the Sponsor or designee if any clinically meaningful changes from baseline ECGs, including but not limited to those listed below, are noted upon review.

- QTcF ≥450 msec (male)
- QTcF ≥470 msec (female)
- A > 60 msec increase in QTcF from baseline
- A 6% or greater increase in QTcF from baseline

New onset findings including but not limited to the following:

- Second degree AV block (Mobitz II)
- Third degree AV block (complete heart block)
- Acute myocardial infarction
- New left bundle branch block (LBBB)
- Severe bradycardia (ventricular rate ≤40 bpm)
- Supraventricular tachycardia (SVT) (ventricular rate ≥150 bpm)
- Torsades de pointes
- Ventricular tachycardia (Three or more beats regardless of rate)
- Ventricular fibrillation
- Atrial fibrillation/atrial flutter (ventricular rate ≥150 bpm)