STATISTICAL ANALYSIS PLAN

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Dose Response of Oral CIN-102 in Adults with Idiopathic and Diabetic Gastroparesis

Protocol Number: CIN-102-121

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Investigational Product: CIN-102

Sponsor: CinDome Pharma, Inc.
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CONFIDENTIAL

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	Date
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

VERSION HISTORY

Version	Version Date	Description
1.0	11 Feb 2021	Initial approved version.

[redacted]

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[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	Alanine aminotransferase
ANMS GCSI-DD	American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BID	Twice daily
BMI	Body mass index
$BT_{½}$	Gastric Emptying Breath Test $T_{1/2}$ (BT $t_{1/2}$)
C_{max}	Maximum plasma concentration
CPGAS	Clinical Patient Grading Assessment Scale
CTCAE	Common Terminology Criteria for Adverse Events
DRC	Data Review Committee
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
GEBT	Gastric emptying breath test
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IRT	Interactive Response Technology
ITT	Intent-to-Treat
MAD	Multiple-ascending dose
MITT	Modified Intent-to-Treat
msec	Millisecond(s)
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders Symptom
PD	Pharmacodynamic(s)
PGx	Pharmacogenomic
PK	Pharmacokinetic(s)
PP	Per-Protocol
QD	Once daily
QTcF	Heart rate-corrected QT interval using Fridericia's formula
SAD	Single-ascending dose
SAE	Serious adverse event
T½	Terminal phase elimination half-life
ULN	Upper limit of normal

1 INTRODUCTION

This statistical analysis plan (SAP) provides a detailed, technical elaboration of the statistical analyses of safety, efficacy, pharmacokinetics (PK), and dose response of oral CIN-102 in adults with idiopathic and diabetic gastroparesis as described in the study original protocol (dated 19 May 2019), Version 2.0 amendment 1 (dated 15 Aug 2019), and version 3.0 amendment 2 (dated 13 Nov 2019). Specifications for tables, listings, and figures are contained in a separate document.

2 STUDY OVERVIEW

2.1 Study Objectives

The objectives of this study are the following:

- To evaluate the safety and tolerability of multiple doses of CIN-102 in subjects with idiopathic or diabetic gastroparesis
- To evaluate the effect of multiple doses of CIN-102 on gastric emptying as measured by the gastric emptying breath test (GEBT) in subjects with idiopathic or diabetic gastroparesis
- To characterize the pharmacokinetic (PK) of multiple doses of CIN-102 in subjects with idiopathic or diabetic gastroparesis

The exploratory objectives of this study include the following:

- To assess the effect of multiple doses of CIN-102 on nausea associated with gastroparesis based on the nausea score on the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD)
- To assess the effect of multiple doses of CIN-102 on ANMS GCSI-DD scores (total and subscales) in subjects with idiopathic or diabetic gastroparesis
- To assess the effect of multiple doses of CIN-102 on a variety of patient reported outcomes
- To characterize exposure-response relationships of CIN-102

2.2 Study Design

2.2.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled Phase 2A study to evaluate the safety, efficacy, PK, and dose response of oral CIN-102 in adults with idiopathic or diabetic gastroparesis.

The study will begin by randomizing subjects in Cohort 1 to either CIN-102 [redacted] twice daily (BID) or placebo BID in a ratio such that 15 subjects receive CIN-102 and 5 subjects receive placebo. Subjects will opt into either a sparse pharmacokinetic sampling subgroup or an intensive PK sampling subgroup. This cohort will be stratified at randomization by idiopathic versus diabetic gastroparesis. Efforts will be made to ensure adequate numbers of idiopathic and diabetic gastroparetic subjects are included. After approximately 15 subjects in Cohort 1 complete the study, an independent Data Review Committee (DRC) will convene to review the data from Cohort 1. The independent Data Review Committee will review emerging safety, PK, 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 for Cohorts 2 and 3 or if further refinement of the proposed dose levels is warranted. Currently planned dose levels for Cohorts 2 and 3 are [redacted] QD and

[redacted] BID, respectively, with approximately 15 subjects receiving the study drug and 5 subjects receiving placebo in each cohort. However, these planned dose levels may be modified and/or additional cohorts may be added based on emerging information from the current study as well as other ongoing studies. The highest dose will not exceed [redacted] BID and no more than 40 additional subjects will be added without a protocol amendment. The DRC will also determine how to advance the cohorts (serially or simultaneously). Further details regarding the role, responsibilities, and procedures of the DRC will be provided in the DRC Charter.

For Cohort 1, subjects will be stratified at randomization based on their etiology for gastroparesis (i.e., diabetic gastroparesis versus idiopathic gastroparesis). For Cohorts 2 and 3, subjects will be stratified by screening GEBT $T_{1/2}$ result (<110 versus >= 110).

2.2.2 Study Indication

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

2.2.3 Dose Escalation

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 idiopathic or diabetic gastroparesis will be formed to review emerging PK and safety data in a blinded manner.

The DRC will convene to review safety and efficacy data through at least Day 14 from approximately 15 of the subjects in each cohort. PK data from approximately 8 subjects receiving CIN-102 in each cohort will be considered adequate for DRC review (these PK data may be a combination of the sparse PK scheme and the intense PK from a subset of subjects). In the event a subject discontinues the study at least 24 hours after steady-state is believed to have been achieved (based on available data from the SAD and MAD studies) for a reason unrelated to safety, the existing data from that individual may be sufficient for decision making by the DRC.

Dose escalation will only take place after the DRC has determined that is appropriate (eg, adequate safety and tolerability have been demonstrated and PK behavior is well enough characterized to support proceeding to a higher dose level and/or study of a lower dose level or frequency is meaningful based on emerging safety data).

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.

2.2.3.1 Criteria for Temporary Suspension of Dosing

Dosing within a cohort or between cohorts will be temporarily suspended until a full cumulative data review is complete 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 subject 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 subjects
- 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 subject 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. Should dosing be temporarily suspended, the DRC can review and discuss all available safety and PK data from all subjects participating in the study up until the time of the event. The DRC will decide whether knowledge of the treatment assignment of any subject(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 subjects originally planned
- Expand the current cohort with additional subjects to obtain more information at that dose level
- Escalate to a higher dose level [redacted]
- 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

2.2.3.2 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 subjects 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).

2.2.4 Study Drug

[redacted]. A matching placebo [redacted] containing the same inactive ingredients without CIN-102 drug substance will also be provided. Both CIN-102 and matching placebo capsules will be provided to the site by the Sponsor or designee.

All subjects will take a dose of blinded study drug (CIN-102 or placebo capsules) orally at [redacted] AM [redacted] For BID treatment groups, a second dose will be taken orally at [redacted] PM [redacted] On Day 14 [±2 days], all subjects will fast for a minimum of 8 hours before the morning dose of study drug and 4 hours following the completion of the GEBT meal. [redacted] Subjects will be provided study drug for self-administration for doses not administered at the site.

2.2.5 Randomization and Blinding

Subjects 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 and randomized treatment assignments will be provided by Medpace Interactive Response Technology (IRT). Subjects will be randomized to either CIN-102 or placebo in a 3:1 ratio in each cohort.

The study will begin by randomizing subjects in Cohort 1 to either CIN-102 [redacted] BID or placebo BID such that 15 subjects receive CIN-102 and 5 subjects receive placebo. Currently planned dose levels for Cohorts 2 and 3 are [redacted] QD and [redacted] BID, respectively, with 15 subjects receiving study drug and 5 subjects receiving placebo in each cohort.

For Cohort 1, subjects will be stratified at randomization based on their etiology for gastroparesis (i.e., diabetic gastroparesis versus idiopathic gastroparesis). For Cohorts 2 and 3, subjects will be stratified by screening GEBT $T_{1/2}$ result (<110 versus >= 110).

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 subject. Subjects 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 subjects receiving CIN-102 only (and possibly limited analysis of samples from subjects 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.

2.2.6 *Breaking the Blind*

Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of subject safety. 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 [redacted] IRT.

2.2.7 *Sample Size Determination*

A total of approximately 60 subjects (15 subjects per treatment) will be randomized to CIN-102 [redacted] BID, CIN-102 [redacted] QD, CIN-102 [redacted] BID, or placebo. 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.

2.3 Study Variables

2.3.1 *Primary Efficacy Variable*

The primary efficacy variable is the change from baseline in gastric emptying as measured by GEBT at Day 14.

2.3.2 *Secondary Efficacy Variables*

The secondary efficacy variables are:

- The change from baseline in gastric emptying as measured by GEBT BT T½ at Day 14
- The change from baseline in ANMS GCSI-DD total scores
- The change from baseline in ANMS GCSI-DD subscale scores

2.3.3 *Exploratory Efficacy Variables*

The exploratory efficacy variables are:

- The change from baseline in gastroparesis symptoms as measured by Patient Assessment of Gastrointestinal Disorders Symptom Severity (PAGI-SYM) questionnaire scores
- The Clinical Grading Assessment Scale at Day 14

2.3.4 *Pharmacokinetic Variables*

The PK variables are concentrations and derived PK parameters of deuterated domperidone following multiple doses of CIN-102.

2.3.5 *Safety Variables*

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

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the CRF.

3.1.3 Definition of Baseline

Baseline will be defined as the last measurement prior to the first dose of study drug unless otherwise specified.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

Geometric mean (GM) and GM CV will also be provided for PK concentrations and parameters. The subjects with a 0 (zero) value will be excluded from the calculation of GM and GM CV.

3.2 Treatment Groups

This study is planned to include 4 treatment groups with approximately 15 subjects each:

- CIN-102 [redacted] BID
- CIN-102 [redacted] QD
- CIN-102 [redacted] BID
- Placebo

The data from placebo subjects of all cohorts will not be pooled for efficacy and PK analyses, but will be pooled for other analyses (e.g., safety).

The duration of the double-blind treatment period will be 14 days (± 2 days) of study drug administration.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Subject disposition information will be summarized overall and by treatment group using randomized subjects (ITT Population):

- Randomized subjects
  - Intensive PK schedule
  - Sparse PK schedule
- Subjects who randomized and received any amount of drug
- Subjects who completed the study

- Subjects who withdrew early from the study
  - Primary reason for early withdrawal
  - Early withdrawal due to COVID-19

Screen failure reasons, including due to COVID-19, will be summarized for all screen failure subjects.

The disposition data will be provided in listings for randomized and screen failure subjects.

3.3.2 Eligibility Criteria

Eligibility criteria (inclusion/exclusion) will be listed based on all randomized subjects (ITT Population).

3.3.3 Randomization

Data for randomization will be listed for the randomized subjects (ITT Population). The data will include if the subject was randomized, the date randomized, randomization number, and cohort.

3.3.4 Protocol Deviations

Protocol deviations will be summarized overall and by treatment group for the randomized subjects (ITT Population), with deviations also provided in a listing.

Visits or visit procedures impacted by COVID-19 will also be listed for randomized subjects (ITT Population).

3.3.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics include, but are not limited to, age at screening, sex, ethnicity, race, gastroparesis type (Idiopathic, Diabetic), screening GEBT, height (at screening), body weight, and BMI.

Demographic and baseline characteristics will be summarized overall and by treatment group for randomized subjects (ITT Population), and may be repeated for other Analysis Populations if different. Data will also be listed.

3.3.6 Medical/Surgical History

Medical/surgical history will be obtained at Screening. MedDRA (version 22.0) will be used for summarizing medical history.

Data will be summarized overall and by treatment group and listed for randomized subjects (ITT Population).

3.3.7 Prior and Concomitant Medications

Any medications administered 28 days prior to the first dose of study drug and/or during the study period must be recorded. Prior and concomitant medications will be coded using the WHO drug dictionary (version March 2019G B3). Prior medication is defined as those taken prior to the first dose of study drug. Concomitant medication is defined as those taken after the first dose of study drug was administered. All prior and concomitant medications will be summarized overall and by treatment group the Safety Population.

Data for prior and concomitant medications will also be listed for the Safety Population.

3.3.8 Rescue Medications

[redacted]Subjects 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.

Data for concomitant use [redacted] will be listed for the Safety Population.

3.3.9 Study Drug Exposure and Compliance

Study drug exposure will be calculated as date of last dose of study drug – date of first dose of study drug + 1.

Exposure will be summarized by treatment group for the Safety Population.

Percent compliance to the study drug regimen will be calculated based on drug accountability as 100 x number of actual capsules taken / number of expected capsules taken. The number of actual capsules taken will be calculated as number of capsules dispensed – number of capsules returned. If study drug is not returned, the number of capsules returned will be considered 0 for the compliance calculation. Percent compliance and compliance category will be summarized by treatment group for the Safety Population, the following compliance categories utilized:

- <75%
- 75-100%
- >100%

[redacted]

Percent compliance will also be calculated using the subject daily diary data responses for morning and evening doses taken. For this data, percent compliance will be calculated as 100 x number of doses reported taken / number of expected doses. Missing responses for doses will be treated as not taken. Percent compliance overall will be summarized by treatment group, as well as within 72 hours (3 days) and 120 hours (5 days) of the end of treatment.

All exposure and drug accountability data will be listed for the Safety Population.

3.4 Analysis Populations

[redacted]

3.4.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat Population will include all randomized subjects.

3.4.2 Modified Intent-to-Treat (MITT) Population

The Modified Intent-to-Treat (MITT) Population will include all randomized subjects who receive at least 1 dose of study drug.

3.4.3 Per-Protocol (PP) Population

The Per-Protocol (PP) Population will include all subjects in the MITT Population without major protocol violations and do not meet any of the following criteria:

- Withdrawal from the study or study drug before completion of Day 14
- Did not meet all inclusion and exclusion criteria

[redacted]

- Poor study drug compliance over the entire treatment period or leading up to Day 14
- Rescue medication use beyond protocol-specified allowance
- Serious or severe adverse event related to study medication
- Missing valid GEBT results for either baseline or Day 14 at any pre- or post-meal timepoint.

3.4.4 PK Population

The PK Population will include all subjects who receive at least 1 dose of CIN-102 and have at least 1 quantifiable postdose plasma CIN-102 concentration.

3.4.5 PK Evaluable Population

The PK Evaluable Population will include subjects who receive CIN-102 and have sufficient plasma concentration data to characterize at least 1 PK parameter.

3.4.6 PD Evaluable Population

The PD Population will include all subjects who receive study drug and have at least 1 prolactin value following the start of study drug administration.

3.4.7 Safety Population

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

3.4.8 Subgroup Analyses

In addition to the analysis populations listed, efficacy, PK, and/or safety analyses may be repeated for certain subgroups. These may include, but are not limited to:

- Screening GEBT $T_{1/2}$ scores of <110 and >=110
- Diabetic and idiopathic gastroparesis types
- Diabetic subjects: with and without neuropathy

3.5 Efficacy Assessments

The efficacy assessments will be analyzed and listed for the ITT Population. The analyses may also be repeated for other Analysis Populations (MITT or PP Population) as well as for subgroups of these Analysis Populations. Meal data recorded as part of the GEBT will also be listed for the ITT Population.

3.5.1 Primary Efficacy Assessments

Gastric empty time (time-weighted average, 1000 × percent ^{13}C dose excreted per minute, and $T_{½}$) will be determined by GEBT at Day 14 (±2 days). The value, change from baseline, and percent change from baseline (gathered on Days -10 to -3) in gastric emptying as measured by GEBT to Day 14 (±2 days) will be summarized by visit and treatment group.

GEBT results are reported using kPCD, a metric which expresses a subject's $^{13}CO_2$ excretion rate at each measurement time as defined below.

- kPCD: a mathematical expression of a test subject's $^{13}CO_2$ excretion rate (per minute, denoted as min^{-1}) at any measurement time t relative to the dose of carbon-13 contained in the test meal.

  kPCD(t) = 1,000 x [percent dose ^{13}C excreted as $^{13}CO_2$ per minute (min^{-1}) at time t]

3.5.2 Secondary Efficacy Assessments

3.5.2.1 GEBT $T_{1/2}$ and Timepoints

The value, change from baseline, and percent change from baseline in gastric emptying BT $T_{½}$ as measured by GEBT at Day 14 (±2 days) will be summarized by treatment group. The value and time-matched (to baseline visit) change from baseline and percent change from baseline of the GEBT results for each post-meal timepoint will also be summarized by treatment group.

3.5.2.2 ANMS GCSI-DD

The ANMS GCSI-DD is scheduled to be completed daily starting at least 14 days prior to randomization through Day 14. The ANMS GCSI-DD will be summarized using two different scoring methods: the protocol specified method and the scoring method as indicated in the User Manual for the ANMS GCSI-DD (section 4.2, September 27, 2018 version). For both methods, baseline for analysis will be defined as the average score for the 3 days preceding randomization.

Both total ANMS GCSI-DD and the subscale scores (and change and percent change from baseline values) will be summarized by treatment group for each scheduled assessment.

3.5.2.2.1 Protocol Specified Scoring Method

The ANMS GCSI-DD covers 5 core relevant symptoms of gastroparesis: nausea, early satiety, postprandial fullness, upper abdominal pain and vomiting. Bloating is included as an exploratory symptom. Symptoms are rated on a severity numeric response scale from 0 (none) to 4 (very severe). Vomiting is captured on a frequency response scale and scored as follows: 0 for no episodes, 1 for one episode, 2 for 2 episodes, 3 for 3 episodes, and 4 for 4 or more episodes. Subjects will be asked to recall symptoms over the previous 24 hours and complete the ANMS GCSI-DD patient-reported symptom questionnaire for at least 14 days prior to randomization, on the day of randomization, and daily from Days 1 to 14 (±2 days). [redacted]

3.5.2.2.2 ANMS Manual Scoring Method

The severity scores of four gastroparesis-related symptoms (nausea, early satiety, postprandial fullness, upper abdominal pain) range from 0-none to 4-very severe. The vomiting score assesses the number of vomiting episodes during the day, capped at a maximum of 4; thus, the scores for vomiting range from 0 (no episodes of vomiting) to 4 (four or more episodes of vomiting). Vomiting frequency is scored as 0 episodes, 1 episode, 2 episodes, 3 episodes, or 4 or more episodes (capped as 4).

The ANMS GCSI-DD total gastroparesis symptom daily score is generated by summing the scores on each of the five symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, and number of vomiting episodes) and then dividing by 5, that is the number of items within the gastroparesis related symptom score. Thus, the maximum total symptom score could be (5 symptoms * maximum score 4 divided by 5); hence, the maximum score is 20/5=4. The ANMS GCSI-DD gastroparesis symptom daily score can range from 0 to 4. High scores on the ANMS GCSI-DD reflect greater symptom severity.

3.5.3 Exploratory Efficacy Assessments

3.5.3.1 PAGI-SYM

The PAGI-SYM questionnaire on gastroparesis symptoms is completed on Days 1 and 14 and includes 6 subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain. The total and subscale scores will be derived based on the PAGI-SYM Information Booklet (section 5, 2nd Edition, 2015). Both total and subscale PAGI-SYM scores, along with change from baseline and percent change from baseline, will be summarized by treatment group.

3.5.3.2 Clinical Grading Assessment Scale

For assessment of global clinical response, the following question will be utilized at Day 14: "In thinking about the last 2 weeks, how would you say your stomach/gastroparesis-related problems/symptoms have been compared to the period before you started treatment on this study?" Responses will be: improved, no change, or worsened. Subjects will be asked to quantify their therapeutic response using the Clinical Patient Grading Assessment Scale (CPGAS). Subjects will pick a number over a range (+7 = completely better; 0 = no change; −7 = very much worse) that best answers the question. The investigator will complete the same assessment based on their judgment of the subject's response to treatment. Responses and CPGAS (subject and Investigator) scores will be summarized by treatment group.

3.6 Pharmacokinetic Assessments

3.6.1 Sample Collections for Pharmacokinetic Analysis

For all subjects, blood samples for PK analysis will be collected at the following visits and timepoints:

- Day 1: [redacted] prior to and [redacted] after the morning dose
- Days 3 [±1 day], 7 [±1 day], and 10 [±1 day]: [redacted] prior to the morning dose
- Day 14 [±2 days]: [redacted] prior to the morning dose and [redacted] after the morning dose on
- Day 15 or Day 16 (+1 day)

Subjects may consent to participate in a more intensive PK subgroup. In this subgroup, PK samples will also be collected as follows:

- Day 1: [redacted] after the morning dose
- Day 14 (±2 days): [redacted] after the morning dose
- Day 15
- Day 16 (+1 day)

Note: in some situations, collection of specific, individual PK samples [redacted] may not be required in this subset of subjects with prior written sponsor approval.

3.6.2 Handling Missing or Below the Lower Limit of Quantification Data

For PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged, and the scheduled time point may be used for the calculation of PK parameters.

In cases of missing pre-dose for each treatment, the missing components may be assumed as zero. For the other missing predose cases beyond first dose, the missing data will not be imputed.

For the individual concentration and PK parameter calculation of each treatment, the following rules will be applied:

- If one or more BLQ values occur before the first measurable concentration, they will be assigned a value of zero.
- If BLQ values occur between measurable concentrations in a profile, the BLQ should be omitted (set to missing).
- If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing).

For the concentration summary and mean concentration plot preparation of each treatment, the following rules will be applied:

- Mean concentration at any individual time point will only be calculated if at least half of the subjects have valid values (i.e. quantifiable and not missing) at this time point for each treatment.
- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to missing.
- BLQ values will be set to zero.

3.6.3 Pharmacokinetic Concentration

Individual plasma concentrations of deuterated domperidone will be summarized by treatment at each nominal time point for the PK Population descriptively. Individual plasma concentrations will also be listed for the PK Population.

Individual plasma concentration will be plotted by treatment on a linear and semi-log scale against actual sampling time points relative to dosing time. Mean (±SD) concentration will be plotted on a linear and semi-logarithmic scale against nominal time points by treatment, when available. LLOQ will be plotted as a reference line in both instances. Trough concentrations will be presented in a similar manner using predoses on Days 7, 10, and 14.

Actual sampling times that are outside the sampling time windows may be excluded from concentration summary and mean concentration plotting but will still be used in the calculations of PK parameters and individual concentration plotting. The following windows will be permitted for the collection of PK samples: ±2 minutes for samples collected ≤2 hours postdose and ±5 minutes for samples collected >2 hours postdose.

Trough concentrations collected throughout the study will be used to confirm compliance and attainment of steady-state.

3.6.4 Pharmacokinetic Parameters

The following PK parameters will be calculated for deuterated domperidone (and any measured metabolites) using plasma concentrations (Day 1) using a noncompartmental method if the data permit:

[redacted]

Parameters	Description
C_{max}	Maximum plasma concentration; determined directly from the concentration time profile; if the maximum plasma concentration occurs at more than one time point, C_{max} is defined as the first maximum value
T_{max}	Time to C_{max}; If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
AUC_{0-12}	Area under the concentration-time curve (AUC) from predose (time 0) to 12 hours

The following PK parameters will be calculated for deuterated domperidone (and any measured metabolites) using measured plasma concentrations following the final dose of CIN-102 (AM of Day 14), if the data permit:

Parameters	Description
C_{max}	Maximum plasma concentration; determined directly from the concentration time profile; if the maximum plasma concentration occurs at more than one time point, C_{max} is defined as the first maximum value
T_{max}	Time to C_{max}; If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
AUC_{tau}	AUC over the dosing interval; calculated using the trapezoidal method
AUC_{0-t}	Area under the plasma concentration vs time curve (AUC) from predose (time 0) to the last quantifiable plasma concentration (C_{last})
AUC_{0-inf}	AUC from time 0 to infinity; calculated as (AUC_{0-t} + $C_{last}/\lambda z$)
$AUC_{\%extrap}$	Percent of AUC_{0-inf} extrapolated, represented as (1 - AUC_{0-t}/AUC_{0-inf})*100
λz	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using points in the terminal log-linear phase.
$T_{½}$	Apparent first-order terminal elimination half-life; calculated as $\ln(2)/\lambda z$
CL/F	Apparent total plasma clearance after oral administration; calculated as Dose/AUC_{0-inf}
Vz/F	Apparent volume of distribution during terminal elimination phase after oral administration; calculated as Dose/[λz*AUC_{0-inf}]
R_{Cmax}	Accumulation ratio based on Cmax after the first dose and the final dose; calculated as Cmax, D14/Cmax, D1
R_{AUC}	Accumulation ratio based on AUCtau after the first dose and last dose; calculated as AUC0-tau, D14/AUCtau, D1

Actual collection times will be used in PK parameter calculations. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of all AUC values. In order to estimate the apparent first-order terminal elimination constant, λz, linear regression of concentration in logarithm scale vs. time will be performed using at least 3 data points. Uniform weighting will be selected to perform the regression analysis to estimate λz. The constant λz will be assigned but flagged if one of the following occurs:

1. the terminal elimination phase is not linear (as it appears on a semi-logarithmic scale)
2. the terminal elimination rate constant indicates a positive slope ($\lambda z > 0$)
3. T_{max} is one of the 3 last data points
4. the adjusted regression coefficient (R^2) is less than 0.8
5. The $AUC_{\%extrap}$ exceeds 20%

These λz values and λz-derived parameters will be listed but excluded from statistical analysis.

No value for λz, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, CL/F, Vz/F, or $T_{½}$ will be reported for cases that do not exhibit an acceptable terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for subjects with 2 or fewer detectable concentrations in their PK profile.

3.7 Pharmacokinetic-Pharmacodynamic Assessments

Scatterplots of PK parameters (C_{max}, AUCs, etc.) and GCSI-DD scores with BT $T_{½}$ (change from baseline) may be created, as may other plots for other plasma concentration and/or PK parameters with select safety measures, prolactin data, and/or measures of gastric emptying time and symptoms of gastroparesis.

3.8 Pharmacogenomics (PGx) Assessment

A single, optional PGx blood sample may be collected at any time during the subject's participation in the study and will be the collection data will be listed for the ITT Population. The PGx samples may be used for genetic research to explore the underlying causes of variability and/or differences in response in PK, PD, and/or safety data following administration of CIN-102. Any analysis of these samples will be detailed in a separate document.

3.9 Safety Assessments

[redacted]

Safety data, including adverse events, physical examinations, ECGs, vital sign assessments, and clinical laboratory evaluations (including prolactin), will be summarized and listed for the Safety Population by treatment group and time of collection, when appropriate (see protocol Appendix A: Schedule of Procedures for collection timing).

3.9.1 Adverse Events

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term by using MedDRA version 22.0. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug.

An overview of AEs will be provided including counts and percentages of subjects (and event counts for any TEAEs) with the following:

- Subjects with any AEs

[redacted]

- Subjects with any TEAEs (overall and by maximum severity)
- Subjects with any study drug related TEAEs (overall and by maximum severity)
- Subjects with any treatment-emergent serious AEs
- Subjects with any Drug-Related treatment-emergent serious AEs
- Subjects with any AEs leading to death
- Subjects with any TEAEs leading to discontinuation
- Subjects with any Drug-Related TEAEs leading to discontinuation

Counts and percentages of subjects (and event counts for any TEAEs) will also be presented by system organ class and preferred term for each of the categories in the overview.

Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug, as well as all AEs.

3.9.2 Clinical Laboratory Tests

[redacted]

Safety laboratory tests will include chemistry, hematology, coagulation, prolactin, and urinalysis (see protocol Appendix B: Clinical Laboratory Analytes for complete list of tests).

3.9.2.1 Chemistry, Hematology, Coagulation, Urinalysis

Continuous safety laboratory data (values and change from baseline) will be summarized by treatment group at baseline and at each post-baseline time point. Categorical data will be summarized using frequency counts and percentages by treatment group at baseline and post-baseline scheduled visits.

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

Data will also be listed.

3.9.2.2 Prolactin

Prolactin values, change from baseline, and percent change from baseline will be summarized by treatment group at baseline and at each post-baseline time point. A shift table of post-baseline out-of-normal shifts will also be presented. All prolactin data will be listed.

3.9.2.3 Serology

An HIV, HBsAg, and HCV screen will only be performed at the Screening Visit and results will be listed.

3.9.2.4 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]). Pregnancy test results will be listed.

3.9.2.5 Urine Drug Screen and Breath Alcohol Test

Results will be listed.

3.9.3 Vital Signs, Height and Weight

Vital signs, including heart rate, blood pressure, respiration rate, height, weight, and temperature will be measured and will be used to calculate BMI. Height will be measured with the subject's

[redacted]

shoes off. Weight will be measured with the subject's shoes off and after the subject's bladder has been emptied. Vital signs values, including change from baseline, will be summarized by treatment group at baseline and post-baseline scheduled visits and listed.

3.9.4 Electrocardiograms

All 12-lead ECGs will be performed in triplicate approximately 1 minute apart after the subject has been resting in the supine position for at least 10 minutes. The central overread ECG data will be utilized for all safety assessments and analyses.

ECG parameters to be analyzed include:

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

The triplicate measurements at each timepoint will be averaged for use as the timepoint's analysis value for the parameter. Baseline will be defined as the last analysis value prior to first dose of study drug. ECG parameters will be summarized by treatment group at baseline and at each post-baseline timepoint. Mean QTcF values by treatment group will also be plotted.

The following clinically meaningful changes from baseline (as defined by protocol Appendix C: Electrocardiogram Alert Criteria Guidance) will be summarized by treatment group:

- 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

3.9.5 Physical Examinations

Complete physical examinations will be performed and consist of general appearance, skin, head, eyes, ears, mouth, oropharynx, neck, heart, lungs, abdomen, extremities, and neuromuscular system. Brief limited physical examinations will also be performed and consist of a minimum of general appearance, skin, heart, lungs, and abdomen.

All complete and limited physical examination findings will be listed.

4 ANALYSIS TIMING

4.1 Interim Analysis

An independent DRC will review emerging safety, PK, and/or efficacy data throughout the study to determine if it is safe and appropriate to continue the study. No formal interim analysis is planned.

5 PROGRAMMING SPECIFICATIONS

5.1 Statistical Software

The creation of analysis datasets and all statistical analyses will be done using SAS Version 9.4 or higher. The Medpace standard operating procedures GL-DS-02 and GL-DS-03 will be followed for the generation and validation of all SAS programs and outputs.

Phoenix WinNonlin version 8.0 or higher will be used in the determination of the PK terminal phase and the calculation of PK parameters. PK parameters will also be calculated via SAS and verified with the Phoenix WinNonlin results.

5.2 Format

The format of tables, listings, and figures will be described in a stand-alone programming specifications document.