Title Page

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Safety and Efficacy of NG101 Administered Orally to Patients with Gastroparesis

Protocol Number: NG101-201

Amendment Number: Not applicable

Compound: NG101 (metopimazine mesylate)

Study Phase: 2

Acronym: Not applicable

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Regulatory Agency Identifier Number(s): [redacted]

Approval Date: 08 November 2019

Protocol Version: Original

Sponsor Signatory:

8 Nov 2019

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1.1. Synopsis

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Safety and Efficacy of NG101 Administered Orally to Patients with Gastroparesis

Rationale:

The purpose of this study is to evaluate the safety and efficacy of NG101 when administered orally across a range of doses to participants aged 18 years or older with diabetic or idiopathic gastroparesis. Results of this study will guide optimal dose selection for phase 3.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the efficacy of NG101 to reduce nausea severity in participants with gastroparesis • To evaluate the safety of NG101 in participants with gastroparesis	• Change from baseline at Weeks 7 through 12 in the nausea severity score in the Diabetic and Idiopathic Gastroparesis Symptoms daily diary (DIGS-DD). • Incidence and severity of treatment-emergent adverse events (TEAEs), treatment-emergent adverse events of special interest (TEAESIs), and treatment-emergent serious adverse events (TESAEs); evaluation of safety laboratory assessments, vital signs, electrocardiogram (ECG) results, and physical examination findings.
Secondary	
• To determine the efficacy of NG101 to: o Reduce the frequency and severity of vomiting o Reduce the symptom severity of early satiety, post-prandial fullness, and abdominal pain o Reduce the duration of nausea o Reduce the duration of abdominal pain o Reduce the overall severity of signs and symptoms of gastroparesis o Reduce the use of rescue medication	*Key Secondary Endpoints* • Change from baseline at Weeks 7 through 12 in the DIGS-DD: o Number of discrete episodes of vomiting o Early satiety severity score o Post-prandial fullness severity score o Abdominal pain severity score o Total severity score (nausea, early satiety, post-prandial fullness, abdominal pain)

	Additional Secondary Endpoints
	• Change from baseline at Weeks 7 through 12 in the:
	  o Number of hours of nausea per 24-hour period
	  o Number of hours of abdominal pain per 24-hour period
	• Change from baseline at Weeks 7 through 12 in the vomiting severity score
	• Percent of nausea-free days
	• Patient Global Impression of Severity (PGI-S) score
	• Patient Global Impression of Change (PGI-C) score
	• Change from baseline to Week 12 in:
	  o Patient Assessment of Upper Gastrointestinal Disorders (PAGI)-Symptoms (SYM)
	  o PAGI- quality of life (QOL)
	  o Total and subscale scores on the Nausea Profile (NP)
	• Change from baseline through Week 4 in each of the components of the DIGS-DD (nausea, vomiting, early satiety, post-prandial fullness, and abdominal pain)
	• Change from baseline in gastroparesis symptoms as measured by the Gastroparesis Cardinal Symptom Index daily diary (GCSI-DD)
	• Change from baseline in weekly Treatment Satisfaction score
	• Weekly use of rescue medication

• To evaluate the pharmacokinetics (PK) of NG101 • To evaluate the pharmacodynamic (PD) effects of NG101	• PK parameters • Prolactin levels at indicated timepoints
Exploratory Objectives	
• To evaluate the efficacy of NG101 to reduce the symptom severity of feeling of abdominal fullness and abdominal bloating • To evaluate the efficacy of NG101 to improve the symptom of nausea	• Change from baseline at Weeks 7 through 12 in the feeling of abdominal fullness severity score and in the abdominal bloating severity score • Level of improvement reported on the Nausea Improvement assessment

• Association of exposure and clinical response	• Association of PK parameters and changes in gastroparesis symptom PRO scores. • Association of PK parameters and safety assessments
• Additional analyses of clinical response in gastroparesis symptoms	• Achievement of threshold levels of improvement or worsening in each of the components of the DIGS-DD (nausea, vomiting, early satiety, post-prandial fullness, and abdominal pain) • Composite symptom severity scores
• Healthcare resource utilization	• Number of visits to healthcare providers
• Association of serum glucose with clinical response	• Association of serum glucose levels and HgbA1c with gastroparesis symptom PRO scores

Abbreviations: DIGS-DD = Diabetic and Idiopathic Gastroparesis Symptoms Daily Diary; ECG = electrocardiogram; GCSI-DD = Gastroparesis Cardinal Symptom Index Daily Diary; PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders -Symptoms Questionnaire; PAGI-QOL = Patient Assessment of Upper Gastrointestinal Disorders -Quality of Life; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcomes; TEAEs = treatment-emergent adverse events; TEAESIs = treatment-emergent adverse events of special interest; TESAEs = treatment-emergent serious adverse events.

Overall Design

This is a randomized, double-blind, parallel-group (4 arms), placebo-controlled, multicenter study to evaluate the safety and efficacy of 3 dose levels of NG101 compared with placebo in participants with diabetic or idiopathic gastroparesis.

Following a Screening Period of up to 4-weeks, eligible participants will enter a 2-week Pretreatment Period, during which time they will complete specified gastroparesis symptom assessments to establish baseline data and to determine compliance with completion of these assessments. Following completion of the Pretreatment Period, a participant's randomization eligibility will be determined (based on all inclusion/exclusion criteria, including the participant's compliance with eDiary completion).

Participants who do not initially meet study screening criteria (ie, are screen failures) may be rescreened (no more than 1 additional screening) after consultation with and approval by the sponsor. A participant's eligibility for the study must be confirmed by the sponsor's Medical Monitor, or designee, prior to randomization.

Participants eligible for the clinical study will be randomized in a 1:1:1:1 ratio to receive either NG101 treatment arms of 5 mg, 10 mg, or 20 mg, or matching placebo during a 12-week Treatment Period. Randomization will be stratified on the following factors: gastroparesis etiology (diabetes vs idiopathic), sex (male vs female), and cannabinoid use (yes vs no). Determination of diabetes etiology will be done according to the medical history data at Screening.

Two weeks following the Week 12 Visit, participants will return to the clinic for an End of Study (EoS) Visit / Follow-up Visit.

If a participant permanently discontinues study medication (for any reason) prior to the Week 12 Visit, the participant must attend the Early Discontinuation Visit as soon as possible, and then the Safety Follow-up Visit 2 weeks later.

Study Assessments:

Study assessments will be performed at the times specified in the Schedule of Activities (SoA – see Section 1.3).

The primary efficacy objective is to determine the efficacy of NG101 to reduce nausea severity in participants with gastroparesis. The primary endpoint is the change from baseline at Weeks 7 through 12 for the nausea severity score in the Diabetic and Idiopathic Gastroparesis Symptoms Daily Diary (DIGS-DD). Key secondary efficacy endpoints will also be assessed by the DIGS-DD and include changes from baseline at Weeks 7 through 12 in the DIGS-DD number of discrete episodes of vomiting, early satiety severity score, post-prandial fullness severity score, abdominal pain severity score, and total severity score (nausea, early satiety, post-prandial fullness, abdominal pain). An eDiary will be used to collect information for the primary and key secondary endpoints.

In addition, blood samples will be obtained from all participants to measure plasma levels of metopimazine and metopimazine acid following single-dose administration (Day 1) and at steady-state after multiple-dose administration (Week 2). Blood samples for PK will be collected at the Day 1 and Week 2 visits for all participants (up to 3 hours after the first dose on each occasion). In a subset of participants (8 to 10 participants per treatment arm; 32 to 40 participants total), intensive sampling will be performed (up to 6 hours after the first dose at the Day 1 and Week 2 visits, as well as 1 and 2 hours after the second dose at the Day 1 visit).

Disclosure Statement:

This is a parallel group treatment study with 4 arms that is participant, investigator, and sponsor blinded.

Number of Participants:

A total of approximately 280 participants will be randomized to achieve an estimated 224 participants completing the 12-week Treatment Period (and approximately 56 participants per treatment arm). At least 120 randomized participants will have diabetic gastroparesis and at least 120 randomized participants will have idiopathic gastroparesis. Up to approximately 140 participants can be cannabinoid users, and of these, up to approximately 56 can be marijuana users.

Intervention Groups and Duration:

The total duration of the study for each participant will be approximately 20 weeks.

On Day 1 of the Treatment Period, eligible participants will be randomized in a 1:1:1:1 ratio to receive either NG101 5 mg, 10 mg, or 20 mg, or matching placebo. Study drug will be administered orally 4 times per day (QID) for 12 weeks. The 20 mg arm will initiate dosing on

Day 1 with 5 mg QID for 4 days, followed by 10 mg QID for 3 days, and then 20 mg QID through Week 12. No titration will occur in the 5 mg and 10 mg arms.

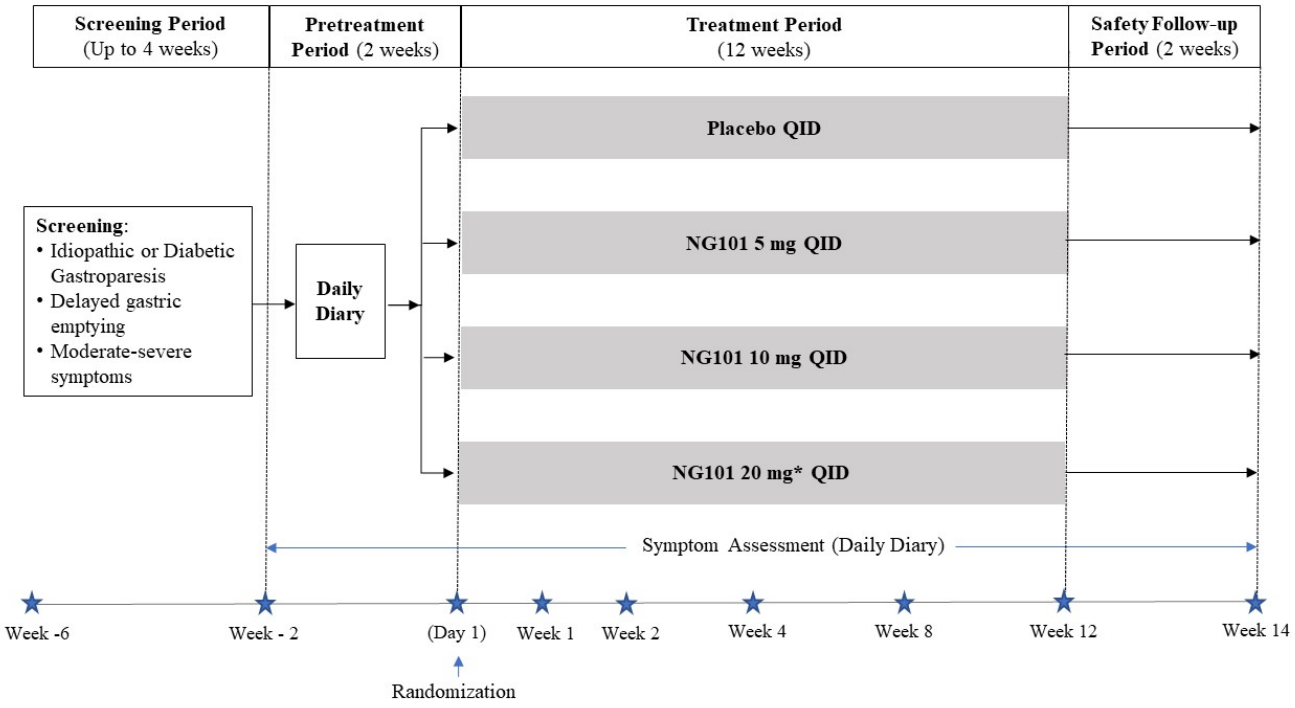
The study drug should be taken by participants approximately 30 minutes before a meal 3 times a day and 30 minutes before bedtime, with a minimum interval of 4 hours between doses.

Data Monitoring Committee and Data Safety Monitoring Board:

A Data Monitoring Committee (DMC) comprised of representatives from the sponsor and CRO will review blinded data on an ongoing basis.

An unblinded independent safety review conducted by a Data Safety Monitoring Board (DSMB) will be triggered if any of the following conditions are met: 3 or more participants in the study exhibit extrapyramidal symptoms (EPS); 1 or more participants have neuroleptic malignant syndrome (NMS); 3 or more participants are discontinued due to orthostatic hypotension-related adverse events (AEs); other events considered of high clinical significance by the sponsor are observed. The DSMB will then make any recommendations to the sponsor regarding conduct of the study.

1.2. Schema



Primary endpoint: Change from baseline in the nausea severity score in the Diabetic and Idiopathic Gastroparesis Symptoms daily diary (DIGS-DD)

★ Clinic visit

* The 20 mg arm will initiate dosing with 5 mg QID for 4 days, followed by 10 mg QID for 3 days, and then (starting on Day 8) 20 mg QID

1.3. Schedule of Activities (SoA)

Procedure	Screening Visit (up to 28 days before Day –14)	Pre-treatment Visit Day -17 to -14	Treatment Period Visits Day 1	Week 1 (± 2d)	Week 2 (± 2d)	Week 4 (± 2d)	Week 8 (± 3d)	Week 12 (± 3d)	E/D Visit	EoS / Follow-up Visit (14 ± 3 days after last dose)	Notes
Informed consent	X										
Inclusion and exclusion criteria	X		X								Recheck clinical status / check compliance before randomization on Day 1
Demography	X										
Medical history	X										Including prior treatments for gastroparesis (dose, regimen, duration), substance use and, for females, menstrual history
Gastric emptying test	X										FDA-approved breath test completed and assessed for eligibility in participants who have not completed the breath test or scintigraphy test within 12 months prior to Screening, or during the Screening Period. Must be a minimum of 7 days between the gastric emptying study and the start of the Pretreatment Period.

Procedure	Screening Visit (up to 28 days before Day –14)	Pre-treatment Visit Day -17 to -14	Treatment Period Visits Day 1	Week 1 (± 2d)	Week 2 (± 2d)	Week 4 (± 2d)	Week 8 (± 3d)	Week 12 (± 3d)	E/D Visit	EoS / Follow-up Visit (14 ± 3 days after last dose)	Notes
Physical examination	X		X			X	X	X	X	X	A physical exam including neurologic, cardiovascular, pulmonary, abdominal and breast exams will be performed at Screening, Day 1, and Weeks 4, 8, and 12 (or E/D) as well as at the Follow-up Visit. Height will be measured on Day 1. For females, menstrual cycle will be recorded during the study.
Weight	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	Vital signs include oral temperature, pulse rate, respiratory rate, and blood pressure. Orthostatic vital signs will also be checked at Screening, and at the Day 1, Week 1, and Week 2 visits. See Section 8.4.2

Procedure	Screening Visit (up to 28 days before Day –14)	Pre-treatment Visit Day -17 to -14	Treatment Period Visits Day 1	Week 1 (± 2d)	Week 2 (± 2d)	Week 4 (± 2d)	Week 8 (± 3d)	Week 12 (± 3d)	E/D Visit	EoS / Follow-up Visit (14 ± 3 days after last dose)	Notes
12-lead ECG	X		X		X			X	X	X	On Day 1 and Week 2, ECGs will be performed in triplicate at the time of PK sampling (ie, predose and at 1 [near anticipated T_{max}], 2, and 3 hours postdose). For the Intensive PK subset, in addition to the ECG assessments described above, triplicate ECGs should be taken at hour 6 (on Day 1 and Week 2) as well as 1 and 2 hours after the second dose at the Day 1 visit. See Section 8.4.3.
HIV, Hepatitis B and C screening	X										
Thyroid stimulating hormone (TSH)	X										If TSH is above the upper limit of normal, then free T4 will be checked
Estimated glomerular filtration rate (eGFR)	X										eGFR will be calculated using Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation. See Appendix 10.7.
Serum pregnancy test (WOCBP only)	X										
Testosterone (males only)	X										If testosterone is below the lower limit of normal, the participant is excluded.

Procedure	Screening Visit (up to 28 days before Day –14)	Pre-treatment Visit Day -17 to -14	Treatment Period Visits Day 1	Week 1 (± 2d)	Week 2 (± 2d)	Week 4 (± 2d)	Week 8 (± 3d)	Week 12 (± 3d)	E/D Visit	EoS / Follow-up Visit (14 ± 3 days after last dose)	Notes
Urine pregnancy test (WOCBP only)			X			X	X	X	X	X	
Urine sample for drug test	X							X	X		
Blood and urine sample for safety laboratory assessments	X		X	X	X	X	X	X	X	X	Hematology and Serum Chemistry – see Appendix 10.3. Blood samples should be drawn prior to dosing on Day 1 and Week 2.
Serum prolactin	X		X		X			X	X	X	Blood samples for prolactin will be drawn at Screening, prior to dosing on Day 1, Week 2 and Week 12, as well as 1-hour after dosing. For the Intensive PK subset, in addition to the samples described above, blood samples will also be drawn 2, 3 and 6 hours after dosing on Day 1 and Week 2. One sample will also be taken at the EoS / Follow-up visit for all participants. See Section 8.8., Table 5
HgbA1c	X		X					X	X		
Blood sample for genetic testing (optional)			X								Where permitted and in participants who consent.
Randomization			X								

Procedure	Screening Visit (up to 28 days before Day –14)	Pre-treatment Visit Day -17 to -14	Treatment Period Visits Day 1	Week 1 (± 2d)	Week 2 (± 2d)	Week 4 (± 2d)	Week 8 (± 3d)	Week 12 (± 3d)	E/D Visit	EoS / Follow-up Visit (14 ± 3 days after last dose)	Notes
Dispense study drug			X	X	X	X	X				Compliance with study drug use will be assessed at each visit.
Dispense rescue medication			X	X	X	X	X				Compliance with rescue medication use will be assessed at each visit.
Study medication			←	—	—	—	—	→			4 × per day (QID) The study drug should be taken approximately 30 minutes before a meal 3 times a day and 30 minutes before bedtime, with a minimum interval of 4 hours between doses. *Day 1:* first dose in clinic, and second dose in clinic for Intense PK subset *Week 1:* a dose in clinic *Week 2:* first dose of the day in clinic *Week 12:* a dose in clinic See Section 6.1.
Healthcare resource utilization			←	—	—	—	—	→			See Section 8.12.
AE / SAE review	←	—	—	—	—	—	—	—	—	→	See Section 8.5.
Concomitant medication review	←	—	—	—	—	—	—	—	—	→	Including cannabinoid use

Procedure	Screening Visit (up to 28 days before Day –14)	Pre-treatment Visit Day -17 to -14	Treatment Period Visits Day 1	Week 1 (± 2d)	Week 2 (± 2d)	Week 4 (± 2d)	Week 8 (± 3d)	Week 12 (± 3d)	E/D Visit	EoS / Follow-up Visit (14 ± 3 days after last dose)	Notes
DIGS-DD and Gastroparesis additional daily assessments		←	———	———	———	———	———	———	———	→	Completed once daily at the same time each day. Compliance with completion of the daily diary will be assessed at each visit.
PGI-S, PGI-C and Treatment Satisfaction Assessment		←	———	———	———	———	———	———	———	→	Completed once weekly on the 7th day of the week. PGI-C and Treatment Satisfaction will be completed after Day 1
GCSI-DD assessment		X						X*			The GCSI-DD is completed once daily during the Pretreatment Period, and *daily during the last week of the Treatment Period (participant will receive the GCSI-DD beginning the day after completing the Week 11 PRO's).
PAGI-SYM, PAGI-QOL, Nausea Profile,			X		X	X	X	X	X	X	At relevant visits, these assessments should be completed first before any other assessments/examinations are completed.
Nausea Improvement Assessment								X	X		Completed once at the end of the study.

Procedure	Screening Visit (up to 28 days before Day –14)	Pre-treatment Visit Day -17 to -14	Treatment Period Visits Day 1	Week 1 (± 2d)	Week 2 (± 2d)	Week 4 (± 2d)	Week 8 (± 3d)	Week 12 (± 3d)	E/D Visit	EoS / Follow-up Visit (14 ± 3 days after last dose)	Notes
Blood sample(s) for plasma drug concentration			X		X						Blood samples for PK will be collected at the Day 1 and Week 2 visits for all participants within 15 to 20 minutes prior to the first dose of study medication of the day and 1, 2 and 3 hours after the first dose. In a subset of participants, intensive sampling will be performed at the Day 1 and Week 2 visits within 15 to 20 minutes prior to the first dose of study medication and at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours after the first dose. At the Day 1 visit, additional samples will be collected 1 and 2 hours after the second dose. See Section 8.7.1, Table 4.

Abbreviations: AE = adverse event; ECG = electrocardiogram; E/D = early discontinuation; eGFR = estimated glomerular filtration rate; EoS = end of study; FDA = Food and Drug Administration; GCSI-DD = Gastroparesis Cardinal Symptom Index – Daily Diary; HIV = human immunodeficiency virus; PAGI-QOL = patient assessment of upper gastrointestinal disorders-quality of life; PAGI-SYM = patient assessment of upper gastrointestinal disorders-symptom severity index; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); PRO = patient-reported outcome(s); QID = four times per day; SAE = serious adverse event; TSH = thyroid stimulating hormone; WOCBP = women of child-bearing potential.

2. Introduction

NG101 is a potent and selective, peripherally-restricted (ie, very limited ability to penetrate the brain), human Ether-à-go-go-related gene (hERG) negative (ie, no hERG inhibition at expected human plasma exposures), dopamine D_2/D_3 receptor antagonist being evaluated for the treatment of gastroparesis. It is also an antagonist with lower affinity for dopamine D_1, adrenergic alpha-1, histamine H_1, and serotonin 5-HT_{2A}/5-HT_{2B} receptors.

2.1. Nonclinical

A complete battery of studies has been conducted to support the safety of the proposed clinical trial in accordance with International Conference of Harmonisation (ICH) M3(R2). Based upon the metabolism and pharmacologic properties of NG101, the rat and dog were considered appropriate models for pivotal nonclinical safety studies. NG101 was administered by the oral route in pivotal toxicology studies, as it is the intended route of administration for clinical trials and marketing.

Briefly, the nonclinical program confirmed that metopimazine (tested as NG101) is a P-glycoprotein substrate with limited penetration of the blood-brain barrier. NG101 is not metabolized via the cytochrome P450 pathway, thereby minimizing potential for drug-drug interactions. Unlike domperidone, NG101 does not produce hERG channel inhibition at expected human plasma exposures. There is a > 100-fold window between expected free plasma concentrations in the proposed Phase 2 study and the hERG half maximal inhibitory concentration (IC50) determined in vitro. Nonclinical studies also demonstrated that metopimazine acid has > 100-fold lower affinity to D_2 and D_3 receptors as compared to the parent drug metopimazine.

Effects seen in the toxicology studies were anticipated given the mechanism of action of metopimazine, and are able to be monitored in the clinic. These include effects related to increased prolactin levels (see Section 2.5.1).

See the NG101 Investigator's Brochure (IB) for further details.

2.2. Clinical Experience

2.2.1. Phase 1 Studies

Two phase 1 studies have been conducted by the sponsor with metopimazine in healthy volunteers: Study NG100-101 and Study NG101-102. A summary of both studies is provided below and further details can be found in the NG101 IB.

2.2.1.1. Study NG100-101 (SAD / MAD Study)

Study Design

Study NG100-101 was a phase 1 double-blind, placebo-controlled, single-ascending and multiple-ascending dose (SAD and MAD) study of the safety, tolerability, and PK of metopimazine administered orally to healthy adult participants ages 18 to 45 years at a single study center in France. The investigational medicinal product administered in this study was the French approved and marketed brand of metopimazine, Vogalene.

In the SAD portion of the study a total of 4 cohorts were enrolled and single ascending doses of 15, 30, 45, and 60 mg were tested. A total of 32 participants (16 females, 16 males) were randomized, and all participants completed the SAD portion of the study.

In the MAD portion of the study, sequential multiple-ascending doses were evaluated in 3 cohorts of 8 participants. Dosing regimens of 15, 30, and 45 mg, were administered every 6 hours (Q6H) for 5 days, followed by a single dose on Day 6. A total of 24 participants (12 females, 12 males) were randomized, and 23 participants completed part 2 (12 females, 11 males).

Results

Pharmacokinetics

Following dosing with metopimazine, maximum plasma concentration (C_{max}) occurred at a median time of 0.8 to 1.1 hours after dosing with median lag time from 0.1 to 0.25 hours after dosing. A high inter-individual variability was observed for C_{max} of metopimazine with coefficient of variations (%CV) ranging from 46 to 75%. The area under the plasma concentration-time curve (AUC) from time 0 to infinity ($AUC_{0\text{-}inf}$) and derived pharmacokinetic (PK) parameters of metopimazine (terminal half-life [$t_{1/2}$], total clearance [Cl/F] and Vz/F) could be estimated at doses of 30 mg and above. The mean $t_{1/2}$ ranged from 2 to 2.3 hours, Vz/F ranged from 430 to 860 L and Cl/F ranged from 170.5 to 335 L/h. Mean PK parameters of metopimazine showed an increase of C_{max} and AUC with dose from 15 to 60 mg. However, dose proportionality may have been obscured by inter-subject variability. Mean PK parameters increased with higher doses in a manner that was close to dose-proportional over a dose range of 15 to 60 mg for single doses and 15 to 45 mg for multiple doses.

Following administration of multiple doses every 6 hours (Q6H), steady-state conditions appeared to be reached by the end of Day 1. After continued Q6H dosing through Day 6, metopimazine accumulated 30 to 40% based on AUC.

Metopimazine was rapidly metabolized to metopimazine acid, with metopimazine acid C_{max} occurring at median times ranging from 2 to 3 hours after dosing across cohorts. The mean metopimazine acid elimination $t_{1/2}$ ranged from 2.7 to 3.5 hours. Relative to parent metopimazine, plasma metopimazine acid exposure was generally 3- to 4-fold higher for C_{max} and 6- to 11-fold higher for AUC. For metopimazine, a close to dose proportional increase was observed for C_{max}, AUC from time 0 to the last measurable concentration ($AUC_{0\text{-}last}$) and $AUC_{0\text{-}inf}$. Accumulation of metopimazine acid was observed after repeated doses (Q6H) with a mean accumulation ratio of 1.6 to 1.7 based on C_{max} and 1.7 to 1.9 based on $AUC_{0\text{-}6}$.

Safety

No serious adverse events (SAEs) were observed during the study, and no participants withdrew due to adverse events (AEs). All adverse events (AEs) were reported to be mild or moderate in severity. No symptoms suggestive of neuroleptic malignant syndrome (NMS) or extrapyramidal symptoms (EPS) were observed and there were no clinically relevant changes in electrocardiogram (ECG) time intervals. No notable trends were observed in changes in laboratory tests.

An increased risk of orthostatic hypotension (OH) was observed with metopimazine, likely due to inhibition of peripheral adrenergic alpha-1 receptors. Orthostatic changes in vital signs considered to be clinically significant were defined as a decrease in systolic or diastolic blood pressure (BP) of at least 20 mm Hg or 10 mm Hg, respectively, or heart rate increase of at least 30 beats/minute and/or heart rate above 120 beats/minute (Freeman et al. 2011; NIH-NINDS Postural Tachycardia Syndrome Information Page 2019).

In the 15 mg and 30 mg groups of the SAD portion of the study, 1 to 2 participants (out of 6 in each dose group) were reported to have “dizziness in standing position”. No vital sign measurements were obtained at the time of these events; however, the preferred term of OH was recorded. A protocol amendment was implemented after cohort 2 (30 mg) of the SAD portion of the study to require vital sign measurements lying, sitting, and standing at prescribed timepoints after dosing. In the 45 mg and 60 mg groups of the SAD, 4 participants (out of 6 in each dose group) experienced OH.

Two participants in the MAD 15 mg Q6H group experienced OH (on Day 1 at Hour 1 after the first dose) and 1 participant in the MAD 30 mg Q6H group experienced OH (on Day 1 at Hour 1 after the first dose). No other episodes of OH occurred with subsequent dosing in these participants, and no other participants in these dose groups experienced OH. On the other hand, most participants in the MAD 45 mg Q6H group experienced OH, and more than half experienced episodes on multiple days during the dosing period. A similar trend was noted for orthostatic tachycardia.

Based on these results, the risk of OH appeared to be dose dependent, with the 45 mg and 60 mg doses associated with a higher risk for OH than the 15 mg and 30 mg doses. These data also suggest that with repeat dosing, participants adapt to the alpha-adrenergic inhibition, which is consistent with the literature on alpha-1 receptor antagonists approved for use in hypertension and benign prostatic hyperplasia (Achari et al. 1998).

2.2.1.2. Study NG101-102 (Comparative PK Study)

Study Design

Study NG101-102 was a phase 1 two-cohort, partial crossover, open-label, randomized, single-dose study to assess the relative bioavailability between NG101 (metopimazine mesylate) and the reference metopimazine formulation (Vogalene) in healthy participants at a single study center in France. The NG101 dose (15 mg) for Cohort 2 of the study was determined from the PK results from Cohort 1 of the study. The reference metopimazine was administered either orally as a 15 mg capsule or via a diluted intravenous (IV) infusion of a 10 mg/mL solution administered as 7.5 mg over 60 minutes.

Cohort 1 was a 3-period, partial crossover in the fasted state with 3 administrations of NG101 7.5 mg PO, Vogalene 15 mg PO, or Vogalene 7.5 mg IV. There was a wash-out period of 48 hours between each administration. A total of 8 participants were enrolled and received each of the 3 treatments.

Cohort 2 was a 3-period, cross-over design with 3 administrations of 15 mg of each of the following: oral formulation of NG101 fasting, oral formulation of NG101 after a high-fat breakfast, oral formulation of the reference metopimazine fasting. There was a wash-out period of 48 hours between each administration. Fifteen participants were enrolled and received each of the 3 treatments.

Results

Relative Bioavailability and Food Effect

Based upon geometric least squares mean ratio, preliminary estimates of the relative bioavailability of NG101 compared to Vogalene, each under fasting conditions, were 109% for AUC_{last} and 86.4% for C_{max}, but the 90% confidence intervals (CIs) were too wide to conclude equivalence. A high degree of inter-subject variability was observed for these PK parameters and several participants had plasma concentrations below the limit of quantification (5 ng/mL) within the first 6 hours after dosing. An elimination $t_{1/2}$ for metopimazine could not be determined for any participant; therefore, $AUC_{0\text{-}inf}$ could not be calculated. Given that the time of last measurable plasma metopimazine concentration varied within participants for the different study treatments, an additional exploratory PK in which AUC_{last} was uniformly truncated at the time of last measurable concentration showed a relative bioavailability of 98%. For metopimazine acid, the 2 formulations met bioequivalence criteria with geometric mean ratios of 92.2% and 93.1% for AUC_{last} and C_{max} respectively.

Overall, NG101 provided generally similar exposure to metopimazine compared to Vogalene under fasting conditions, although the current limit of quantification for metopimazine (5 ng/mL) limited some of the PK objectives.

For metopimazine, administration of NG101 with a high-fat breakfast resulted in an approximate 15% reduction in C_{max} and an approximate 5% reduction in AUC_{last} with 90% CIs outside of the bioequivalence range. An additional exploratory PK analysis was performed in which AUC_{last} was uniformly truncated at the time of last measurable concentration for each participant, which showed a 12% reduction in AUC_{last} with a high-fat breakfast. For metopimazine acid, NG101 given with a high fat breakfast resulted in a 30% reduction in C_{max} and a 27% reduction in AUC_{last}. Overall, these PK differences are unlikely to be of clinical significance.

Pharmacokinetics

For the NG101 7.5 mg dose, few timepoints after C_{max} were quantifiable above the limit of quantification (5 ng/mL) with the time of the last measurable concentration (T_{last}) ranging from 1.25 to 2 hours. As such, the terminal elimination rate constant (Lambda z) and the derived parameters ($t_{1/2}$, AUC_{inf}, Cl/F and Vd/F) could not be reliably determined. For the 15 mg Vogalene dose, T_{last} ranged from 2 to 6 hours and terminal $t_{1/2}$ for metopimazine was determined for 2/6 participants.

For Cohort 1, the dose-adjusted metopimazine C_{max} for participants administered NG101 was similar compared to those administered Vogalene. Based on AUC_{last}, NG101 appeared to result

in approximately 50% lower and absolute relative bioavailability; however, this determination was influenced by the duration of quantifiable metopimazine exposure. When the AUC was limited uniformly to 2 hours post-dose, metopimazine dose-adjusted AUC in participants administered NG101 was approximately 91% compared to those administered Vogalene. For the metopimazine acid metabolite, the relative bioavailability based on dose-adjusted AUC_{last} was approximately 86%. The absolute bioavailability of Vogalene was approximately 19% (also based on AUC_{last}), which is consistent with published studies (Herrstedt et al. 1990). The results from Cohort 1 indicated that plasma metopimazine exposure for NG101 was generally similar compared to Vogalene and an NG101 dose of 15 mg was selected for Cohort 2.

Following oral administration of 15 mg of metopimazine as NG101 in fasted conditions, metopimazine plasma peaks occurred at a median time of 0.75 hours after dosing. Mean metopimazine C_{max} and $AUC_{0\text{-}last}$ values were 20.6 ng/mL and 39.9 ng.h/mL, respectively. A lag time of 0.25 hours (median) was observed after dosing. The terminal elimination rate constant (Lambda z) and the derived parameters ($t_{1/2}$, AUC_{inf}, Cl/F and Vd/F) could not be reliably determined. A high inter-individual variability was observed with %CV between 60.4 and 82.6%. Metopimazine C_{max} and $AUC_{0\text{-}2h}$ appeared to be approximately dose proportional between the 7.5 mg dose of NG101 in Cohort 1 and the 15 mg dose in Cohort 2.

Safety

No serious adverse events (SAEs) were observed during the study, and no participants withdrew due to adverse events (AEs). All adverse events (AEs) were reported to be mild or moderate in severity. In each of the three 15-participant treatment groups, 2 to 4 participants reported AEs that were related to postural change (consistent with results observed in the SAD / MAD study). However, no consistent pattern was observed within individual participants across the treatments (ie, some participants had the AEs with 1 treatment but not another). A small increased risk of orthostatic related AEs was observed upon fasting (ie, 3 fasting versus 1 fed). All OH events occurred at 1 hour after dosing, with the exception of 1 OH event that occurred at hour 8. There were no other trends indicative of clinically important treatment-related laboratory abnormalities.

2.2.2. Previous Human Experience

Metopimazine (Vogalene®) has been used extensively as an antiemetic for over 40 years in France. In a dose-ranging open-label safety and tolerability study involving 38 patients undergoing chemotherapy, metopimazine was administered orally every 4 hours at increasing doses (Herrstedt et al. 1997a). A total of 36 patients completing 46 cycles of chemotherapy received 20, 30, 40, 50 and 60 mg oral metopimazine every 4 hours over a 44-hour period. The metopimazine dose-limiting toxicity was moderate to severe dizziness caused by OH, as seen in 0, 0, 17%, 42% and 50% of the patients at the respective dose levels. No information was provided on the timing of the occurrence of dizziness during the 44-hour period. Few other side effects were reported, and most were mild. A single possible extrapyramidal AE was observed in a patient in the 60 mg x 11 dose group. Metopimazine was demonstrated to be safe at a dosage of 30 mg, 6 times (180 mg) daily.

Further, in a randomized, double-blind comparison of ondansetron vs ondansetron plus metopimazine as antiemetic prophylaxis during platinum-based chemotherapy in patients with cancer, metopimazine was administered at 35 mg/m^2 IV followed by 30 mg, 4 times a

day (120 mg daily), for 4 days. A total of 94 patients completed the crossover study. Results suggested that metopimazine plus ondansetron was significantly superior to ondansetron alone on all efficacy parameters assessed. Reported adverse reactions were mild and without significant differences between the 2 treatments. However, an asymptomatic decrease in standing BP was observed when patients received the combination antiemetic therapy (Herrstedt et al. 1997a).

In a randomized, double-blind trial assessing the efficacy and safety of sublingual metopimazine compared to ondansetron in chemotherapy-induced delayed emesis, patients received either 45 mg/day of metopimazine (15 mg every 8 hours) or 16 mg/day of ondansetron (8 mg every 12 hours). Metopimazine was comparable in efficacy to ondansetron. Furthermore, the incidence of gastrointestinal (GI) disorders was significantly lower in the metopimazine group, particularly abdominal pain and constipation (Herrstedt et al. 1997b; Bethune-Volters et al. 2006).

Since metopimazine market approval as an antiemetic in France (10 January 1977), a number of other open-label or randomized, placebo-controlled efficacy studies involving oral or IV administration of metopimazine have been published. These studies conclude that metopimazine is safe and well tolerated with no reports of severe central nervous system (CNS) or cardiovascular (CV) AEs (Paradis and Brault 1967; Guerin et al. 1969; Arbus and Parente 1971; Berry et al. 1971; Arnaud and Sportouch 1972; Bertrand and Thillier 1975; Barale et al. 1977; Israel 1978; Rodary et al. 1979; Ballester et al 1980; Gosselin et al 1981; Badji et al 1988; Herrstedt et al. 1990; Herrstedt et al. 1997b; Lebeau et al. 1997; Sigsgaard et al. 2001; Croom and Keating 2006).

Generally, studies in chemotherapy-induced nausea and vomiting suggest that doses of metopimazine higher than approved for common nausea and vomiting conditions tend to be more efficacious while remaining safe and well tolerated. Doses ranging from 45 to 120 mg per day were evaluated in these studies (Israel and Rodary 1978; Herrstedt et al. 1997b; Lebeau et al. 1997; Sigsgaard et al. 2001; Bethune-Volters et al. 2006).

2.3. Study Rationale

The purpose of this study is to evaluate the safety and efficacy of NG101 when administered orally across a range of 3 doses to participants aged 18 years or older with diabetic or idiopathic gastroparesis. Results of this study will guide optimal dose selection for phase 3.

2.4. Background

Gastroparesis is a chronic disorder of the stomach characterized by delayed gastric emptying without evidence of mechanical obstruction (Camilleri et al. 2013; Stein et al. 2015). The core set of symptoms of gastroparesis include nausea, vomiting, early satiety, post-prandial fullness, and abdominal pain (Food and Drug Administration [FDA] 2019; Camilleri et al. 2013). The most common etiologies of gastroparesis are of idiopathic and diabetic origin (Parkman 2018; Camilleri et al. 2013). While the overall incidence of gastroparesis is not well understood, the 10-year incidence in Olmsted County Minnesota, United States (US), was 5.2% in patients with type 1 diabetes, 1% in patients with type 2 diabetes, and 0.2% among non-diabetic controls (Choung et al. 2012). Evidence suggests gastroparesis is associated with increased healthcare costs, including an increased frequency of hospitalizations (Wadhwa et al. 2017;

Camilleri et al. 2013). Overall, gastroparesis adversely affects the lives of patients, and there is urgent need to develop treatments with a favorable risk-benefit profile.

Neurogastrx, Inc. is developing NG101, a mesylate salt of metopimazine, a potent and selective, peripherally-restricted (ie, very limited ability to penetrate the brain), hERG negative (ie, no hERG inhibition at expected human plasma exposures), dopamine D_2/D_3 receptor antagonist for the treatment of gastroparesis. Metopimazine (oral capsules, orally disintegrating tablet, suppositories, liquid drops or syrup) has been approved in France for over 40 years under the current trade name Vogalene® (15 mg oral capsule; 7.5 mg orally disintegrating tablet) for the short-term symptomatic treatment of nausea and vomiting. An IV formulation (10 mg) is approved and is almost exclusively used for the treatment of chemotherapy-induced nausea and vomiting in adults and children. The vast majority of prescriptions for adults and infants / children are for seasonal gastroenteritis or acute nausea and vomiting of various etiologies. Metopimazine is also available as an over-the-counter medication (Vogalib®, 7.5 mg orally disintegrating tablets).

Dopamine antagonism has been well validated as an effective treatment for gastroparesis. Metoclopramide and domperidone, existing D_2 antagonists, have gastroprokinetic properties as well as anti-nausea/anti-emetic effects. However, these agents are associated with limiting CNS and CV side effects, respectively. Although metopimazine belongs to the chemical family of phenothiazines (most of which are associated with CNS and/or CV side effects), its use is rarely associated with CNS side effects, and has not been associated with significant cardiac risk when used at the current marketed doses in France. As such, NG101 is a promising candidate for the treatment of gastroparesis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of metopimazine is provided in the NG101 IB.

2.5. Benefit / Risk Assessment

A summary of the benefit-risk assessment for conducting Study NG101-201 is provided in the following sections (Section 2.5.1, Section 2.5.2, and Section 2.5.3).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of NG101 may be found in the IB.

2.5.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Study Drug		
Orthostatic hypotension (OH)	OH has been observed in the phase 1 studies with metopimazine free base (Vogalene) and NG101. This is likely due to partial alpha-1 receptor inhibition.	*Exclusion criterion:* Participants with severe postural symptoms and/or absolute systolic BP < 90 mm Hg upon standing. *Monitoring:* During the study, participants will be observed in the clinic on Day 1 for 3 hours after taking the first dose of NG101 (approximately 1 to 2 hours after the time of maximum concentration [T_{max}]). At the Week 1 and Week 2 visits, participants will be observed for 2 and 3 hours after dosing, respectively. Participants will have hourly orthostatic BP and AE assessments while in the clinic for these visits. Participants who have systolic BP that decreases at least 20 mm Hg upon standing, and who have concomitant postural AEs during study visits will be further assessed in the clinic and/or after returning home. Postural AEs can include feelings of lightheadedness, general weakness, warmth, diaphoresis, nausea, palpitations or blurry vision (Whitledge et al. 2019). If, in the investigator's judgement, a participant's postural symptoms constitute a safety risk of potential harm upon release from the clinic, that participant will remain in the clinic under observation (beyond the scheduled observation on Day 1 and Weeks 1 and 2) with continued orthostatic BP and AE assessments. If the participant has persistent moderately symptomatic OH through the 6-hour dosing interval, or the investigator has significant concern that BP decreases and postural symptoms will recur upon subsequent dosing, the participant should receive the next dose under observation in the clinic. If, in the investigator's medical judgement, the participant continues to be at significant risk of harm with continued dosing upon release from clinic, that participant will be stopped and withdrawn from the study. Otherwise, once the participant is asymptomatic for OH on 2 successive measurements, the participant may be released from the clinic, and will be contacted by phone after returning home that day, and on subsequent days as necessary, to monitor for

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
		continued AEs. Participants with recurrent postural AEs on subsequent days will return to the study site for further evaluation. *Individual stopping criteria*: Participants with OH (defined by a decrease in systolic BP of at least 20 mm Hg) and associated severe postural symptoms will be stopped and withdrawn from the study. These severe symptoms include presyncope, syncope, and other severe AEs that are considered of substantial clinical relevance by the investigator. Presyncope is defined as "feeling like one was going to pass out but without actual loss of consciousness" (Whitledge et al. 2019). Syncope is "the sudden loss of consciousness, associated with inability to maintain postural tone, with immediate and spontaneous recovery without requiring electrical or chemical cardioversion" (da Silva 2014). Participants meeting this discontinuation criterion while under observation during clinical visits must be monitored in the clinic until postural symptoms are no longer severe, and will be withdrawn from the study. Participants who develop severe postural symptoms at home will hold any further dosing and return to the study site as soon as possible for further evaluation. *Other mitigation:* Participants in the 20 mg treatment arm will be initiated with a dose titration, beginning with daily dosing with 5 mg 4 times daily (QID). Repeated dosing is associated with counter regulation to alpha blockade and reduction in blood pressure effects. Participants will be trained to recognize signs and symptoms of OH, and how to manage it should it occur. For the first 24 hours of dosing, participants should avoid situations in which injury might occur (eg, driving) should there be orthostatic symptoms.
Neuroleptic malignant syndrome (NMS)	Observed within the class of D_2 antagonists	As a Pg-P substrate, metopimazine is not expected to have significant penetration of the CNS. Nevertheless, clinical assessment for early detection of NMS will be included in the study.

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Hyperprolactinemia-related effects, including gynecomastia, galactorrhea, menstrual irregularities, impotence, and decreased libido	Dopamine blockade is associated with increases in serum prolactin levels.	Clinical assessment for prolactin-related AEs.
Extrapyramidal symptoms (EPS)	EPS is associated with centrally acting dopamine blockade. NG101 has low penetration of the blood brain barrier, and thus low risk for EPS.	Clinical assessment for EPS.
Study Procedures		
Minimal risk from blood draws.	Blood draws are standard procedures in clinical trials.	Standard techniques.
Other		
No other known risks.		

Abbreviations: AE = adverse event; BP = blood pressure; CNS = central nervous system; EPS = extrapyramidal symptoms; NMS = neuroleptic malignant syndrome; OH = orthostatic hypotension; QID = 4 times daily; T_{max} = time of maximum concentration.

2.5.2. Benefit Assessment

Patients with gastroparesis arising from diabetic or idiopathic origin may benefit from receiving NG101, which has the potential to alleviate the significant symptom burden associated with the condition. Use of metopimazine in France has been associated with benefit in the treatment of nausea and vomiting (Vogalene Summary of Product Characteristics, 2017). In addition, participants may benefit from the clinical monitoring and continuation of background medications during the study.

2.5.3. Overall Benefit: Risk Conclusions

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with NG101 are justified by the potential benefits that may be afforded to participants with gastroparesis. In France, metopimazine is approved for the symptomatic treatment of nausea and vomiting, and has been prescribed for over 40 years. The body of evidence generated to date reflects a positive benefit risk balance in that indication.

3. Objectives and Endpoints

The following objectives and endpoints are included in this study:

Objectives	Endpoints
Primary	
• To determine the efficacy of NG101 to reduce nausea severity in participants with gastroparesis	• Change from baseline at Weeks 7 through 12 in the nausea severity score in the Diabetic and Idiopathic Gastroparesis Symptoms daily diary (DIGS-DD).
• To evaluate the safety of NG101 in participants with gastroparesis	• Incidence and severity of treatment-emergent adverse events (TEAEs), treatment-emergent adverse events of special interest (TEAESIs), and treatment-emergent serious adverse events (TESAEs); evaluation of safety laboratory assessments, vital signs, ECG results, and physical examination findings.
Secondary	
• To determine the efficacy of NG101 to: o Reduce the frequency and severity of vomiting o Reduce the symptom severity of early satiety, post-prandial fullness, and abdominal pain o Reduce the duration of nausea o Reduce the duration of abdominal pain o Reduce the overall severity of signs and symptoms of gastroparesis o Reduce the use of rescue medication	*Key Secondary Endpoints* • Change from baseline at Weeks 7 through 12 in the DIGS-DD: o Number of discrete episodes of vomiting o Early satiety severity score o Post-prandial fullness severity score o Abdominal pain severity score o Total severity score (nausea, early satiety, post-prandial fullness, abdominal pain) *Additional Secondary Efficacy Endpoints* • Change from baseline at Weeks 7 through 12 in the: o Number of hours of nausea per 24-hour period o Number of hours of abdominal pain per 24-hour period • Change from baseline at Weeks 7 through 12 in the vomiting severity score • Percent of nausea-free days • Patient Global Impression of Severity (PGI-S) score • Patient Global Impression of Change (PGI-C) score

	• Change from baseline to Week 12 in:
	  o Patient Assessment of Upper Gastrointestinal Disorders (PAGI)-Symptoms (SYM)
	  o PAGI- quality of life (QOL)
	  o Total and subscale scores on the Nausea Profile (NP)
	• Change from baseline through Week 4 in each of the components of the DIGS-DD (nausea, vomiting, early satiety, post-prandial fullness, and abdominal pain)
	• Change from baseline in gastroparesis symptoms as measured by the Gastroparesis Cardinal Symptom Index daily diary (GCSI-DD)
	• Change from baseline in weekly Treatment Satisfaction score
	• Weekly use of rescue medication

• To evaluate the PK of NG101	• PK parameters
• To evaluate the PD effects of NG101	• Prolactin levels at indicated timepoints
Exploratory	
• To evaluate the efficacy of NG101 to reduce the symptom severity of feeling of abdominal fullness and abdominal bloating	• Change from baseline at Weeks 7 through 12 in the feeling of abdominal fullness severity score and in the abdominal bloating severity score
• To evaluate the efficacy of NG101 to improve the symptom of nausea	• Level of improvement reported on the Nausea Improvement assessment
• Association of exposure and clinical response	• Association of PK parameters and changes in gastroparesis symptom PRO scores.
	• Association of PK parameters and safety assessments
• Additional analyses of clinical response in gastroparesis symptoms	• Achievement of threshold levels of improvement or worsening in each of the components of the DIGS-DD (nausea, vomiting, early satiety, post-prandial fullness, and abdominal pain)
	• Composite symptom severity scores
• Healthcare resource utilization	• Number of visits to healthcare providers
• Association of serum glucose with clinical response	• Association of serum glucose levels and HgbA1c with gastroparesis symptom PRO scores

Abbreviations: DIGS-DD = Diabetic and Idiopathic Gastroparesis Symptoms Daily Diary;
ECG = electrocardiogram; GCSI-DD = Gastroparesis Cardinal Symptom Index Daily Diary;

PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders -Symptoms Questionnaire; PAGI-QOL = Patient Assessment of Upper Gastrointestinal Disorders -Quality of Life; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcomes; TEAEs = treatment-emergent adverse events; TEAESIs = treatment-emergent adverse events of special interest; TESAEs = treatment-emergent serious adverse events.

4. Study Design

4.1. Overall Design

This is a randomized, double-blind, parallel-group (4 arms), placebo-controlled, multicenter study to evaluate the safety and efficacy of 3 dose levels of NG101 compared with placebo in participants with diabetic or idiopathic gastroparesis.

The total duration of the study for each participant will be approximately 20 weeks. Following a Screening Period of up to 4-weeks, eligible participants will enter a 2-week Pretreatment Period during which time they will complete specified gastroparesis symptom assessments to establish baseline data and to determine compliance with completion of these assessments. Following completion of the Pretreatment Period, a participant's randomization eligibility will be determined (based on all inclusion/exclusion criteria, including the participant's compliance with eDiary completion).

Participants who do not initially meet study screening criteria (ie, are screen failures) may be rescreened (no more than 1 additional Screening) after consultation with and approval by the sponsor. A participant's eligibility for the study must be confirmed by the sponsor's Medical Monitor, or designee, prior to randomization.

Participants eligible for the clinical study will be randomized in a 1:1:1:1 ratio to receive either NG101 treatment arms of 5 mg, 10 mg, or 20 mg, or matching placebo during a 12-week Treatment Period. Randomization will be stratified on the following factors: gastroparesis etiology (diabetes vs idiopathic), sex (male vs female), and current cannabinoid use (yes vs no). Determination of diabetes etiology will be done according to the medical history data at Screening.

NG101 will be administered orally (PO) QID for 12 weeks. The 20 mg arm will initiate dosing on Day 1 with 5 mg QID for 4 days, followed by 10 mg QID for 3 days, and then 20 mg QID through Week 12. No titration will occur in the 5 mg and 10 mg arms. The study drug should be taken by participants approximately 30 minutes before a meal 3 times a day and 30 minutes before bedtime, with a minimum interval of 4 hours between doses.

Two weeks following the end of treatment / Week 12 Visit, participants will return to the clinic for an End of Study (EoS) Visit / Follow-up Visit.

If a participant permanently discontinues study medication (for any reason) prior to the Week 12 Visit, the participant must attend the Early Discontinuation Visit as soon as possible, and then the Safety Follow-up Visit 2 weeks later.

The sponsor will review blinded data on an ongoing basis. Independent reviews of safety data will be done if needed.

Study Assessments:

Study assessments will be performed at the times specified in the Schedule of Activities (SoA – Section 1.3).

The primary efficacy objective is to determine the efficacy of NG101 to reduce nausea severity in participants with gastroparesis. The primary endpoint is the change from baseline at Weeks 7 through 12 for the nausea severity score in the Diabetic and Idiopathic Gastroparesis Symptoms

Daily Diary (DIGS-DD). Key secondary efficacy endpoints will also be assessed by the DIGS-DD and include changes from baseline at Weeks 7 through 12 in the DIGS-DD number of discrete episodes of vomiting, early satiety severity score, post-prandial fullness severity score, abdominal pain severity score, and total severity score (nausea, early satiety, post-prandial fullness, abdominal pain). An eDiary will be used to collect information for the primary and key secondary endpoints.

In addition, blood samples will be obtained to measure plasma levels of metopimazine and metopimazine acid following single-dose administration (Day 1) and at steady-state after multiple-dose administration (Week 2). Blood samples for PK will be collected at the Day 1 and Week 2 visits for all participants (up to 3 hours after the first dose on each occasion. In a subset of participants (8 to 10 participants per treatment arm; 32 to 40 participants total), intensive sampling will be performed (up to 6 hours after the first dose at the Day 1 and Week 2 visits, as well as 1 and 2 hours after the second dose at the Day 1 visit).

4.2. Scientific Rationale for Study Design

Patients with gastroparesis arising from either diabetic or idiopathic etiology will be enrolled in this study. Both subsets of patients may derive improvement in symptoms from D_2 inhibition, and thus treatment with metopimazine. Documentation of delayed gastric emptying is required in order to confirm the diagnosis of gastroparesis. A minimum severity of symptoms is required in order to facilitate demonstration of study drug treatment effect. The 12-week duration of the Treatment Period will enable assessment of the durability of response to treatment with metopimazine.

Dose selection for this study is based on the evaluation of a range of estimated target receptor (D_2) occupancies, phase 1 study results, and the clinical experience with marketed metopimazine in France (see Section 4.3). The dose escalation in the 20 mg QID treatment arm is included as mitigation against potential OH AEs, and to assess adaptation to alpha-1 receptor inhibition.

The primary endpoint of this study is the change in nausea severity. This endpoint was chosen since nausea is one of the most frequently reported symptoms of gastroparesis, and also has a major impact on patient quality of life (FDA 2019). Moreover, nausea is likely to be the most sensitive symptom of gastroparesis to facilitate detection of a treatment effect from D_2 inhibition.

A novel PRO tool to assess the signs and symptoms of gastroparesis, the DIGS-DD, is being developed and employed in this study since no qualified assessment tools for gastroparesis currently exist. The DIGS-DD will assess the impact of NG101 on the symptoms of gastroparesis in this study, and results will enable a determination of appropriateness and reliability of the DIGS-DD for use in future potentially pivotal studies.

Rescue medication rules have been designed to balance the need to treat a participant's symptoms and the ability to detect a treatment effect of metopimazine. Stratification factors were identified as potentially impacting the clinical course and/or treatment response, and have been incorporated into planned analyses.

4.2.1. Participant Input into Design

No specific input into the study design was sought from patients directly; however, interviews were conducted with patients with gastroparesis to develop the outcome assessments included in this study.

4.3. Justification for Dose

Nonclinical support for dosing in humans is based on findings from the NG101 animal toxicology studies (13-week studies 1365-18032 [rat] and 1365-18033 [dog]). Results were consistent with the pharmacology of NG101 and the phase 1 safety profile; therefore, the proposed phase 2 doses are considered appropriate.

The sponsor's phase 1 program with metopimazine (Vogalene) and NG101 demonstrated an acceptable safety profile for the doses proposed in phase 2. Single doses up to 60 mg, and multiple doses up to 45 mg Q6H for 5.25 days were administered. Analyses of safety data revealed a trend only for an increased risk of orthostatic changes. Notably, this risk has a clear causative mechanism (alpha receptor inhibition), was dose-dependent, and at doses of 15 and 30 mg the orthostatic hypotension only occurred on Day 1 and only at Hour 1. This pattern of adaptation and reduced risk of orthostasis with continued dosing is consistent with what has previously been reported for alpha receptor inhibition. The top dose of 20 mg QID is expected to have an acceptable safety profile, manageable in a similar way to approved alpha receptor inhibitors (ie, with dose titration).

4. [redacted]

Dosing will occur approximately 30 minutes before a meal 3 times a day and 30 minutes before bedtime, with a minimum interval of 4 hours between doses. This regimen will provide maximal coverage for participants during and just after meals, when symptoms are reported to be highest. An additional dose will be given before bedtime in order to provide optimal potential efficacy, and potentially minimize morning symptoms.

In accordance with FDA draft guidance (FDA 2019), treatment duration is 12 weeks. Given that steady-state conditions for metopimazine were achieved by Day 1 of the NG100-101 study, the 30 to 40% accumulation demonstrated on Day 6 represents the extent of accumulation anticipated with the 12 weeks of dosing planned for the study. Treatment for a 12-week duration will allow for a confirmation of the durability of response as well as a quantitative evaluation of the proposed PRO (the DIGS-DD).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the Week 12 visit and the EoS/Safety Follow-up Visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Note: "Enrolled" means a participant, or their legally acceptable representative, agreed to participate in a clinical study following completion of the informed consent process.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥ 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participant has a diagnosis of diabetic or idiopathic gastroparesis with:
   - Documented evidence of no mechanical obstruction, as determined by a gastroenterologist such as by esophagogastroduodenoscopy or upper gastrointestinal series, and in the investigator's opinion there is no current indication of obstruction, *and*
   - Diagnosis and symptoms consistent with gastroparesis (eg, nausea, vomiting, early satiety, post-prandial fullness, and abdominal pain) for at least 6 consecutive months preceding the Screening Visit, *and*
   - Delayed gastric emptying of solids during the Screening Period or within 12 months prior to the Screening Visit as demonstrated on either the US FDA-approved breath test (demonstrating delayed gastric emptying at 4 hours) or scintigraphy (demonstrating ≥ 10% residual food remaining at 4 hours).
     Note: There must be a minimum of 7 days between the gastric emptying study and the start of the Pretreatment Period, *and*
   - No known cause other than diabetes (ie, participants with gastroparesis due to other causes such as surgery, Parkinson's disease, post-abdominal irradiation, atrophic gastritis, suspected arterial occlusion, Crohn's disease, Chagas disease, etc., would be excluded).
     N*ote*: A minimum of 120 participants with diabetic gastroparesis and a minimum of 120 participants with idiopathic gastroparesis will be randomized.
3. Participants using a gastric stimulator must have had stable symptoms for at least 3 months prior to the Screening Visit following either:
   - Discontinuation of the gastric stimulator, *or*
   - Initiation of a stable treatment regimen. The participant must agree to maintain the same stable treatment regimen for the duration of the clinical study.

4. Participant must have all of the following during each week of the Pretreatment Period on the DIGS-DD:
    - Sum of the mean severity scores for each of the 4 gastroparesis symptoms ≥ 12. (The 4 symptoms are: nausea, early satiety, post-prandial fullness, and abdominal pain.)
    - A mean nausea severity score that is ≥ 4 and also greater than the mean severity score for abdominal pain.
    - Compliance with eDiary completion, as measured by adequately responding to at least 5 of 7 days of eDiary questions for each of the 2 weeks in the Pretreatment Period.
5. Participant is ambulatory (eg, not bed-ridden, nursing home resident, etc.).
6. Participant agrees to refrain from making any major changes in diet, weight, exercise, or other major lifestyle patterns after signing the informed consent form (ICF) and through the EoS Visit.
7. Participant must be able to independently complete PRO assessments without assistance from others.

Sex

8. Participant is male or female.

Contraceptive use by women of childbearing potential (WOCBP) should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female participants are eligible if:

- She is not pregnant (confirmed by negative serum pregnancy test at Screening and a negative urine pregnancy test prior to study drug administration on Day 1) or breastfeeding, and at least 1 of the following conditions applies:
    - She is not a WOCBP as defined in Appendix 10.6), *or*
    - She is a WOCBP who agrees to use 1 highly effective method of birth control during the study and at least 3 months after the last dose of study drug. A highly effective method of birth control is defined as that which results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, such as implants, injectable or combined oral contraceptives, patches, intrauterine devices (IUDs), sexual abstinence or vasectomized partner (or partner who follows the specifications outlined below).

Males participants are eligible if:

- He is of procreative capacity (ie, surgically sterile) or of procreative capacity and agrees to use an acceptable method of contraception from randomization through 1 month following the last dose of study medication. (Examples of acceptable contraception for

males include abstinence, use of a barrier method, or sterilized or post-menopausal partner [or partner who follows the specifications outlined above].)

Informed Consent

9. Participant is capable of giving signed informed consent.
10. Participant has signed an ICF before any study-specific procedures are performed.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical History

1. Participant has another active disorder that, in the opinion of the investigator, can cause abdominal pain or discomfort, nausea, vomiting, fullness, bloating, or other gastrointestinal symptoms that may confound the assessment of gastroparesis symptoms.
2. Participant has been hospitalized within the 2 months prior to the Screening Visit for uncontrolled diabetes mellitus, gastroparesis, or associated malnutrition.
3. Participant has had surgery that meets any of the following criteria:
   - Gastric surgery, including fundoplication, gastric banding, bypass, resection, or gastric per-oral endoscopic pyloromyotomy, at any time before the Screening Visit.
   - Surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit.
   - An appendectomy or cholecystectomy during the 3 months before the Screening Visit.
   - Other major surgery during the 3 months before the Screening Visit.
4. Participant has evidence of unexplained recurrent dizziness or syncope within 6 months prior to the Screening Visit.
5. Participant has a history of intolerance to phlebotomy, (eg, experiences dizziness or syncope).
6. Female participants with a history of galactorrhea, or unexplained amenorrhea.
7. Participant has history of or current clinically significant cardiac arrhythmia, including ventricular tachycardia, ventricular fibrillation, Torsade des Pointes, bradycardia, sinus node dysfunction, heart block, or family history prolonged QT syndrome. Participants with minor forms of ectopy (eg, premature atrial contractions) are not necessarily excluded.
8. Significant CV events (eg, myocardial infarction, unstable angina, hospitalization for congestive heart failure, cardiac surgery, ischemic or hemorrhagic stroke, or transient ischemic attack) within 6 months before the Screening visit.
9. Participant has a history of cancer, including prolactinoma (resected basal cell or squamous cell carcinoma of the skin is acceptable). *Note:* Participants with a history of cancer are eligible provided that the malignancy has been in complete remission

(disappearance of all signs of cancer in response to treatment) for at least 5 years before the Screening Visit.

10. Participant has a history of active alcoholism or drug addiction within 12 months prior to the Screening Visit.
11. Participant engages in daily recreational use of marijuana. *Note:* If participants are currently using marijuana or other cannabinoids, concomitant use is allowed if it is considered stable over the 4 weeks before Screening. Use must not increase during the study. Up to approximately 140 participants can be cannabinoid users (see Section 9.1), and of these up to approximately 56 can be marijuana users.
12. Urine drug screen positive for non-prescribed drugs, except cannabinoids if use is reported by the participant.
13. Participant engages in vaping.
14. Participant has been hospitalized for a psychiatric condition or has made a suicide attempt within 12 months prior to the Screening Visit.
15. Participant has a history of clinically significant hypersensitivity or allergies to any of the excipients contained in the study medication (NG101 or placebo).
16. Participant has an acute or chronic condition that, in the investigator's opinion or sponsor's opinion, would limit the participant's ability to complete or participate in this clinical study.
17. Participant has a body mass index < 18 kg/m^2 or > 39 kg/m^2.

Prior / Concomitant Therapy

18. Participant has had endoscopic pyloric injections of botulinum toxin within the 6 months prior to the Screening Visit.
19. Participant has received and tolerated an adequate course (at least 10 mg administered at least 3 times a day for at least 1 month) of treatment with domperidone and showed no notable symptomatic improvement in gastroparesis symptoms.
20. Use prior to Screening (within the previous 14 days or 7 half-lives, whichever is longer) or intended use during the study of any prohibited medications (see Appendix 10.2).
21. Initiation of treatment or change in dose or dose regimen within 3 months prior to the Screening Visit for any drug that prolongs QT interval. *Note:* Concomitant use of drugs that prolong QT interval is permitted provided that the participant has been receiving the drug for at least 3 months, has a normal QT interval at the Screening Visit, and remains on same dose and regimen during the clinical study (see Appendix 10.2).
22. Use of ondansetron or promethazine as an anti-emetic more than 2 times/day (total daily doses should not exceed 16 mg ondansetron or 50 mg promethazine).
23. Use of anti-emetics (ie, ondansetron or promethazine) within 24 hours prior to the Day 1 visit.
24. Participant is receiving parenteral nutrition or using a feeding tube.
25. Change in use of any alternative treatment (eg, acupuncture, hypnosis) from 2 weeks prior to the Screening Visit until the EoS.

26. Changes in dose or dose regimen from 30 days prior to the Screening Visit until the EoS visit for any chronically administered concomitant medications listed in the permitted medications section (see Appendix 10.2).

Prior / Concurrent Clinical Study Experience

27. Current enrollment or past participation within the last 30 days before signing of consent in any other clinical study involving an investigational study treatment or device or is planning to receive another investigational intervention at any time during the study (see Appendix 10.2).

Diagnostic Assessments

28. Participant has uncontrolled diabetes defined as HgbA1c > 10% at the Screening Visit.
29. Participant has thyroid stimulating hormone (TSH) below the lower limit of normal, or above the upper limit of normal (ULN) if free T4 is below the lower limit of normal.
30. Male participants with serum testosterone below the lower limit of normal at Screening.
31. Participant has prolactin levels > 2 x ULN
32. Participant has QTcF > 450 msec for male participants or QTcF > 470 msec for female participants, or QTcF > 480 msec in participants with right bundle branch block (participants with left bundle branch block are excluded).
33. Participant experiences any clinically significant finding on a physical exam, 12-lead ECG, or clinical laboratory test after signing the ICF but prior to randomization. The investigator will determine if a particular finding is clinically significant. In making this determination, the investigator will consider whether the particular finding could prevent the participant from performing any of the protocol-specified assessments, could represent a condition that would exclude the participant from the study, could represent a safety concern if the participant continues in the study, or could confound the study-specified assessments of safety or efficacy.
    Note: By definition, a positive drug screen is clinically significant (with the exception of marijuana).
34. Participant has severe postural symptoms and/or absolute systolic BP < 90 mm Hg upon standing. *Note:* these severe symptoms include presyncope, syncope, and other severe AEs that are considered of substantial clinical relevance by the investigator (see Table 3 for additional details and definitions).
35. Estimated glomerular filtration rate ≤ 45 mL/minute/1.73 m^2 (based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation; see Appendix 10.7).
36. Aspartate aminotransferase or alanine aminotransferase > 2 x ULN; alkaline phosphatase or bilirubin >1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).

Other Exclusions

37. Donation of blood or blood loss > 400 mL within 90 days prior to the Screening Visit.

5.3. Lifestyle Considerations

No restrictions to lifestyle considerations are required for this study. However, as indicated in Section 5.1 (inclusion criterion 6), participants must agree to refrain from making any major changes in diet, weight, exercise, or other major lifestyle patterns after signing the ICF and through the EoS Visit.

5.3.1. Meals and Dietary Restrictions

Refrain from consumption of Seville oranges, grapefruit or grapefruit juice for a minimum of 7 days prior to starting study drug until after the final dose.

The study drug should be taken by participants approximately 30 minutes before a meal 3 times a day and 30 minutes before bedtime, with a minimum interval of 4 hours between doses.

Day 1 and Week 2 Visits:

For the Day 1 and Week 2 PK assessments, participants who are not in the Intensive PK Subset should arrive at the clinic in the morning after fasting (water is allowed) for at least 4 hours, and either prior to taking any study drug or within 4 to 6 hours after the first dose of study drug of the day. (See also Section 8.7.1.)

For the Day 1 and Week 2 PK assessments in the Intensive PK Subset, participants should arrive at the clinic in the morning after fasting (water is allowed) for at least 8 hours and prior to the first dose of study drug of the day. (See also Section 8.7.1.)

At the Day 1 and Week 2 visits, study drug should be administered in the clinic approximately 30 minutes before eating. The first dose should be administered with 240 mL of water. No additional water is permitted until 30 minutes after dosing, after which time, water is allowed ad libitum.

5.3.2. Caffeine, Alcohol, and Tobacco

The intake of alcohol, caffeine and tobacco should not be increased during the study.

5.3.3. Activity

No study-specific activity restrictions apply, except to refrain from making any major changes in diet, weight, exercise, or other major lifestyle patterns after signing the ICF and through the EoS Visit.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, and any serious adverse event (SAE).

Participants who do not initially meet study Screening criteria (ie, are screen failures) may be re-screened (no more than 1 additional Screening) after consultation with and approval by the sponsor Medical Monitor or designee.

5.5. Pretreatment Period Failures

Pretreatment failures are defined as participants who do not meet the prespecified criteria for eligibility regarding the Pretreatment Period assessments (see Section 5.1, inclusion criterion 4).

Participants who are pretreatment failures may be re-screened upon approval from the sponsor and/or Medical Monitor or designee.

6. Study Drug

Study drug is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Drug(s) Administered

The study drugs planned for use are described in Table 1 below:

Table 1: Study Drugs

Arm Name	NG101 5 mg Arm	NG101 10 mg Arm	NG101 20 mg Arm	Placebo Arm
Intervention Name	Metopimazine mesylate	Metopimazine mesylate	Metopimazine mesylate	Placebo
Type	Drug	Drug	Drug	Placebo
Dose Formulation	Capsule	Capsule	Capsule	Capsule
Dosage Level(s)	NG101 5 mg, QID	NG101 10 mg, QID	NG101 20 mg, QID	Placebo, QID
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental	Placebo comparator
IMP and NIMP	IMP	IMP	IMP	NIMP
Sourcing	Provided by the sponsor	Provided by the sponsor	Provided by the sponsor	Provided by the sponsor
Packaging and Labeling	NG101 5 mg capsules will be provided in a blister pack labeled as required per country requirement	NG101 10 mg capsules will be provided in a blister pack labeled as required per country requirement	NG101 20 mg capsules will be provided in a blister pack labeled as required per country requirement	Placebo capsules will be provided in a blister pack labeled as required per country requirement

Study drug will be dispensed at each visit during the Treatment Period. Each participant will also be dispensed an extra blister pack in case dispensed study drug becomes depleted. Participants will be required to return for clinic visits with all dispensed medication (ie, study drug and rescue medication) to ensure use is recorded properly. Note that during the following visits, study drug will be administered in the clinic:

- **Day 1:** first dose in the clinic, and second dose of the day in the clinic for those participants in the Intense PK subset
- **Week 1:** a dose in the clinic (ie, not necessarily the first dose of the day)
- **Week 2:** first dose of the day in the clinic
- **Week 12:** a dose in the clinic (ie, not necessarily the first dose of the day)

All study drug capsules will be identical in appearance in order to maintain the blind.

Participants in the 20 mg treatment arm will be titrated up to the target dose in a blinded fashion. Specifically, the 20 mg arm initiation blister pack will contain a 4-day supply of 5 mg QID, and a 3-day supply of 10 mg QID, after which the blister packs will contain a 7-day supply of 20 mg QID. (Note: For participants in the placebo, 5 mg, or 10 mg arms, the blister pack will contain only the assigned treatment doses.)

If a dose is missed, (eg, not taken by at least 1 hour after a meal), then participants should skip the missed dose and resume dosing with the next planned dose (30 minutes before the next meal or before bedtime).

6.2. Preparation / Handling / Storage / Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The study drug will be shipped with a temperature monitor and under ambient storage conditions.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug s are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants eligible to participate in the clinical study will be randomized in a 1:1:1:1 ratio to receive either NG101 treatment arms of 5 mg, 10 mg, or 20 mg, or matching placebo. Randomization will be stratified on the following factors: gastroparesis etiology (diabetes vs idiopathic), sex (male vs female), and cannabinoid use (yes vs no). Determination of diabetes etiology will be done according to the medical history data at Screening.

All participants will be centrally assigned to randomized study drug using interactive response technologies (IRT). Before the study is initiated, the log in information and directions for the IRT will be provided to each site.

Study drug will be dispensed at the study visits summarized in the SoA.

Returned study drug should not be re-dispensed to the participants.

Blind Break:

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor's medical monitor or designee prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

6.4. Study Compliance

Compliance with completing study visits and assessments per protocol will be assessed throughout the study.

Compliance with completing daily diaries during the Pretreatment Period and the Treatment Period will also be assessed.

When participants are dosed at the site (Day 1, Week 1 and Week 2), they will receive study drug under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

Compliance with study drug will be assessed at each visit. Compliance will be assessed by counting returned capsules during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. A record of the number of capsules dispensed to and taken by each participant must be maintained and reconciled with study drug and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The prohibited medications indicated in Appendix 10.2 are excluded within the previous 14 days or 7 half-lives (whichever is longer) before the Screening Visit.

Participants should be on a stable dose of permitted concomitant medications, as indicated in Appendix 10.2, including herbal treatments, for at least 30 days prior to the Screening Visit. Participants should intend to maintain their usual medication regimen throughout the study.

6.5.1. Rescue Medicine

The study site will supply anti-emetic rescue medication that will be provided by the sponsor. The following rescue medications may be used:

- Ondansetron (4 mg tablet)
- Promethazine (25 mg tablet)

The use of rescue medications is allowed up to 2 times daily during the Pretreatment Period and the Treatment Period, except on the day prior to (within 24 hours) and the day of clinic visits.

Participants will be instructed to use rescue medication only during a day when nausea or vomiting is intolerable. For participants taking ondansetron, a second 4 mg tablet may be taken 1 hour after the first dose if there has been insufficient relief of nausea; thus, participants are allowed up to 4 tablets (16 mg) per day.

Participants are required to use only the study-provided rescue medications. Use of rescue medication will be captured in the daily diary; compliance with regard to rescue medication will be assessed at each study visit and captured in the source documents. As described in Section 9.3.4, weekly use of rescue medication will also be assessed as an additional secondary endpoint.

6.6. Dose Modification

Participants will receive either NG101 5, 10 or 20 mg QID or matching placebo QID for 12 weeks. Participants in the 20 mg treatment arm will be titrated up to the target dose in a blinded fashion.

Dose modification is not permitted; however, if deemed medically necessary, study medication may be temporarily interrupted and restarted after consultation with the Medical Monitor or designee. See Section 7.1.1.

6.7. Intervention after the End of the Study

No extension study is planned.

Upon completing the Treatment Period or End of Treatment / Early Termination Visit, participants should be treated according to the local standard of care.

7. Discontinuation of Study Drug and Participant Discontinuation / Withdrawal

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study drug. If study drug is definitively discontinued, the participant will remain in the study to be evaluated for follow-up.

If a clinically significant finding in clinical laboratory or ECG parameters is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any changes in participant management are needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

For any female participants, or partners of male participants, who become pregnant during the study, see guidance in Appendix 10.6.

See the SoA for data to be collected at the time of discontinuation of study drug and follow-up, and for any further evaluations that need to be completed (Section 1.3).

Criteria for Withdrawal from Treatment:

- AE(s) which, in the opinion of the investigator or sponsor, make continued treatment in the study inappropriate
- AEs consistent with EPS, such as acute dyskinesias and dystonic reactions, tardive dyskinesia, Parkinsonism, akinesia, or akathisia.
- Neuroleptic malignant syndrome.
- Worsening of gastroparesis signs and/or symptoms that cannot be adequately controlled by the participant's current treatment regimen (including the protocol-allowed rescue treatment), and thus make continued treatment in the study inappropriate.
- Significant non-compliance
- Withdrawal of consent to receive the study treatment
- Orthostatic hypotension (decrease in systolic BP of at least 20 mm Hg) with associated severe postural symptoms (including presyncope, syncope, and other severe AEs that are considered of substantial clinical relevance by the investigator). See Table 3 for additional details and definitions.
    - Participants meeting this discontinuation criterion while under observation during clinical visits must be monitored in the clinic until postural symptoms are no longer severe, and will be withdrawn from the study. Participants who develop severe postural symptoms at home will hold any further dosing and return to the study site as soon as possible for further evaluation.

7.1.1. Temporary Interruption

Temporary interruption of study drug may occur in cases where necessary. If the study drug must be interrupted for longer than 3 days, consult the Medical Monitor about the participant's continuation in the study. If this temporary interruption is due to an AE, this should be indicated as an outcome of the AE in the CRF.

7.1.2. Reinitiation

Reinitiation of study drug after interruptions of at least 3 days should be discussed with the Medical Monitor.

In order to maintain the blind, all participants who have treatment interrupted for at least 3 days will reinitiate dosing using a blinded initiation blister pack.

Since participants in the 20 mg treatment arm will initially titrate up to the targeted dose of 20 mg, all participants in this arm who temporarily interrupt study drug will reinitiate dosing via titration beginning with 5 mg QID. Specifically, the 20 mg arm reinitiation blister pack will contain a 4-day supply of 5 mg QID, and a 3-day supply of 10 mg QID. (Note: For participants in the placebo, 5 mg, or 10 mg arms, the blister pack will contain only the assigned treatment doses.)

7.2. Participant Discontinuation / Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). The participant will be permanently discontinued both from the study drug and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, the investigator must document this in the site study records, and the sponsor representative should be notified.

Participants who either complete the Treatment Period or have an Early Discontinuation visit should be treated according to the local standard of care. However, if possible, prohibited medications should be avoided during the 2-week Follow up Period.

Criteria for Withdrawal from Study

- Withdrawal of consent to participate in the study
- Lost to follow up (despite attempts to contact the participant)
- Death

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.9.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.

When several procedures are scheduled at the same theoretical time and/or visit, in general the study assessments should be performed in the following order:

- PRO assessments
- 12-lead ECG
- Vital signs
- Blood samples

8.1. Total Volume of Blood

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 224 mL (Table 2). Repeat or unscheduled samples may be taken for safety reasons, or for technical issues with the samples.

Table 2: Total Volume of Blood Required for Each Assay

Assay	Number of samples	Volume per sample (mL)	Total volume (mL)	
			Males	Females
Optional genetic testing sample	1	5	5	5
Serum pregnancy test (females only)	1	2	--	2
HgbA1c	4	1	4	4
Thyroid stimulating hormone (TSH)	1	3	3	3
Serum testosterone (males only)	1	0.5	0.5	--
Serum prolactin				
All participants	8	2	16	16
Intensive PK subset	14	2	28	28
Serology				
Hepatitis B surface antigen				
Hepatitis C antibody				
Hepatitis C viral load RNA	1	8	8	8
HIV 1 and 2 antibody				
Geenius HIV 1/2 differentiation				
Hematology	9	2	18	18
Serum chemistry	9	4	36	36
PK blood sample collection				
Sparse PK (all participants)	8	6	48	48
Intensive PK Subset	20	6	120	120
	Total Volume - Sparse PK (all participants)		**138.5**	**140**
	Total Volume - Intensive PK Subset		**222.5**	**224**

8.2. Gastric Emptying Test

The Gastric Emptying Breath Test (GEBT), to be used with the GEBT test meal, is intended for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastroparesis (GEBT Summary of Safety and Effectiveness, 2015). The GEBT is a non-radioactive, non-invasive, orally administered test for measurement of the rate of solid phase gastric emptying in adults. The GEBT has been validated against the reference method of gastric scintigraphy. The GEBT utilizes the stable isotope carbon-13 (^{13}C). The GEBT measures how fast the stomach empties solids after ingestion of a cooked egg test meal, labeled with ^{13}C-Spirulina particles. The GEBT may be administered in a primary care facility, clinic or tertiary care setting.

The GEBT procedure is conducted over a 4-hour period. Following an overnight (or ≥ 8 hour) fast, duplicate pre-meal breath samples are collected from the participant (used to establish a participant's baseline $^{13}CO_2$ level). Following pre-meal breath sample collection, the participant is administered the test meal. Single post-meal breath samples are subsequently collected at 45, 90, 120, 150, 180, and 240 minutes from the end of test meal consumption. Breath samples, collected in capped glass tubes before and after test meal administration and are analyzed by gas isotope ratio mass spectrometry to determine the ratio of $^{13}CO_2/^{12}CO_2$ in each sample. By measuring the change in this ratio over time as compared to the pre-meal value, the rate of $^{13}CO_2$ excretion can be calculated and the individual's gastric emptying rate determined.

Contraindications

Individuals with known hypersensitivity to Spirulina, egg, milk or wheat allergens should avoid the GEBT (GEBT Summary of Safety and Effectiveness, 2015).

Because the GEBT is an indirect multi-compartmental method of measuring gastric emptying, GEBT results may be inaccurate in individuals compromised with significant small bowel, pancreatic, liver and/or lung disease. Consequently, the GEBT should not be administered to patients with pulmonary dysfunction (eg, COPD) and/or small bowel malabsorption.

8.3. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.3.1. Diabetic and Idiopathic Gastroparesis Symptoms Daily Diary (DIGS-DD)

Participants will be required to complete the Diabetic and Idiopathic Gastroparesis Symptoms daily diary (DIGS-DD) to record daily symptoms of gastroparesis. The DIGS-DD consists of 4 questions asking participants to rate their nausea, early satiety, post-prandial fullness, and abdominal pain at its worst in the past 24 hours using a 0 to 10-point numeric rating scale. A score of 0 indicates no symptoms and a score of 10 indicates the worst possible symptoms. There are also questions asking participants to record the number of times they vomited/threw up in the past 24-hours, and rate their vomiting severity.

A summary of the questions included in the DIGS-DD is provided in Appendix 10.4.

8.3.1.1. Gastroparesis - Additional Daily Assessments

Additional assessments related to the DIGS-DD will be conducted to fully assess the symptoms of gastroparesis. These questions will assess the previous 24 hours in terms of the number of hours of nausea, the impact of nausea on the participant's life, and the number of hours of abdominal pain, feeling of fullness, and abdominal bloating.

8.3.2. Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD)

The American Neurogastroenterology and Motility Society's Gastroparesis Cardinal Symptom Index Daily Diary (GCSI-DD) is designed to assess gastrointestinal symptoms associated with idiopathic or diabetic gastroparesis (Revicki et al. 2018; Parkman et al. 2018). The instrument asks participants to rate the severity of 4 symptoms: nausea, inability to finish a normal-sized meal (ie, early satiety), feeling excessively full after meals (ie, post-prandial fullness), and upper abdominal pain. The severity response is rated by the participant as the worst severity of the symptom over the previous 24 hours, using a 5-point scale (none, mild, moderate, severe, very severe). For vomiting, the number of vomiting episodes (emesis) over the last 24 hours is recorded by the participant. In addition, overall severity of gastroparesis is assessed. The overall severity of gastroparesis takes into account that other symptoms might impact a participant's condition.

8.3.3. Patient Assessment of Upper Gastrointestinal Disorders -Symptoms Questionnaire

The Patient Assessment of Upper Gastrointestinal Disorders (PAGI)- Symptoms (SYM) questionnaire will be assessed during the Treatment Period (with the exception of Week 1) and at the Early Discontinuation and End of Study visits. The PAGI-SYM is intended to cover the main symptom groupings for the following upper GI disorders: gastroesophageal reflux disease, dyspepsia, and gastroparesis, for application in clinical trials and other studies (Rentz et al. 2004).

The PAGI-SYM contains 20 items and 6 subscales covering heartburn/regurgitation (7 items), nausea/vomiting (3 items), post-prandial fullness/early satiety (4 items), bloating (2 items), upper abdominal pain (2 items), and lower abdominal pain (2 items). A 6-point Likert response scale, ranging from 0 (none) to 5 (very severe), is used for rating the severity of each symptom item over a 2-week recall period.

8.3.4. Patient Assessment of Upper Gastrointestinal Disorders -Quality of Life Questionnaire

The PAGI- quality of life (QOL) questionnaire will be assessed during the Treatment Period (with the exception of Week 1) and at the Early Discontinuation and End of Study visits. The PAGI-QOL was designed to comprehensively measure QOL outcomes for patients with upper GI disorders (de la Loge et al. 2004).

The PAGI-QOL consists of 30 items each having a 6-point Likert-type scale and five dimensions: Daily Activities (DAC; 10 items related to avoiding or having difficulties in performing DAC), Clothing (CLO; 2 items, one related to feeling constricted and 1 to the frustration felt about not being able to dress as wanted), Diet and Food Habits (DIE; 7 items

related to restrictions made and induced frustration), Relationship (REL; 3 items, describing impact of the disease on relationships with partner, relatives and friends), and Psychological Well-Being and Distress (PSY; 8 items describing impact of the disease on feelings or emotional state).

8.3.5. Nausea Profile

The nausea profile (NP) will be assessed during the Treatment Period (with the exception of Week 1) and at the Early Discontinuation and End of Study visits. The NP is a subjective symptom checklist with the goal of obtaining a more in-depth description of what patients are experiencing when they report the feeling of nausea (Muth 1996).

The NP self-reported instrument will be administered to evaluate participants' nausea over time. The NP evaluates 17 descriptors of nausea across 3 subscales (somatic distress, gastrointestinal distress, and emotional distress) and overall. Scores for each descriptor range from 0-9, where 0 indicates that the participants felt the nausea descriptor (eg, shaky) 'not at all' and 9 indicates that the participants felt the nausea descriptor (eg, shaky) 'severely'. The NP was validated against a Visual Analog Scale measure of nausea (Muth 1996) and has been adapted for use in patients with gastroparesis (Jaffe 2011).

8.3.6. Patient Global Impression of Severity Questionnaire

The Patient Global Impression of Severity (PGI-S) questionnaire will be assessed weekly using a 5-point Likert rating scale as an anchor-based approach to estimate the severity of the participants' condition. The responses to this participants-completed scale range from 0 = no signs and symptoms; to 4 = very severe.

8.3.7. Patient Global Impression of Change Questionnaire

The Patient Global Impression of Change (PGI-C) questionnaire will be assessed weekly using a 5-point Likert rating scale as an anchor-based approach to estimate meaningful change in a participant's condition. The responses to this participant-completed scale range from 0 = no signs and symptoms; to 4 = very severe.

8.3.8. Treatment Satisfaction Assessment

Treatment satisfaction will be assessed weekly using a 5-point Likert rating scale to determine how satisfied the participant is with the study medication's ability to relieve symptoms (Chey et al. 2014). The responses to this participant-completed scale range from 1 = not at all satisfied, to 5 = very satisfied.

8.3.9. Nausea Improvement

The Nausea Improvement assessment is a 5-category response scale asking whether the participant experienced any improvement in nausea symptoms over the course of the study and, if so, the level of importance.

This assessment will be conducted as an End of Study assessment.

8.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.4.1. Physical Examinations

A complete physical exam, including neurologic, cardiovascular, pulmonary, abdominal and breast exams, will be performed at Screening, Day 1, and Weeks 4, 8, and 12 as well as at the Follow-up Visit. Weight will be measured at all visits. Height (without shoes) will also be measured and recorded on Day 1. Investigators should pay special attention to clinical signs related to previous serious illnesses. For female participants, menstrual cycle will be recorded during the study.

Only clinically significant changes in physical examination findings will be recorded at subsequent visits, as indicated in the SoA (Section 1.3).

8.4.2. Vital Signs

Vital signs, including oral temperature, pulse rate, respiratory rate, and BP will be measured at each study visit while the participant is in the sitting position. A standardized oscillometric automated BP device will be used; manual auscultatory assessment will be used only if the BP reading cannot be captured by the standardized automated device (eg, based on specific physiologic condition, or if the automated device is not functional). Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Additional information regarding the standardized automated office BP assessment will be outlined in the training manual provided by the cardiac safety laboratory.

Orthostatic vital signs will be assessed as follows (and as clinically indicated; see also the SoA in Section 1.3).

- At Screening, BP and heart rate will be measured while sitting and after 1 minute in the standing position.
- At the Day 1 Visit, BP and heart rate will be measured before dosing and at 1, 2, and 3 hours after dosing. Measurements will be done while the participant is sitting, as well as after 1 minute in the standing position.
- At the Week 1 Visit, BP and heart rate should be measured before dosing and at 1 hour after dosing. Measurements will be done while the participant is sitting, as well as after 1 minute in the standing position.
- At the Week 2 visit, BP and heart rate will be measured before dosing, and at 1, 2, and 3 hours after dosing. Measurements will be done while the participant is sitting, as well as after 1 minute in the standing position.

For participants in the Intensive PK subset, in addition to the assessments described above, orthostatic vital signs will also be assessed at the Day 1 and Week 2 visits at hours 4, 5, and 6, as well as 1 and 2 hours after the second dose in the clinic on Day 1.

8.4.3. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

Participants must rest in the recumbent position for at least 10 minutes before the ECG recording is started. A qualified physician will review the ECGs promptly and any clinically important finding will be recorded on the appropriate CRF. The investigator is responsible for reviewing all ECGs. All ECGs will also be centrally read.

8.4.4. Clinical Safety Laboratory Assessments

See Appendix 10.3 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

All clinical laboratory assessments will be conducted by a central laboratory. The use of local laboratories is allowed in cases where safety assessment is time sensitive and the central laboratory results will not be available before potential actions need to be taken for safety reasons.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participants condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 10.3, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.5. Adverse Events and Serious Adverse Events

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the participant to discontinue the study drug (see Section 7).

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected starting after the ICF is signed until the End of Study / Follow-up Visit as specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.5.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

8.5.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.5.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits / contacts. All AEs considered related to study drug, SAEs, (and AEs of special interest, as defined in Section 8.5.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.5.3.

8.5.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the

regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded by the sponsor (or designee) to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study drug and the participant will be followed until the outcome of the pregnancy is known.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.6.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.5.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Worsening of gastroparesis will not be considered an AE since it is captured by PRO efficacy assessments. However, the signs, symptoms, and / or clinical sequelae resulting from worsening of disease will be reported as an SAE if the definition of an SAE is fulfilled, or if they are considered by the investigator not to be adequately captured by the protocol-specified disease-related assessments (see Appendix 10.5.1 and Appendix 10.5.2, respectively).

8.5.7. Adverse Events of Special Interest

Treatment-emergent AESIs are based on the known effects of D_2 and alpha-1 antagonists, as well as observations in the nonclinical and phase 1 studies. The rationale for inclusion of each TEAESI is provided in Table 3 below:

Table 3: Adverse Events of Special Interest: Rationale for Inclusion and Criteria for Diagnosis

AESI	Rationale and Criteria for Diagnosis
Gynecomastia **Galactorrhea** **Menstrual irregularity** **Decreased libido** **Impotence**	**Rationale:** Effects of treatment with NG101 in animals were consistent with the non-CNS effects seen with other D_2 antagonists. These are considered secondary to increased prolactin levels resulting from D_2 receptor antagonism. **Criteria for diagnosis:** Per the opinion of the treating investigator.
Extrapyramidal symptoms (EPS)	**Rationale:** Although metopimazine is not expected to penetrate the CNS, AEs from central D_2 blockade may include events of EPS. **Criteria for diagnosis:** Extrapyramidal symptoms can include events categorized as acute (dystonia, akathisia and parkinsonism) or tardive (tardive dyskinesia and tardive dystonia; Pierre 2005).
Neuroleptic malignant syndrome (NMS)	**Rationale:** Although metopimazine is not expected to penetrate the CNS, AEs from central D_2 blockade may include events of NMS. **Criteria for diagnosis**: Neuroleptic malignant syndrome is considered in cases with recent dopamine antagonist exposure, or dopamine agonist withdrawal. Clinical features include hyperthermia; rigidity; mental status alteration; creatine kinase elevation; sympathetic nervous system lability; tachycardia plus tachypnea; and a negative work-up for other causes. The following are critical values for quantitative criteria (Gurrera et al. 2011): hyperthermia, > 100.4°F or > 38.0°C on at least 2 occasions; creatine kinase elevation, at least 4 x ULN; blood pressure elevation ≥ 25% above baseline; blood pressure fluctuation, ≥ 20 mm Hg (diastolic) or ≥ 25 mm Hg (systolic) change within 24 hours; tachycardia, ≥ 25% above baseline; and tachypnea, ≥ 50% above baseline.

Orthostatic hypotension (OH)	**Rationale**: OH was observed in phase 1 studies, and likely occurs due to partial inhibition of α-1 receptors. **Criteria for diagnosis:** OH is defined by a decrease in systolic BP of at least 20 mm Hg, and/or decrease in diastolic BP of at least 10 mm Hg, with associated severe postural symptoms. Postural AEs can include feelings of lightheadedness, general weakness, warmth, diaphoresis, nausea, palpitations or blurry vision (Whitledge et al. 2019). Severe postural symptoms include presyncope, syncope, and other severe AEs that are considered of substantial clinical relevance by the investigator. Presyncope is defined as "feeling like one was going to pass out but without actual loss of consciousness" (Whitledge et al. 2019). Syncope is "the sudden loss of consciousness, associated with inability to maintain postural tone, with immediate and spontaneous recovery without requiring electrical or chemical cardioversion" (da Silva 2014).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BP = blood pressure; CNS = central nervous system; D_2 = dopamine receptor; EPS = extrapyramidal symptoms; NMS = neuroleptic malignant syndrome; OH = orthostatic hypotension; ULN = upper limit of normal.

8.6. Treatment of Overdose

For this study, participants are expected to take no more than 4 capsules in 1 day.

In the event of an overdose, participants should notify the investigator and the investigator should:

1. Contact the Medical Monitor immediately.
2. Continue to monitor the participant for any AE / SAE and laboratory abnormalities
3. Document the quantity of the excess dose.
4. Consider skipping the next dose of NG101. NG101 can be reinitiated, with the timing depending on the amount of overdose and considering the half-life of metopimazine (approximately 2 hours). Reinitiation should be discussed with the medical monitor.

Participants should be treated according to the symptoms they are experiencing. If a participant has symptoms suggestive of orthostasis, then the participant should sit down or lie down, depending on the severity of symptoms. Participants will be trained to recognize the signs and symptoms of OH.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.7. Pharmacokinetics

Pharmacokinetic data collected in this study will be analyzed according to a separate PK Analysis Plan and reported separately from the primary study results.

As noted in Section 8, when several procedures are scheduled at the same theoretical time and/or visit, study assessments should be performed in the following order: PRO assessments; 12-lead ECG; vital signs; blood samples.

8.7.1. Pharmacokinetic Assessment Methods and Timing

All participants will participate in PK assessment. A subset of participants who consent will participate in intensive PK sampling. The timing of blood sample collections is provided in Table 4 below.

At the Day 1 and Week 2 visits, participants should arrive at the clinic after fasting (see Section 5.3.1 for further details). Participants may have water during the fasting period, but no food should be consumed. Study drug should be taken 30 minutes before eating, at which point 240 mL of water should be provided with the dose. No additional water is permitted until 30 minutes after dosing, after which time, water is allowed ad libitum and a meal will be consumed.

Table 4: Pharmacokinetic Sampling Times

Study Day	Sparse PK	Intensive PK Subset
	PK Sample Timepoint (Hours after dose) (± Time window)	**PK Sample Timepoint (Hours after dose) (± Time window)**
Day 1	Predose[a]	Predose[a]
	--	0.5 hours (± 5 minutes)
	1 hour (± 5 minutes)	1 hour (± 5 minutes)
	--	1.5 hours (± 5 minutes)
	2 hours (± 10 minutes)	2 hours (± 10 minutes)
	3 hours (± 10 minutes)	3 hours (± 10 minutes)
	--	4 hours (± 10 minutes)
	--	5 hours (± 10 minutes)
	--	6 hours (± 10 minutes)
	--	**Administer second dose**
	--	1 hour (± 5 minutes)
	--	2 hours (± 10 minutes)
Week 2	Predose[a]	Predose[a]
	--	0.5 hour (± 5 minutes)
	1 hour (± 5 minutes)	1 hour (± 5 minutes)
	--	1.5 hours (± 5 minutes)
	2 hours (± 10 minutes)	2 hours (± 10 minutes)
	3 hours (± 10 minutes)	3 hours (± 10 minutes)
	--	4 hours (± 10 minutes)
	--	5 hours (± 10 minutes)
	--	6 hours (± 10 minutes)

Abbreviations: PK = pharmacokinetic

[a] Within 15 to 20 minutes before dosing.

Note: For the Week 2 assessment in the Sparse PK group, participants should arrive at the clinic in the morning after fasting for at least 4 hours, and either prior to taking any study drug or within 4 to 6 hours after the first dose of study drug of the day.

Note: For the Week 2 assessment in the Intensive PK group, participants should arrive at the clinic in the morning after fasting for at least 8 hours and prior to the first dose of study drug of the day.

8.7.1.1. Blood Sample Assessment

Venous blood samples (6 mL) for the determination of plasma concentrations of metopimazine and metabolite (metopimazine acid) will be drawn by direct venipuncture or via an IV catheter into K2 EDTA Vacutainer® tubes at the times indicated in Table 4. Additional information regarding blood collection and sample preparation are provided in the Laboratory Manual.

Drug concentration information will be masked prior to database lock since these parameters have the potential to unblind a participant's dose group.

Sample handling and labelling

Each aliquot of plasma will be identified as follows:

- Line 1: **Study NG101-201**
- Line 2: randomization number,
- Line 3: Study Day (ie, Day 1 or Week 2) and time since the first dose administered in clinic on that day.
- Line 4: Plasma PK assay, Aliquot number

Sample Shipment and Storage

The samples will be shipped in a container filled with enough dry ice to ensure that the samples are kept frozen.

The study samples will be shipped to the Sample Custodian as defined in the Lab Manual.

Bioanalytical Method

Plasma concentrations of metopimazine and metopimazine acid will be measured by [redacted]. using a fully validated method.

8.7.1.2. Pharmacokinetic Parameters

Pharmacokinetic data collected in this study may be analyzed according to a separate PK Analysis Plan and reported separately from the primary study results.

8.8. Pharmacodynamics

Inhibition of dopamine receptors is associated with an increase in serum prolactin levels. This is because dopamine has an inhibitory effect on the anterior pituitary lactotrophs which secrete prolactin. Thus, prolactin levels will be measured in this study (as indicated in Table 5) to characterize the pharmacodynamic effects of NG101. Blood samples for serum prolactin assessment will be sent to the central laboratory [redacted]. Results of prolactin level measurements after the pre-dose assessment on Day 1 will remain blinded until database lock.

Note that during the following visits, study drug will be administered in the clinic:

- **Day 1:** first dose in the clinic, and second dose of the day in the clinic for those participants in the Intense PK subset
- **Week 1:** a dose in the clinic (ie, not necessarily the first dose of the day)
- **Week 2:** first dose of the day in the clinic
- **Week 12:** a dose in the clinic (ie, not necessarily the first dose of the day)

Table 5: Serum Prolactin Sampling Times

Study Day	All Participants (± Time window)	Intensive PK Subset (± Time window)
Screening Visit	Screening Visit	Screening Visit
Day 1	Predose[a]	Predose[a]
	1 hour (± 5 minutes)	1 hour (± 5 minutes)
	--	2 hours (± 5 minutes)
	--	3 hours (± 10 minutes)
	--	6 hours (± 10 minutes)
Week 2 Visit	Predose[a]	Predose[a]
	1 hour (± 5 minutes)	1 hour (± 5 minutes)
	--	2 hours (± 10 minutes)
	--	3 hours (± 10 minutes)
	--	6 hours (± 10 minutes)
Week 12 or E/D Visit	Predose[a]	Predose[a]
	1 hour (± 5 minutes)	1 hour (± 5 minutes)
EoS / Follow-up Visit	EoS / Follow-up Visit	EoS / Follow-up Visit

Abbreviations: E/D = Early discontinuation; EoS = End of study; PK = pharmacokinetic
[a] Within 15 to 20 minutes before dosing.

8.9. Genetics

Genetic research will be conducted in this study. A 5 mL blood sample will be collected for the analysis of one or more genes or genetic markers throughout the genome. Genetic analysis is noted as optional on the consent form, and participants will have the opportunity to consent or opt out without impacting their participation in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Appendix 10.8 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

8.10. Biomarkers

No additional biomarkers are planned to be evaluated in this study.

8.11. Immunogenicity Assessments

Immunogenicity will not be evaluated in this study.

8.12. Healthcare Resource Utilization

Health economics data associated with medical encounters will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and interventions (including physician urgent care clinic or emergency room visits, tests and procedures, and medications).

9. Statistical Considerations

9.1. Sample Size Determination

A total of approximately 280 participants will be randomized to achieve an estimated 224 participants completing the 12-week treatment period (and approximately 56 participants per treatment arm). At least 120 randomized participants will have diabetic gastroparesis and at least 120 randomized patients will have idiopathic gastroparesis. Up to approximately 140 participants can be cannabinoid users, and of these, approximately 56 can be marijuana users.

A sample size of 280 participants provides approximately 83% power to detect a mean treatment difference in the nausea severity score of 1.0 (on an 11-point scale) between an active dose group versus placebo at the 2-sided 0.05 significance level. This is based on a standard deviation of 1.8, a 20% drop-out rate, and a 2-sample t-test.

9.2. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Intensive PK	All Enrolled participants who consented to the intensive PK sampling. Participants will be analyzed according to the study medication they actually received.
Intent-to-Treat (ITT)	All Enrolled participants who are randomized. Participants will be analyzed according to the study medication to which they were randomized.
Per Protocol (PP)	All participants in the ITT population who do not have any major protocol violations. Participants will be analyzed according to the study medication they actually received.
Safety	All participants who take at least 1 dose of study drug. Participants will be analyzed according to the study drug they actually received.

9.3. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to unblinding and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.3.1. General considerations

Continuous variables will be summarized using the number of observations, mean, standard deviation (SD) median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

9.3.2. Efficacy Endpoints

The following algorithm will be applied to the daily GI assessments in the DIGS-DD and other GI assessments to create the baseline and weekly treatment period scores:

- A participant's baseline score will be the mean of the scores during the 2-week Pretreatment Period (ie, each weekly score is the mean of the daily scores)
- For each week in the 12-week Treatment Period, a participant's score for that week will be the mean of the daily scores for that week.
- Change from baseline for a particular week in the Treatment Period is that week's score minus the baseline score.
- If a participant has < 4 non-missing values for a week, the weekly score will be set to missing.

9.3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline at Weeks 7 through 12 for the nausea severity score on the DIGS-DD (described in Section 8.3.1).

The primary efficacy endpoint will be analyzed using a mixed-effect model for repeated measures (MMRM) on the weekly mean change from baseline scores in the Treatment Period (ie, Weeks 1 through 12). The model will have treatment group, baseline nausea score, sex, gastroparesis etiology, cannabinoid use, study week, treatment group × study week (interaction effect), baseline nausea score × study week (interaction effect), sex × study week (interaction effect), and gastroparesis etiology × study week (interaction effect), and cannabinoid use × study week (interaction effect) as fixed effects and participant as a random effect. The average value across Weeks 7 through 12 will be calculated for each treatment group using the MMRM along with the difference between each NG101 group versus the placebo group.

The primary analysis will be performed on the PP population using an observed-case analysis for handling missing data. For each NG101 group versus the placebo group, the average value across Weeks 7 through 12 will be tested at the 2-sided 0.05 level.

Subgroup analyses on the primary endpoint will be performed on the randomization stratification factors (sex, gastroparesis etiology, and cannabinoid use) to assess the consistency of treatment effect. Additional sensitivity and supportive analyses for the primary endpoint analysis will be provided in the SAP.

The primary analysis will not exclude or censor observations due to rescue medication use. Supplemental analyses which exclude observations due to rescue medication use will be detailed in the SAP.

9.3.3. Key Secondary Efficacy Endpoints

The following are the set of key secondary endpoints. These endpoints are derived from the PROs in the DIGS-DD assessment (described in Section 8.3.1).

- Change from baseline at Weeks 7 through 12 in the number of discrete episodes of vomiting
- Change from baseline at Weeks 7 through 12 in the early satiety severity score
- Change from baseline at Weeks 7 through 12 in the post-prandial fullness severity score
- Change from baseline at Weeks 7 through 12 in the abdominal pain severity score
- Change from baseline at Weeks 7 through 12 in the total severity score (nausea, early satiety, post-prandial fullness, and abdominal pain)

These endpoints will be analyzed in a manner similar to the primary endpoint (Section 9.3.2.1), the difference being that the baseline nausea severity score covariate will be replaced with the corresponding baseline value for the endpoint being analyzed.

9.3.4. Additional Secondary Efficacy Endpoints

Below are the set of additional secondary endpoints. The analysis methods for the additional secondary endpoints will be provided in the SAP.

- Change from baseline at Weeks 7 through 12 in the number of hours of nausea per 24-hour period. This endpoint is derived from the Gastroparesis – Additional Daily Assessments described in Section 8.3.1.1.
- Change from baseline at Weeks 7 through 12 in the number of hours of abdominal pain per 24-hour period reported. This endpoint is derived from the Gastroparesis – Additional Daily Assessments described in Section 8.3.1.1.
- Change from baseline at Weeks 7 through 12 in the vomiting severity score. This endpoint is derived from the vomiting PROs in the DIGS-DD assessment (described in Section 8.3.1).
- Percent of nausea-free days. The percent of nausea-free days is derived from a score of zero on the nausea component of DIGS-DD.
- Change from baseline to Week 12 in PGI-S score. The PGI-S endpoint is derived from the PGI-S questionnaire described in Section 8.3.6.
- Change from baseline to Week 12 in PGI-C score. The PGI-C endpoint is derived from the PGI-C questionnaire described in Section 8.3.7.
- Change from baseline to Week 12 in the PAGI-SYM. The PAGI-SYM is composed of 20 items and 6 subscales (see Section 8.3.3). Subscale scores are calculated by averaging across items comprising the subscale; scores vary from 0 (none or absent) to 5 (very severe) (Revicki et al. 2004). The overall PAGI-SYM score is the average of the 6 subscale scores (Rentz et al. 2004).
- Change from baseline to Week 12 in the PAGI-QOL total score. The PAGI-QOL assessments are presented in Section 8.3.4. Each of the 5 PAGI-QOL dimensions are

calculated by taking the mean of the items in each subscale after reversing item scores. The PAGI-QOL total score is calculated by taking the mean of the corresponding subscales (de la Loge et al. 2004).

- Change from baseline to Week 12 in total and subscale scores on the NP. The NP assessments are described in Section 8.3.5. The Total NP score is calculated as the percent of total points scored. Similarly, the 3 dimensions scores are calculated as the percent of total points scored of the assessments associated with that dimension.
- Change from baseline at Week 4 in each of the 5 symptom scores on the DIGS-DD: nausea, vomiting, early satiety, post-prandial fullness, and abdominal pain. These endpoints are derived from the DIGS-DD assessment (described in Section 8.3.1).
- Change from baseline in gastroparesis symptoms as measured by the Gastroparesis Cardinal Symptom Index daily diary (GCSI-DD). The GCSI-DD is described in Section 8.3.2.
- Change from baseline to Week 12 in Treatment Satisfaction score. The Treatment Satisfaction endpoint is derived from the Treatment Satisfaction questionnaire described in Section 8.3.8.
- Weekly use of rescue medication: As described in Section 6.5.1, rescue medication use will be captured in the daily diary.
- PK parameters
- Change from baseline in prolactin levels at indicated timepoints.

9.3.5. Exploratory Endpoint(s)

The following are exploratory endpoints:

- Change from baseline at Weeks 7 through 12 in the feeling of abdominal fullness severity score. This endpoint is derived from the Gastroparesis – Additional Daily Assessments described in Section 8.3.1.1.
- Change from baseline at Weeks 7 through 12 in the abdominal bloating severity score. This endpoint is derived from the Gastroparesis – Additional Daily Assessments described in Section 8.3.1.1.
- Level of improvement reported on the Nausea Improvement assessment (see Section 8.3.9).
- Association of PK parameters and changes in gastroparesis symptom PRO scores.
- Association of PK parameters and safety assessments.
- Achievement of threshold levels of improvement or worsening in each of the 4 numeric rating scale symptom assessments on the DIGS-DD (nausea, vomiting, early satiety, post-prandial fullness, and abdominal pain).
- Composite symptom severity scores
- Number of visits to healthcare providers (see Section 8.12).

- Association of serum glucose levels and HgbA1c with gastroparesis symptom PRO scores.

The analysis methods for the exploratory endpoints will be provided in the SAP. Additional exploratory endpoints may also be defined in the SAP and / or the PK Analysis Plan.

9.3.6. Safety Endpoints

The safety endpoints are the incidence of TEAEs, TEAESIs (eg, dopamine-receptor antagonist effects and alpha-1 antagonist effects), and TESAEs; evaluation of clinical safety laboratory assessments, vital signs, ECG results, and physical exam findings.

AEs will be coded using the Medical Dictionary for Regulatory Activities. Incidence rates for TEAEs will be summarized overall, by maximum severity, and by relationship to study drug for each treatment group. Treatment-emergent AESIs and SAEs will also be summarized by treatment group.

Summary descriptive statistics will be provided for other safety parameters (laboratory tests, ECG parameters, and vital signs).

9.4. Interim Analyses

To assist with designing future studies, an interim analysis of this study may be performed. Selected sponsor members will be unblinded at the treatment group level, remaining blinded to subject-level treatment assignments. The results of this interim analysis will not be used to modify the study design or stop the study early due to positive efficacy results.

9.5. Data Monitoring Committee (DMC) and Data Safety Monitoring Board (DSMB)

A Data Monitoring Committee (DMC) comprised of representatives from the sponsor and CRO will review blinded data on an ongoing basis.

An unblinded independent safety review conducted by a Data Safety Monitoring Board (DSMB) will be triggered if any of the following conditions are met: 3 or more participants in the study exhibit extrapyramidal symptoms (EPS); 1 or more participants have neuroleptic malignant syndrome (NMS); 3 or more participants are discontinued due to orthostatic hypotension-related adverse events (AEs); other events considered of high clinical significance by the sponsor are observed. The DSMB will then make any recommendations to the sponsor regarding conduct of the study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

Participants willing to provide a sample for genetic analysis will sign consent via the ICF.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Data Safety Monitoring Board

If an independent safety review committee is needed, a Data Safety Monitoring Board (DSMB) will be available on an ad hoc basis. The committee will include members who each have expertise in at least 1 of the following: neurology, cardiovascular disease, endocrinology, gastroenterology and statistics. Additional details are available in the DSMB Charter.

10.1.6. Dissemination of Clinical Study Data

The sponsor is committed to making study-related data available in accordance with standard industry procedures.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Data Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Study monitors / CRAs will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after shipment and delivery of the drug for investigational use is discontinued, or as long as required by local regulations, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The definition of what constitutes source data can be found in the Data Management Plan.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon discussion with the sponsor or designee, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Prohibited and Permitted Medications

Prohibited Medications:

Unless otherwise stated, the following medications are excluded within the previous 14 days or 7 half-lives (whichever is longer) before the Screening Visit. Note that many of these medications have more than one reason for exclusion; in those cases, they are only listed once.

Chronic use of systemic glucocorticoids	Systemic short course (≤ 7 days), inhaled, and topical administration is permitted
D_2 agonists / partial agonists/ antagonists	Agonists: • Apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole. Partial Agonists: • Brexpiprazole, cariprazine. Antagonists: • Metoclopramide, domperidone. • 1st generation antipsychotics (typical antipsychotics also known as neuroleptics): *Phenothiazine drugs:* Chlorpromazine, fluphenazine, levomepromazine, pericyazine, perphenazine, pipotiazine, prochlorperazine, promazine, promethazine (except as rescue medication), thiethylperazine, thioridazine, trifluoperazine, triflupromazine. *Non-phenothiazine drugs:* Benperidol, clopenthixol, clotiapine, droperidol, flupenthixol, fluspirilene, haloperidol, loxapine, pimozide, thiothixene, zuclopenthixol. • 2nd generation antipsychotics (atypical antipsychotics also known as serotonin-dopamine antagonists): aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, olanzapine / fluoxetine, paliperidone, quetiapine, risperidone, ziprasidone.
Drugs associated with NMS	Carbamazepine, mibefradil
Drugs associated with orthostatic hypotension	• Antihypertensive agents with alpha-1 adrenergic antagonist activity (eg, terazosin prazosin, doxazosin); agents with preferential selectivity for alpha-1a receptors in the prostate are allowed if blood pressure change upon standing at the Screening Visit is ≤ 10 mm Hg.) • Others: bretylium, dronabinol, tizanidine.
Acetylcholinesterase inhibitors	Donepezil, galantamine, neostigmine, pyridostigmine, rivastigmine.

Drugs affecting gastric motility	• Drugs with known pharmacological activity at 5-hydroxytryptophan (HT)1, 5-HT3, or 5 HT4 receptors (eg, ondansetron [except as rescue medication] cisapride, mosapride, prucalopride, tegaserod, tropisetron, granisetron, dolasetron, naratriptan, sumatriptan, and zolmitriptan). Note: buspirone and mirtazapine are permitted provided that the participant has been on a stable dose for at least 3 months prior to the Screening Period and can remain on the same stable dose for the duration of the study. • Anti-cholinergic and anti-muscarinic agents (eg, benztropine mesylate, biperiden, clomipramine, darifenacin, dicyclomine, flavoxate, hyoscyamine, oxybutynin, propantheline, scopolamine, solifenacin, tolterodine, trihexyphenidyl, and trospium). Note: inhaled ipratropium and tiotropium are permitted. • GLP-1 receptor agonists (eg Dulaglutide, Lixisenatide) • Pramlintide • Acarbose • All narcotics either alone or in combination (eg, codeine, diphenoxylate, morphine, paregoric, and propoxyphene). Notes: narcotics used as anesthesia for an esophagogastroduodenoscopy require a 5-calendar-day wash-out prior to the participant entering the Pretreatment Period. Loperamide may be used as needed (prn) for diarrhea. Occasional use (up to 2 times per week) of tramadol is permitted for pain. • Macrolide antibiotics (eg, azithromycin, clarithromycin, erythromycin, spiramycin, telithromycin, troleandomycin). • Any fundic-relaxing agents not otherwise excluded such as, but not limited to, clonidine, nitrates, and triptan containing medications. Note: intermittent use (no more than once a week) of triptan-containing medications is permitted to treat migraine headache. • Other medicines which may affect gastric emptying (eg, colchicine and misoprostol). Note: linaclotide and lubiprostone may be used to treat concurrent constipation.
Clinical P-glycoprotein inhibitors	Amiodarone, carvedilol, dronedarone, itraconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, tamoxifen, telaprevir, tipranavir, verapamil.
Any investigational or imported drugs that have not been approved for human use by the FDA	

Permitted Medications

Participants should be on a stable dose of allowed concomitant medications, including herbal treatments and probiotics, for at least 30 days prior to the Screening Visit and should intend to maintain their usual medication regimen throughout the study. Insulin and other medications for glucose control can be adjusted as needed.

The following concomitant medications are permitted during the study:

Cannabinoids	Cannabinoid (eg, marijuana, CBD) use provided that use is stable over the previous 4 weeks. Recreational use of marijuana and other THC containing cannabinoids must not be daily. Use must not be expected to increase during the study.
D_2 antagonists / H_1 antagonists	Promethazine (25 mg) up to 2 times / day as an anti-emetic rescue medication
$5HT_3$ receptor antagonist	Ondansetron (4 mg) up to 2 times / day as an anti-emetic rescue medication. A 4 mg dose of ondansetron may be repeated after 60 minutes if relief is insufficient.
Alpha$_1$ receptor antagonists	Prostate specific inhibitors of alpha - receptors (eg, tamsulosin) if at Screening the systolic BP decreases ≤ 10 mm Hg upon standing for 1 minute.
Glucocorticoids	Systemic short course (≤ 7 days), inhaled, and topical administration of glucocorticoids.
Drugs affecting gastric motility	• Buspirone and mirtazapine (provided that the participant has been on a stable dose for at least 3 months prior to the Screening Period and can remain on the same stable dose for the duration of the study). • Inhaled ipratropium and tiotropium. • Loperamide, as needed (prn), for diarrhea. • Tramadol (up to 2 times per week) for pain. • Triptan-containing medications (no more than once a week) for migraine headache. • Linaclotide, plenacatide, Miralax, Magnesium based laxatives, bisacodyl and senna for concurrent constipation.

10.3. Appendix 3: Clinical Laboratory Tests

The tests detailed in Table 6 will be performed by the central laboratory.

The use of local laboratories is allowed in cases where safety assessment is time sensitive and the central laboratory results will not be available before potential actions need to be taken for safety reasons.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	

Hematology	• Platelet Count
	• Red blood cell (RBC) count
	• Hemoglobin
	• Hematocrit
	• RBC indices:
	  o MCV
	  o MCH
	  o %Reticulocytes
		• White blood cell (WBC) count with differential:
		  o Neutrophils
		  o Lymphocytes
		  o Monocytes
		  o Eosinophils
		  o Basophils
		• HgbA1c

Clinical Chemistry[1]	• Blood urea nitrogen (BUN) • Potassium • Creatinine • Sodium • Calcium • Chloride • Phosphorus • Magnesium • Bicarbonate • Glucose (nonfasting) • Prolactin • Thyroid stimulating hormone (TSH)[a]	• Aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT) • Alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT) • Alkaline phosphatase • Gamma glutamyltransferase (GGT) • Total and direct bilirubin • Total protein • Albumin • Uric acid
Serum Prolactin	• See Table 5	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, and nitrite by dipstick • Microscopic examination (if blood or protein is abnormal)	

Other Screening Tests	• Highly sensitive serum and urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • Serum testosterone test (for male participants only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Urine drug test (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, phencyclidine). The results of each test must be entered into the CRF.
NOTES: [a] If TSH is above ULN at Screening then free T4 will be checked. [b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).	

Investigators must document their review of each laboratory safety report, with designation for clinically significant (CS) / not clinically significant (NCS) for out of range results.

Laboratory / analyte results that could unblind the study (eg, prolactin test results) will not be reported to investigative sites or other blinded personnel until the study has been unblinded or for safety issues.

[redacted]

[redacted]

10.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.5.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and / or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.5.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.5.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Neurogastrx in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Neurogastrx. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Neurogastrx.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship as either related or unrelated:
    - A related event is defined as an event where there is a reasonable possibility of a causal relationship between the event and the study medication.
    - An unrelated event is any other event.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Neurogastrx. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Neurogastrx.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Neurogastrx to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Neurogastrx within 24 hours of receipt of the information.

10.5.4. Reporting of SAEs

SAE Reporting to Neurogastrx via an Electronic Data Collection Tool

- The initial report of an SAE to Neurogastrx must be within 24 hours.
- The primary mechanism for reporting an SAE to Neurogastrx will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Neurogastrx Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the Study Contact Information.

SAE Reporting to Neurogastrx via Paper CRF

- Facsimile transmission of the SAE paper CRF may be used to transmit this information to the Neurogastrx Medical Monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Contact Information.

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:

    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner • *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive NG101.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 8.5.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

10.7. Appendix 7: Estimated Glomerular Filtration Rate

The Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation should be used to calculate estimated glomerular filtration rate (eGFR). The CKD-EPI equation is:

$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

Where:

S_{cr} = serum creatinine in mg/dL

$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min indicates the minimum of S_{cr}/κ or 1
max indicates the maximum of S_{cr}/κ or 1

10.8. Appendix 8: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study drug, susceptibility to, and severity and progression of disease. Variable response to study drug may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to NG101 or gastroparesis and related diseases. They may also be used to develop tests/assays including diagnostic tests related to NG101 and gastroparesis. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed genetic variations associated with clinical responses. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on NG101 or gastroparesis continues but no longer than 10 years or other period as per local requirements.

10.9. Appendix 9: Abbreviations

Abbreviation	Definition
AE	Adverse event
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
BP	Blood pressure
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cl/F	Total clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRF	Case report form
CV	Cardiovascular
DIGS-DD	Diabetic and Idiopathic Gastroparesis Symptoms Daily Diary
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
E/D	Early discontinuation
eGFR	Estimated glomerular filtration rate
EoS	End of study
EPS	Extrapyramidal symptoms
FDA	Food and Drug Administration
GEBT	Gastric emptying breath test
GCSI-DD	Gastroparesis Cardinal Symptom Index Daily Diary
GI	Gastrointestinal
hERG	human Ether-à-go-go-related gene
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technologies
ITT	Intent-to-treat

IV	Intravenous
MAD	Multiple ascending dose
MMRM	Mixed-effect model for repeated measures
NMS	Neuroleptic malignant syndrome
NP	Nausea Profile
OH	Orthostatic hypotension
PAGI-QOL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptoms
PD	Pharmacodynamic
PK	Pharmacokinetic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PO	Orally
PRO	Patient reported outcomes
QID	4 times daily
Q6H	Every 6 hours
QOL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
Study drug	NG101
$t_{1/2}$	Terminal half-life
T_{last}	Time of the last measurable concentration
T_{max}	Time of maximum plasma concentration
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TESAE	Treatment-emergent serious adverse event
THC	Tetrahydrocannabinol
TSH	Thyroid stimulating hormone
WOCBP	Women of child bearing potential
ULN	Upper limit of normal
US	United States

11. References

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INVESTIGATOR'S STATEMENT

I agree to conduct the trial in accordance with the protocol and with all applicable government regulations and good clinical practice guidance.

_____ _____

Investigator's Signature Date

_____

Investigator's Name