Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Twice-Daily Oral Administration of a Peripherally Acting Dopamine Receptor D2/D3 Antagonist, TAK-906 for the Treatment of Adult Subjects with Symptomatic Idiopathic or Diabetic Gastroparesis

NCT Number: NCT03544229

Protocol Approve Date: 13 July 2020

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA PHARMACEUTICALS
PROTOCOL
Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Twice-Daily Oral Administration of a Peripherally Acting Dopamine Receptor D_2/D_3 Antagonist, TAK-906 for the Treatment of Adult Subjects With Symptomatic Idiopathic or Diabetic Gastroparesis

Short Title

TAK-906, Parallel-Group, Phase 2b Dose Response, Efficacy and Safety Study in Adult Subjects With Symptomatic Idiopathic or Diabetic Gastroparesis

Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA 02139

Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".

Study Number: TAK-906-2002

IND Number: 125296 **EudraCT Number:** 2018-001275-21

Compound: TAK-906

Date: 13 July 2020 **Version/Amendment Number:** 8

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
13 July 2020	Amendment 8	Substantial	Global
27 August 2019	Amendment 7	Nonsubstantial	Japan
08 August 2019	Amendment 6	Substantial	Global
23 May 2019	Amendment 5	Nonsubstantial	Belgium
15 November 2018	Amendment 4	Nonsubstantial	Japan
26 September 2018	Amendment 3	Nonsubstantial	Japan
06 August 2018	Amendment 2	Substantial	Global
16 July 2018	Amendment 1	Substantial	Global
23 March 2018	Initial protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America (US) Contact	European Contact
Serious adverse event and pregnancy reporting	PPD	
Medical Monitor (medical advice on protocol and compound)		

US: United States.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories, as applicable can be found on the signature page.

Electronic signatures are provided on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (Appendix F).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in (Appendix H) of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 8 Summary and Rationale

This document describes the changes from the protocol incorporating Amendment No. 8. Results from a recently completed drug-drug interaction study with organic anion transporting polypeptide (OATP) 1B1 and 1B3 inhibitor, rifampin showed a potential risk of high exposure of TAK-906 necessitating the exclusion of the concomitant use of OATP1B1/1B3 inhibitors with TAK-906.

The lower range of body mass index (BMI) will be changed from ≥19 to ≥18 to allow inclusion of subjects in different regions where the general gastroparesis population tend to have lower BMI ranges.

Changes in Amendment 8:

1. Updated the signatories in Section 1.2.
2. Updated number of study sites.
3. Updated period of evaluation from 17 to 22 weeks from screening to follow-up.
4. Updated and revised Section 4.2 with new nonclinical data.
5. Added information about Study TAK-906-1004 and TAK-906-1009 to Section 4.3.1 Clinical Pharmacology.
6. Revised Section 9.1.18.1 to remove Gastric Emptying Breath Test (GEBT) at Visit 5 (Week 4) and Visit 7 (Week 12).
7. Allow historical documented delayed gastric emptying (GEBT or scintigraphy or wireless motility capsule) as inclusion criteria.
8. Discontinued randomization into the 5 mg dose arm.
9. Removed the minimum number of diabetic gastroparesis (DG) and idiopathic gastroparesis (IG) subjects in each dose arm.
10. Shorten safety visit follow up phone call from 40 to 30 days in schedule of assessments.
11. Revised Section 7.1 Inclusion Criteria – Revising the lower end of the BMI range in inclusion Criterion No. 8 from ≥19 to ≥18 kg/m^2.
12. Revised Section 7.2 Exclusion Criteria – Exclusion Criteria Nos. 32, 33, and 35 were combined under 1 inclusive liver disease Criterion (No. 32).
13. Revised Section 7.2 Exclusion Criteria – Added exclusion Criterion #41 for any subject with suspected or known coronavirus disease-2019 (COVID-19) infection.
14. Revised Section 7.3 Excluded Medications – added OATP1B1/1B3 inhibitors and Otilonium bromide/Spasmomen to excluded medications.
15. Revised Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject – added criteria for any subject with identified COVID-19 infection during the study.

16. Revised Section 9.1.6 Vital Signs Procedure – revised wording to read "When vital signs are scheduled at the same time as blood sampling, vital signs will take priority and vital signs will be obtained within 0.5 hour before the scheduled blood draw."
17. Revised Section 9.1.13 ECG Procedure to add PR interval and standardize when assessments were to be taken.
18. Revised Section 9.1.14, Table 9.b by removing biomarker sample collection times.
19. Revised Section 9.1.18.2 Patient Outcomes Measures with Food and Drug Administration (FDA) recommended changes.
20. Added Section 9.5 to address possible changes to study procedures necessitated by the COVID-19 pandemic.
21. Added COVID-19-related disease and COVID-19 pneumonia to Table 10.a Takeda Medically Significant AEs.
22. Revised Section 13.1.3.1 Primary Efficacy Analysis for clarity and completeness.
23. Revised Section 13.2 to address removal of interim efficacy analysis.
24. Revised Section 13.3 Determination of Sample Size to address reduction in number of subjects to be enrolled and revised wording of sample size justification and power estimate.
25. Revised language for collection of prolactin samples for clarification.
26. Revised Appendix A Schedule of Study Procedures and footnotes.
27. Revised pharmacokinetic (PK) sampling scheme in Appendix A Schedule of Study Procedures to reduce patient burden.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 1.2 Approval	Updated signatories.	A new global clinical lead has been assigned to the study.
Section 2.0 Study Summary	Updated number of study sites.	Updated the number of study sites
Section 2.0 Study Summary	Updated period of evaluation from 17 to 22 weeks.	The period of evaluation from first screening visit to safety follow-up phone call is 22 weeks.
Section 4.2 Nonclinical Information	Revised Section 4.2 with new nonclinical data provided in the Investigator's Brochure (IB) update.	To align with IB Edition 04 update.
Section 4.3.1 Clinical Pharmacology	Added results from Studies TAK-906-1004 and TAK-906-1009.	Updates on the TAK-906-1004 and TAK-906-1009 study results.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 5.1.3 Additional Objectives Section 5.2.4 Additional Endpoints Section 6.1 Study Design Section 6.2.1 Rationale for Study Design Section 9.1.18.1 GEBT Section 2.0 Study summary Appendix A Schedule of Study Procedures	Removed GEBT) at Visit 5 (Week 4) and Visit 7 (Week 12).	To reduce patient burden.
Section 6.1 Study Design Section 7.1 Inclusion Criteria Section 9.1.18.1 GEBT Section 2.0 Study Summary Appendix A Schedule of Study Procedures	Allow historical documented delayed gastric emptying GEBT or scintigraphy or wireless motility capsule as inclusion criteria (in lieu of requiring GEBT at screening – GEBT required if no previously documented test demonstrating gastric emptying).	To reduce subject burden for patients who already have a diagnostic test demonstrating delayed gastric emptying documented in the medical record.
Section 6.1 Study Design Figure 6.a Schematic of Study Design Section 6.2.1 Rationale for Study Design Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling Section 8.4 Study Drug Blind Maintenance Section 13.3 Determination of Sample Size Section 2.0 Study Summary	Discontinued randomization into the 5 mg dose arm.	Randomization into the 5 mg dose arm is being discontinued to improve operational feasibility in the setting of the COVID-19 pandemic and to reduce the number of subjects being exposed to a potentially minimally efficacious dose that likely approaches the lower end of the dose response curve.
Section 6.2.1 Rationale for Study Design Section 2.0 Study Summary	Removed the minimum number of DG and IG subjects in each dose arm.	To mitigate the impact of the COVID-19 pandemic on enrollment rates.
Section 7.2 Exclusion Criteria	Updated exclusion criteria to adapt for removal of GEBT at Visits 5 and 7.	Updated chronic smoker exclusion criteria to adapt for removal of GEBT at Visits 5 and 7.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 6.1 Study Design Section 10.2.1 Collection and Reporting of AEs Section 2.0 Study Summary Appendix A Schedule of Study Procedures	Revised safety visit follow up phone call from 40 to 30 days.	To shorten safety visit follow-up to standard timeframe of 30 days
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Revision of the accepted BMI range.	In order to reflect the lower BMI seen in the gastroparesis population.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Summarized and combined exclusion Criteria Nos. 32, 33, and 35 under Criterion No. 32.	To create one inclusive liver disease exclusion criterion.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Added exclusion criterion for any subjects with suspected or known COVID-19 infection.	To include this exclusion, related to the COVID-19 pandemic situation.
Section 7.3 Excluded Medications	Added OATP1B1/1B3 inhibitors and otilonium bromide/Spasmomen to excluded medications.	A recently completed OATP (drug-drug interaction (DDI) study (Study TAK-906-1009) suggested that coadministration of TAK-906 with a single dose of rifampin (OATP1B1 and 1B3 inhibitor) resulted in high exposure of TAK-906,which may potentially increase the safety risk (eg, adverse events [AEs], toxicities). Thus, the concomitant use of OATP1B1/1B3 inhibitors will be excluded. Added otilonium bromide/Spasmomen to the list of excluded medications due to its anticholinergic and antispasmodic effects.
Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject	Revised Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject.	Added criteria for any subject with identified COVID-19 infection during the study.
Section 9.1.6 Vital Signs Procedure	Revised wording to standardize timing of vital signs procedures.	To standardize vital signs collection in relation to blood draws.
Section 9.1.13 ECG Procedure Appendix A Schedule of Study Procedures	Revised wording of electrocardiogram (ECG) procedures.	To clarify that PR interval should be part of ECG assessment and to standardize time of assessments.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.1.14 PGx and PK Sample Collection Section 6.1 Study Design Appendix A Schedule of Study Procedures	Removal of biomarker samples collection.	To reduce the number of blood collections and streamline at home study procedures.
Section 9.1.18.2 Patient Outcome Measures Appendix E Patient Global Impression Scales	Revised wording to acknowledge the use of an updated Patient Global Impression of Severity (PGI-S) scale and the use of PGI-Change (C) scale instead of the PGI- Improvement (I) scale and added an appendix.	To comply with FDA recommended changes
Section 9.5 Possible Changes to the Procedures to Address Interruptions Due to Pandemic Outbreak	Added Section 9.5	To implement any changes needed to study procedures, related to the impact of the COVID-19 pandemic.
Section 10.1.4 SAEs	Added COVID-19-related disease and COVID-19 pneumonia to Table 10.a.	To follow the general company's guidance, the preferred terms COVID-19-related disease and COVID-19 pneumonia are added into the list of Takeda medically significant AEs.
Section 13.1.3.1 Primary Efficacy Analysis Section 2.0 Study Summary	Revised language in Section 13.1.3.1 Primary Efficacy Analysis	Updates made for clarity and completeness.
Section 13.2 Interim Analysis	Revised Section 13.2 interim analysis.	To address removal of interim efficacy analysis.
Section 13.3 Determination of Sample Size Section 2.0 Study Summary	Updated number of subjects and revised wording of sample size justification and power estimate.	Sample size is adjusted in order to manage the likelihood of statistical, clinical and operational success of this study in the setting of the COVID-19 pandemic. Specifically, to manage the risk associated with statistical decision-making and operational delays, the statistical testing is revised from 2-sided (with a significance level of 5%) to 1-sided (with a significance level of 5%). In addition, the planned sample size is reduced by 10 subjects per arm and randomization into the 5 mg dose arm will be discontinued. As a result, the study power is re-estimated and remains approximately 80%.

Protocol Amendment 8		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Appendix A Schedule of Study Procedures	Revised language for collection of prolactin samples.	To clarify that Visits 2 and 3 prolactin samples are not mandatory.
Appendix A Schedule of Study Procedures	Aligned wording in footnotes of Schedule of Study Procedures with changes in the text.	To align footnotes with changes in the text regarding clarification of assessments and timing of assessments.
Appendix A Schedule of Study Procedures	Revised the PK sampling scheme of Schedule of Study Procedures.	To reduce the patient burden by reducing the number of blood PK collections

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** TAK-906	
Title of Protocol: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Twice-Daily Oral Administration of a Peripherally Acting Dopamine Receptor D_2/D_3 Antagonist, TAK-906 for the Treatment of Adult Subjects With Symptomatic Idiopathic or Diabetic Gastroparesis	**IND No.:** 125296	**EudraCT No.:** 2018-001275-21
Study Number: TAK-906-2002	**Phase:** 2b	

Study Design: This is a global multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b study to evaluate the efficacy and safety of twice daily (BID) oral (PO) capsule administration of a peripherally acting dopamine (DA) receptor D_2/D_3 antagonist, TAK-906, in adult male and female subjects aged 18 to 85 years, inclusive, with symptomatic idiopathic or diabetic gastroparesis ([IG and DG], respectively). Gastroparesis is a disorder of the stomach characterized by delayed gastric emptying, in the absence of mechanical obstruction.

Subjects will attend the study site for a screening/consent visit (Visit 1, Day -35), when their consent will be obtained, and general eligibility to participate in the study will be reviewed. After signing the informed consent form, subjects will have a blood sample taken to assess their laboratory values. Subjects will discontinue all excluded medications and return to the site 3 to 17 days later to perform a 4-hour ^{13}C-Spirulina Gastric Emptying Breath Test (GEBT) (Visit 2, Day -21). Subjects with confirmed delayed gastric emptying by an accepted diagnostic method that is documented in the subject's medical records prior to screening do not have to undergo the Visit 2 GEBT and may skip Visit 2. Subjects who are not taking any medications at the screening visit that require washout may attend the clinic for Visit 2 earlier than 2 weeks and only after laboratory results have been reviewed by the investigator. An 8-hour fast is required before the GEBT. Subjects who required the Visit 2 GEBT will then complete Visit 3 (Day -14) within 7 days after the GEBT visit to confirm their eligibility based on the gastric emptying criteria. Once the subject is confirmed to have delayed gastric emptying, subjects will be instructed on the use of an electronic patient reported outcomes tool (ePRO) for collecting the daily symptoms of gastroparesis, daily dosing and meal time recordings, and capture of rescue medication use. The instrument used to capture symptom data will be the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD) along with a bloating severity scale. Subjects will record their symptoms once daily (in the evening) and will return to the clinic approximately 2 weeks later to assess their gastroparesis symptom eligibility based on the ANMS GCSI-DD (Visit 4, randomization). Subjects need to be compliant with completing the Daily Symptom Diary, defined as ≥80% diary completions, during the 2-week symptom assessment period.

Subjects will be randomized 1:1:1 into 1 of 3 treatment groups: TAK-906 maleate (TAK-906M) 25, and 50 mg capsule BID or matching placebo BID, stratified by IG and DG. Medication should be taken 1 dose in the morning approximately 1 hour before the first meal of the day and another dose in the evening approximately 1 hour before the main last meal of the day, at a regular dose interval. Subjects will take their first dose of study medication at the randomization visit (Day 1) and will take their morning dose in clinic at Visits 5, 6, and 7. Subjects will complete the Daily Symptom Diary daily for 12 weeks and complete visits at Weeks 4 (Visit 5), 8 (Visit 6), and 12 (Visit 7). At Day 1 and Weeks 4, 8, and 12/early termination, pharmacokinetic (PK) samples will be taken both predose and postdose. A safety follow-up phone call will be made approximately 30 days after last dose of study medication.

Subjects who withdraw prematurely will be followed up by the physician for an early termination visit as soon as possible and will continue completing the Daily Symptom Diary until this termination visit using the ePRO device. Subjects will be contacted for a follow-up safety call approximately 30 days after the last dose of study medication to check if any adverse events occurred during this follow-up period.

Primary Objective:

To assess the efficacy of treatment with 2 dose levels of TAK-906 in adult subjects with gastroparesis compared with placebo during 12 weeks of treatment.

Secondary Objectives:

To evaluate the safety and tolerability of TAK-906 doses compared with placebo during 12 weeks of treatment.

Additional Objectives:

- To evaluate the PK of TAK-906 in subjects with gastroparesis.
- To evaluate the effect of TAK-906 on quality of life compared with placebo.

Subject Population: Men and women with DG and IG aged ≥18 to 85 years, inclusive.

Number of Subjects:	**Number of Sites:**
Approximately 205 subjects TAK 906M 5 mg capsule BID: approximately 25 subjects prior to discontinuation of randomization into this dose arm TAK-906M 25 mg capsule BID: n=60 TAK-906M 50 mg capsule BID: n=60 Placebo capsule BID: n=60	Estimated total: Up to 120 sites in North America, Europe, and Japan
Dose Level(s):	**Route of Administration:**
TAK 906M 5 mg capsule BID: approximately 25 subjects prior to discontinuation of randomization into this dose arm TAK-906M 25 mg capsule BID TAK-906M 50 mg capsule BID Placebo capsule BID	PO
Duration of Treatment:	**Period of Evaluation:**
12 weeks	Approximately 22 weeks from screening through safety follow-up.

Main Criteria for Inclusion:

Subject eligibility is determined according to the following criteria before entry into the study:

- Adult men and women aged 18 to 85 years, inclusive, and with body mass index (BMI) ≥18 to ≤40 kg/m^2 inclusive.
- Subjects should have symptoms of gastroparesis (eg, postprandial fullness, nausea, vomiting, upper abdominal pain, and early satiety) for at least 3 months before screening as assessed by a physician.
- Subjects must have an average composite ANMS GCSI-DD symptom score ≥2 during the 7 days before randomization. The predominant symptom experienced by subjects must not be abdominal pain.
- Subjects must experience nausea: nausea subscale (of ANMS GCSI-DD) symptom score ≥2 at least 4 of 7 days or an average nausea subscale symptom score ≥2 during the 7 days before randomization. Nausea symptoms must not be attributable to a central disorder (eg, motion sickness, glaucoma, menstrual cycles, migraine headache).
- Subjects must have confirmed delayed gastric emptying using an accepted diagnostic testing method that is documented in the subject's medical records prior to screening, OR that is confirmed by the GEBT performed at Visit 2. Delayed gastric emptying is defined as time to gastric half emptying ($t_{1/2}$) ≥79 minutes (80th percentile).
- Absence of gastric outlet obstruction confirmed by upper gastrointestinal (GI), computed tomography, or endoscopy.

Special Inclusion for Subjects with Diabetes Mellitus

- Subjects must have glycosylated hemoglobin (HbA1c) ≤11% before the randomization visit.

Main Criteria for Exclusion:

Any subject who meets any of the following criteria will not qualify for entry into the study:

- Known secondary causes of gastroparesis including but not limited to Parkinson disease, cancer, viral illness, or connective tissue diseases.
- Predominant gastroparetic symptom is epigastric pain, diffuse abdominal pain, or pain associated with bowel movement.
- Is taking medications that affect gastric emptying including opioids, glucagon-like peptide-1 analogs (eg, exenatide, liraglutide), amylin analogs (eg, pramlintide), and cannabinoids.
- Prior history of gastric surgery, including but not limited to gastrectomy, gastric bypass, gastric banding bariatric surgery pyloroplasty, vagotomy, or fundoplication, which has manipulated the natural anatomy of the stomach.
- History of intrapyloric botulinum toxin injection within 3 months of screening or currently has a functioning implantable gastric electric stimulator.
- Nasogastric, percutaneous endoscopic gastrostomy, or percutaneous endoscopic jejunostomy feeding tube or inpatient hospitalization for gastroparesis within 2 weeks before the screening visit.
- Required parenteral nutrition for treatment of gastroparesis within 2 months before the screening visit.
- Previous diagnosis of gastric bezoar (the presence of retained liquid, bile, or small amounts of poorly organized food residue is permitted).
- Poor control of diabetes within 30 days before study entry, including diabetic ketoacidosis, hypoglycemia requiring medical intervention, admission for control of diabetes or diabetic complications.
- Elevated serum prolactin (>upper limit of normal [ULN]) at screening. A high prolactin level at the screening visit that is considered to be due to stress of venipuncture, chest wall stimulation, or other physiological causes may be retested after a few days and if normal, the subjects may be enrolled in the study.
- Medical history of hypogonadism, current clinically significant menstrual abnormalities, or other clinical features of hyperprolactinemia will be excluded.
- The subject has acute or chronic liver disease meeting any of the criteria described below:
  - The subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin >2.0 times the ULN.
  - The subject has pre-existing liver cirrhosis that meets Child-Pugh Class B (moderate; total score 7 to 9 points) or C (severe; total score 10 to 15 points) (see Appendix B).
  - The subject has acute or chronic hepatitis B or C virus infection, manifesting as one of the following at screening:
    - Positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). NOTE: if a subject tests negative for HBsAg, but positive for HBcAb, the subject would be eligible if the Investigator has documentation of other test results showing that the subject does not have active hepatitis B infection.
    - Subjects with positive hepatitis C antibody (HCV IgG) and quantitative HCV polymerase chain reaction (PCR). HCV PCR is performed only if HCV IgG is positive.
- Any signs/symptoms or history of extrapyramidal system disease and other clinically relevant central nervous system or neuropsychiatric disease including but not limited to tardive dyskinesia, neuroleptic malignant syndrome, acute dystonia, parkinsonian like symptoms, severe depression, and history of suicide attempt.
- The subject has known COVID-19 infection, or suspected COVID-19 infection (as assessed by the investigator).

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD composite score (nausea, early satiety, upper abdominal pain, and postprandial fullness).

Secondary Endpoints:

- Proportion of subjects with at least 50% reduction from baseline in ANMS GCSI-DD composite score at Week 12.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD nausea symptom score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD early satiety symptom score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD postprandial fullness symptom score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD upper abdominal pain symptom score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD recorded vomiting frequency.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD overall severity of gastroparesis symptoms score.
- Change from baseline to Week 12 of the treatment period in the bloating severity scale score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD total score (nausea, early satiety, upper abdominal pain, postprandial fullness, bloating, and vomiting).
- Proportion of symptomatic weeks (weeks with symptoms assessed as >mild [average ANMS GCSI-DD composite score ≥2]) during 12 weeks of treatment.
- Change from baseline to Week 12 of the treatment period in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) total score.

Safety and Tolerability Endpoints

- Safety and tolerability will be evaluated using the following general assessments:
  - Treatment-emergent adverse events.
  - Vital signs.
  - 12-lead electrocardiograms.
  - Clinical laboratory parameters (hematology, clinical chemistry, and urinalysis).

Additional Endpoints:

- Percentage of symptomatic days (days with symptoms assessed as >mild (ANMS GCSI-DD score ≥2) using the ANMS GCSI-DD during 12 weeks of treatment.
- Proportion of subjects with ≥20% reduction in ANMS GCSI-DD composite score from baseline in the last 6 consecutive weeks of the study.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD core symptom score (nausea, early satiety, upper abdominal pain, postprandial fullness, and vomiting).
- Change from baseline to Week 12 of the treatment period in Clinician Symptom Severity Rating form.
- Change from baseline to Week 12 of the treatment period in Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index (PAGI-QOL) total score.
- Differences at Week 12 in Overall Treatment Effect (OTE) Scales.
- Change from baseline to Week 12 in Clinical Global Impression Scale–Severity of Illness scale (CGI-S).
- Differences at Week 12 in Clinical Global Impression -Improvement scale (CGI-I).
- Change from baseline to Week 12 in Patient Global Impression of Severity (PGI-S).
- Differences at Week 12 in Patient Global Impression of Change (PGI-C).
- TAK-906 predose (trough) plasma concentration at Week 12.
- Change from baseline to Week 12 of the treatment period in Short Form-12 (SF12) Health Survey subscale scores.
- Use of rescue medication during the 12-week treatment period.

Statistical Considerations:

The full analysis set (FAS) will include all subjects who were randomized, received at least 1 dose of study drug, have baseline and at least 1 postbaseline value for assessment of efficacy. In the FAS efficacy summaries, subjects will be analyzed by the treatment to which they were randomized.

The safety set will include all subjects who were randomized and received at least 1 dose of double-blind study medication. In safety summaries, subjects will be analyzed according to the treatment they received. If a subject receives more than 1 treatment, the actual treatment will be defined as the one that is used most frequently. If the 2 most common treatments are used with equal frequency, then the randomized treatment will be used as the actual treatment.

Primary Efficacy Analysis: The primary endpoint is the change from baseline to Week 12 in weekly ANMS GCSI-DD composite score. Analysis will be based on a mixed model for repeated measurements (MMRM) with treatment, center, week, subject disease population (DG and IG), and treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured covariance structure if applicable. The point-estimates, nominal p-values and confidence intervals (CIs) for the primary analysis will be based on the Week 12 statistical comparisons between each of the 2 TAK-906 dose groups and placebo with respect to the primary endpoint. The 2 statistical tests for the primary efficacy analysis are 1-sided and will be conducted using a 5% level of significance. Nominal p-values will be evaluated for statistical significance. In addition, point estimates and CIs along with descriptive statistics for change from baseline scores in ANMS GCSI-DD at earlier time points, will be presented. The MMRM-based analysis assumes that missing data follow a missing-at-random (MAR) assumption.

Secondary Efficacy Analysis: The secondary endpoint of proportion of subjects with at least 50% reduction from baseline in ANMS GCSI-DD composite score will be analyzed at all time points by logistic regression adjusting for baseline score, subject disease population and treatment by the last observation carried forward method to handle missing data.

Sample Size Justification:

In order to manage the likelihood of statistical, clinical, and operational success of this study in the setting of the COVID-19 pandemic, the sample-size considerations are revisited in Protocol Amendment 8. The statistical testing is revised from 2-sided (with a significance level of 5%) to 1-sided (with a significance level of 5%), the planned sample size is reduced by 10 subjects per arm and randomization into the 5 mg dose arm is to be discontinued.

The sample-size rationale for the resultant reduced sample size and updated 1-sided statistical testing is as follows: Assuming a SD of 1.25 and a true difference of 0.625 between TAK-906M active dose and placebo in the change from baseline in the ANMS GCSI-DD composite score, and a 15% dropout rate, a total of 205 subjects is sufficient to achieve approximately 80% power to detect the treatment effect of 0.625 at a 1-sided 5% significance level. The total of 205 subjects consists of approximately 25 subjects who have already been randomized to receive 5 mg capsule BID prior to terminating randomization of subjects into the 5 mg dose arm, and 60 subjects per treatment groups of placebo, TAK-906M 25 mg, and TAK-906M 50 mg.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities except for those identified in the Study-Related Responsibilities template. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANMS GCSI-DD	American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression Scale–Global Improvement Scale
CGI-S	Clinical Global Impression Scale–Severity of Illness Scale
CI	confidence interval
CNS	central nervous system
C_{max}	maximum observed concentration
COVID-19	coronavirus disease-2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P-450
DA	dopamine
DG	diabetic gastroparesis
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ePRO	electronic patient reported outcomes
EPS	extrapyramidal symptoms
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEBT	Gastric Emptying Breath Test
GGT	γ-glutamyl transferase
GI	gastrointestinal
HbA1c	glycosylated hemoglobin

HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
hERG	human ether-à-go-go–related gene
HBsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IG	idiopathic gastroparesis
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IV	intravenous(ly)
LFT	liver function test
MAR	missing-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
NOAEL	no-observed-adverse-event level
OATP	organic anion transporting polypeptide
OTE	overall treatment effect
PAGI-QOL	Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
Pgp	P-glycoprotein
PGx	pharmacogenomics
PI	principal investigator
PK	pharmacokinetic(s)
PO	oral
PPS	per-protocol set
QD	once daily
QTc	QT and corrected QT
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan

SF12	Short Form-12 Health Survey
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	time to gastric half emptying
t_{max}	time of first occurrence of maximum observed concentration
TAK-906M	TAK-906 maleate
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

3.4 Corporate Identification

MPI	Millennium Pharmaceuticals, Inc., a subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	MPI, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

TAK-906 is being developed as an oral (PO) therapy for moderate to severe, diabetic gastroparesis (DG) and idiopathic gastroparesis (IG). A significant unmet medical need for safe and effective chronic therapies remains for these patients. Gastroparesis is a disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction. It is estimated that there is in the range of 5 to 10 million gastroparetics (approximately 3% of the total population) in the United States (US) [1], with idiopathic (36%), diabetic (29%), postsurgical (13%), and Parkinson (7%) etiologies comprising the majority of cases in the tertiary referral setting [2]. Symptoms consist of nausea, vomiting, early satiety, abdominal pain, and postprandial fullness that are chronic with episodic symptom exacerbation [3]. Gastroparesis causes nutritional compromise, impaired glucose control, and a reduced quality of life, independent of other factors such as age, tobacco and alcohol use, or type of diabetes [3]. The impact of gastroparesis has a serious outcome on day-to-day functioning is well-documented both for the patient's deteriorating quality of life, productivity, and on the direct and indirect economic burden placed on society [4].

Currently in the US, there exists a significant unmet medical need because there are no approved therapies for the chronic treatment of DG. Validated targets for gastroparesis are the dopamine (DA) receptors D_2 and D_3. The D_2 receptor antagonist metoclopramide is indicated for the short-term treatment of acute and recurrent DG and has been limited in dose and duration of treatment because of well-documented toxicities, the most notable of which are extrapyramidal symptoms (EPS) [5]. EPS are caused by the blockade of the D_2 receptor in the dorsal striatum and thus are

potential side effects of all centrally-acting drugs that share this mechanism of action, including D_2 receptor antagonists. Of greatest concern is tardive dyskinesia, a severe and often irreversible EPS. The risk of developing tardive dyskinesia increases with dose level and duration of treatment (total cumulative dose), and consequently, the US package insert for metoclopramide includes a black box warning regarding the chronic use of metoclopramide for longer than 12 weeks [6].

Domperidone is a peripherally-acting DA receptor D_2/D_3 antagonist marketed for use as an antiemetic and prokinetic agent in a number of countries worldwide, although not in the US because of its cardiovascular safety profile, which includes a risk for drug-induced QT prolongation, torsades de pointes, and sudden cardiac death [7]. DA receptor antagonists are effective in the treatment of delayed gastric emptying and gastroparesis symptoms because of the role of DA receptors D_2 and D_3 in the upper gastrointestinal (GI) tract and in the area postrema, which controls vomiting [8-10]. Both of these areas are outside of the blood brain barrier. Therefore, a peripherally-selective D_2/D_3 antagonist could achieve the desired efficacy without the undesired central nervous system (CNS) effects such as EPS [11,12].

TAK-906 is a peripherally acting (ie, limited penetration of the blood brain barrier) DA receptor D_2/D_3 antagonist.

4.2 Nonclinical Information

4.2.1 Nonclinical Pharmacology

In vitro studies of receptor binding affinity and activity and in vivo studies of pharmacodynamic effects on prolactin secretion in rats and apomorphine-induced emesis in dogs have demonstrated primary pharmacologic actions of TAK-906 consistent with D2/D3 antagonism. Overall, TAK 906 is expected to be effective in the treatment of gastroparesis, based on nonclinical pharmacology data demonstrating D2/D3 antagonism with a potency comparable to or greater than domperidone and metoclopramide.

4.2.2 Safety Pharmacology

A series of safety pharmacology studies evaluated TAK-906 as outlined in International Conference on Harmonisation (ICH) S7A, including assessments of cardiovascular safety, CNS safety, and respiratory safety. TAK-906 weakly blocked human ether-à-go-go–related gene (hERG) potassium channel current (50% inhibitory concentration [IC_{50}] = 15.6 µM). In a dog cardiovascular safety pharmacology study, small decreases in systolic and pulse pressure were observed at ≥10 mg/kg with a compensatory increase in heart rate with associated lower QT and PR interval electrocardiogram (ECG) parameters observed at 30 mg/kg. There were no changes in corrected QT interval (QTc). Changes in locomotor activity (rearing, basic, and fine movement) were observed at ≥100 mg/kg in the repeat-dose 28-day rat study, but TAK-906 was not associated with any other biologically significant changes in CNS or respiratory parameters.

4.2.3 Pharmacokinetics and Product Metabolism

Absorption, distribution, metabolism, excretion, and pharmacokinetic (PK) properties of TAK-906 and [^{14}C]TAK-906 were evaluated using in vitro or in vivo assays. Using the maleate form intended for the clinic, studies in rats and dogs demonstrated that TAK-906 is absorbed following PO administration. The absolute bioavailability (BA) of TAK-906 was approximately 19% in rats following PO gavage administration, and up to 18% in dogs following PO capsule administration. At pharmacologically relevant PO doses, time of first occurrence of maximum observed plasm concentration (t_{max}) was 20 to 30 minutes. TAK-906 administered PO shows a somewhat greater than proportional increase in TAK-906 exposure with dose across the wide range of doses studied; 3 to 1000 mg/kg in rats and 1 to 500 mg/kg in dogs. Exposure in female animals was generally greater than that in males but usually by less than 2-fold. Accumulation was not observed with repeated dosing. An in vitro permeability study of [^{14}C]TAK-906 using human colonic adenocarcinoma (Caco-2) cells showed that TAK-906 has moderate permeability.

[^{14}C]TAK-906-derived radioactivity distributed widely into tissues, and almost completely eliminated from them by 72 hours after a single PO dose to albino rats; in pigmented rats, [^{14}C]TAK-906-derived radioactivity had little affinity for melanin. Plasma protein binding of TAK-906 in mouse, rat, dog, and human plasma was ≥90% and mainly to human serum albumin (HSA). Penetration of TAK-906 into the brain is minimal as demonstrated by plasma-to-cerebrospinal fluid(CSF) level comparisons in rats and dogs using the PO route of administration, and by plasma to whole brain level comparisons in mice using the intraperitoneal (IP) route of administration.

In vitro, using hepatocytes from humans, rats, and dogs, TAK-906 is metabolized to a ketone reduction metabolite (M23) and unidentified metabolites. No unique human metabolites are observed. TAK-906 is mainly metabolized by a non-cytochrome P-450 (CYP) pathway and via CYP2C8 and CYP3A4/5. In vitro investigations demonstrated that formation of M23 occurred in human liver cytosol and not in CYP-expressing liver microsomes. Therefore, M23 is likely formed by a cytosolic nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reductase like aldo-keto (AKR) and/or short-chain dehydrogenase (SDR) rather than by CYP. A metabolic stability study with TAK-906 in human liver S9 with or without a pan CYP inhibitor (ABT), indicated the relative contribution of CYP and non-CYP toward in vitro metabolism of TAK-906 was 43.3% and 56.7%, respectively. In vivo metabolic profiling of plasma and excreta from rats and dogs indicated the presence of TAK-906, M23, *N*-dealkylated metabolite (M28), and unidentified metabolites. TAK-906 was the major component in rat and dog plasma. In fasted rats, the excretion of radioactivity was largely via feces. Biliary excretion was the major excretory route for TAK-906 and related substances in bile duct-cannulated rats. Similarly, in fasted dogs, urinary and fecal excretion were 8.0% and 91.3%, respectively, over 96 hours.

TAK-906 showed little potential to inhibit or induce CYP. TAK-906 is a substrate of P-glycoprotein (Pgp), OATP1B1 and OATP1B3, but not breast cancer resistance protein, organic anion transporter 1/3, organic cation transporter 2, multidrug and toxin extrusion transporter 1, and multidrug and toxin extrusion transporter 2-K. In vitro investigations using human hepatocytes and OATP1B1/1B3-expressing cells demonstrated that uptake of [^{14}C]TAK-906 into

human hepatocytes is primarily mediated by OATP1B1. TAK-906 is unlikely to inhibit transporter proteins at clinically relevant concentrations.

4.2.4 Toxicology

The safety of TAK-906 was tested in range-finding and pivotal repeat-dose toxicity studies up to 13 weeks in duration in rats and dogs with once daily oral administration. Rat and dog repeat dose studies with twice daily dosing (BID) up to 28-days were completed to be consistent with the BID clinical dose regimen and to guide dose selection for 6-month rat and 9-month dog BID studies. A full battery of genotoxicity assays (in vitro Ames and chromosome aberration and in vivo rat micronucleus assays), embryo-fetal development studies in rats and rabbits, a fertility and early embryonic development study in rats, and a phototoxicity study in rats were also conducted. Mouse repeat dose BID studies were conducted to guide dose selection for a 6-month transgenic mouse carcinogenicity study.

Dose-limiting toxicity was seen in the form of tremors and weight loss in dogs treated with TAK-906 at ≥250 mg/kg for up to 4 days. At lower repeated doses (<100 mg/kg/day), slight tremor and the presence of expected class-related pharmacological effects, including signs associated with mild sedation, were observed in dogs.

In the pivotal 13-week repeat-dose toxicity study in rats with TAK-906 administered once daily (QD) by PO gavage, the no-observed-adverse-event level (NOAEL) was 1000 mg/kg/day. Target organ effects in male and female mammary tissue, mucification in the cervix and vagina, and corpus luteum hypertrophy in the ovary were associated with hyperprolactinemia, which is a known indicator for target engagement for this drug class and may result in reproductive changes consistent with hyperprolactinemia (ie, amenorrhea, infertility in females, gynecomastia in males).

In the pivotal 13-week repeat-dose toxicity study in dogs with TAK-906 administered QD PO by capsule, the NOAEL was 50 mg/kg/day, at which CNS-associated pharmacological effects typical of this pharmacologic class occurred at 50 mg/kg/day, including decreased activity, tremors, incoordination (ataxia), decreased muscle tone (drooping eye lids), partly closed eyes (squinting), and protruding nictitating membrane (periocular swelling). Based on the overall nonclinical safety profile, the dog is considered the more sensitive species.

In 28-day repeat dose toxicity studies with TAK-906 in both rats and dogs, NOAELs were lower with BID versus QD administration. The 28-day rat BID NOAEL was determined to be 150 mg/kg BID (300 mg/kg/day), as doses of 500 mg/kg BID (1000 mg/kg/day) were not tolerated and adverse liver findings (hepatocellular vacuolation with occasional inflammation) were noted at 375 mg/kg BID (750 mg/kg/day). The 28-day female dog BID NOAEL was determined to be 10 mg/kg BID (20 mg/kg/day) due to adverse prolactin-related mammary gland inflammation and fibrosis at 30 mg/kg BID (60 mg/kg/day).

TAK-906 was nongenotoxic in in vitro mutagenicity and chromosomal aberration assays or in an in vivo micronucleus assay in rats at a limit dose of 1000 mg/kg BID (2000 mg/kg/day total dose) administered by PO gavage. TAK-906 was negative for cutaneous and ocular phototoxicity in pigmented rats at doses up to 500 mg/kg BID (1000 mg/kg/day).

In the pivotal rat embryo-fetal development study at QD doses of 30, 100, and 300 mg/kg/day, TAK-906-related clinical observations of squinting eyes, clear ocular discharge, hypoactivity, and dilated vagina were observed at 300 mg/kg/day. TAK-906 did not cause fetal toxicity or developmental effects at any dose level. The maternal and fetal NOAELs were 100 mg/kg/day and 300 mg/kg/day, respectively. In the pivotal rabbit embryo-fetal development study at doses of 50, 150, and 500 mg/kg BID (100, 300, and 1000 mg/kg/day), TAK-906 did not result in maternal toxicity, fetal toxicity, or developmental effects at any dose level. Based on a lack of adverse effects, the rabbit maternal and fetal NOAEL was 500 mg/kg BID (1000 mg/kg/day). In the pivotal rat fertility and early embryonic development study at doses of 50, 150, and 325 mg/kg BID (100, 300, and 650 mg/kg/day) in males and females, TAK-906 was associated with effects on gross necropsy findings and/or organ weights in the prostate, uterus, and ovary, reproductive performance, and intrauterine parameters at ≥100 mg/kg/day. The NOAEL for female reproductive toxicity and early embryonic toxicity could not be determined because all doses were considered adverse. The effects on reproduction performance in males were considered secondary to the effects noted for the females. The NOAELs for systemic toxicity were 300 mg/kg/day and 650 mg/kg/day for males and females, respectively.

4.3 Human Experience

4.3.1 Clinical Pharmacology

To date, 6 clinical studies with TAK-906 maleate (TAK-906M) capsule have been completed, and 1 clinical study is ongoing in subjects with DG and IG.

Study AT-01C consisted of 2 phases: a single ascending dose phase and a multiple ascending dose phase. In general, PO administration of single (5 to 300 mg) or multiple (50 or 100 mg BID over 5 days) doses of TAK-906M was safe and well tolerated in healthy male and female subjects.

TAK-906 showed a rapid absorption (median plasma TAK-906 t_{max} across both single and multiple PO doses of TAK-906M across all cohorts was approximately 1.1 hours) and a rapid elimination over 24 hours (mean plasma TAK-906 terminal disposition phase half-life was approximately 4.0 hours across all cohorts in the single ascending dose phase and was 11.0 and 6.2 hours at the 50 and 100 mg BID doses, respectively, on Day 5 in the multiple ascending dose phase). Food significantly reduced exposure to TAK-906M 25 mg; maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) in fed subjects were approximately 40% lower compared with the same subjects when fasting. With single PO doses of TAK-906M between 5 and 300 mg, TAK-906 exposure increased in a manner proportional to dose increment. With BID dosing of 50 and 100 mg TAK-906M for 5 days, accumulation was minor. Additionally, TAK-906 PK profiles were generally similar between Japanese men (TAK-906-1004) and non-Japanese healthy men and women (Study AT-01C).

M23, the major and pharmacologically inactive metabolite identified in rat and dog plasma, represented approximately 11% of the TAK-906 (parent) AUC. Following PO administration of TAK-906, approximately 1.5% of the administered dose was excreted as unchanged TAK-906 in the urine of humans. Based on preliminary population PK analysis (utilizing data from first in

human AT-01C and TAK-906-1002), estimated glomerular filtration rate (eGFR) had no significant effect on exposure of TAK-906 in healthy subjects or DG and IG subjects.

Coadministration of itraconazole (potent inhibitor of CYP3A4 and Pgp) with TAK-906 increased geometric mean C_{max} by approximately 1.98-fold and area under the concentration-time curve from time 0 to infinity of TAK-906 by approximately 1.28-fold (TAK-906-1003). AUC_{∞} and C_{max} of TAK-906 decreased approximately 12% to 13% when coadministered with 40 mg esomeprazole compared to 25 mg TAK-906 administration alone in healthy subjects (TAK-906-1006).

Coadministration of a single intravenous (IV) infusion of 600 mg rifampin (a prototypic inhibitor of OATP1B1 and OATP1B3) with a single oral dose of 25 mg TAK-906 increased the mean area under the concentration-time curve from time 0 to infinity (AUC_{∞}), and C_{max} by approximately 5.2 and 6.2-fold (TAK-906-1009).

The prolactin increase following PO administration of single doses of TAK-906M, which was substantial compared with placebo, was rapid and short-lived. Serum prolactin concentration did not increase in a dose-proportional manner. There was little if any accumulation in serum prolactin concentration with BID dosing for 5 days.

The concentration QT interval with Fridericia correction method (QTcF) analysis of data from Study AT-01C was performed using linear mixed effects modeling methods. The analysis demonstrated that TAK-906M in single doses from 5 to 300 mg, which resulted in plasma concentrations of up to 171 ng/mL, did not have a clinically meaningful effect (<10 msec) on the placebo-adjusted change from baseline in QTcF (at relevant concentration range <200 ng/mL).

In summary, given the efficacy associated with D_2 antagonist drugs and the nonclinical and phase 1 clinical observations, TAK-906 may be a promising new therapeutic for the treatment of gastroparesis.

Please refer to the TAK-906 Investigator's Brochure (IB) for complete information on the investigational product.

4.4 Rationale for the Proposed Study

The prevalence of gastroparesis in the US is 24.2 per 100,000 [1]. The most common causes of gastroparesis in these countries are idiopathic (~36%) and diabetes (~29%). Domperidone and metoclopramide are D_2 antagonists, which have been shown to reduce symptoms associated with gastroparesis but are associated with serious cardiovascular (domperidone) and CNS (metoclopramide) side effects. There is, therefore, a significant unmet need for a safe and efficacious chronic treatment of gastroparesis in patients. TAK-906 is a peripherally acting D_2/D_3 antagonist with minimal known CNS penetration and cardiac effects, likely attributable to structural difference or chemotype difference from metoclopramide and domperidone. In phase 1 studies in healthy volunteers, TAK-906 demonstrated suitable PK and pharmacodynamic (PD) properties without the CNS liabilities of metoclopramide or cardiac liabilities associated with domperidone. Given the positive on-target effects and good tolerability, TAK-906 is being developed for use in patients with gastroparesis.

TAK-906-2002 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b study to evaluate the efficacy and safety of BID PO administration of TAK-906M capsules in adult male and female subjects aged 18 to 85 years inclusive, with symptomatic IG or DG.

Pharmacogenomic (PGx) analysis may be conducted to evaluate the contribution of genetic variance and/or gene expression on drug response, for example, its efficacy and safety. Participation of study subjects in PGx sample collection is optional.

As PGx is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or disease, which may lead to additional hypothesis-generating exploratory research on stored samples.

4.5 Benefit/Risk Profile

Gastroparesis causes nutritional compromise, impaired glucose control, and a reduced quality of life, independent of other factors such as age, tobacco and alcohol use, or type of diabetes [4]. The serious negative impact of gastroparesis on day-to-day functioning is well-documented both for the patient's deteriorating quality of life, productivity and on the direct and indirect economic burden placed on society.

DA receptors D_2 and D_3 have been shown to be validated targets for gastroparesis since D_2 receptors are known to be involved in the control of nausea and vomiting, and D_3 receptors play a role in gastric motility [8-10]. Blocking D_2 receptors is associated with a reduction in nausea and vomiting and blocking D_3 receptors is associated with an increase in gastric motility [8-10].

However, DA receptor D_2/D_3 antagonist domperidone's safety profile includes a risk for drug-induced QT prolongation, cardiac arrhythmia, and death [7], and DA receptor D_2 antagonist metoclopramide's neurological safety profile includes increased risk of adverse events (AEs) related to EPS and the potential for tardive dyskinesia. In addition, DA receptor D_2/D_3 antagonists elevate serum prolactin levels, which may lead to AEs related to reproductive endocrinology such as infertility, galactorrhea, amenorrhea, gynecomastia, and impotence in some subjects.

Consequently, there currently exists a significant unmet medical need because there are no approved therapies for the chronic treatment of DG or IG.

TAK-906 is a peripherally acting DA receptor D_2/D_3 antagonist with a high safety margin between in vitro hERG channel inhibition and projected efficacious clinical exposures; no effects in dog ECG parameters in nonclinical safety studies, no clinically significant cardiovascular AEs in the phase 1 healthy subject study or in the drug-drug interaction studies were observed. Therefore, treatment with TAK-906 is not expected to result in the adverse effects associated with cardiotoxicity especially the QT prolongation observed with domperidone. EPS side effects such as tardive dyskinesia, acute dystonia and Parkinson-like symptoms have been reported with the use of metoclopramide. However, TAK-906 is a peripherally acting DA receptor D_2/D_3 antagonist with limited CNS penetration expected. As such, the risk of CNS and extrapyramidal system effects are anticipated to be low. Hyperprolactinemia and prolactin related symptoms are

expected of all D_2 receptor antagonists such as domperidone, metoclopramide and neuroleptics. However, given the relatively short (12 weeks) duration of the study, this risk is considered manageable and risk mitigation measures have been included in this study to ensure safety of subjects who may develop hyperprolactinemia or prolactin related symptoms.

Therefore, given the significant unmet medical need and the expected reduced cardiovascular and CNS safety risk and manageability of risk of hyperprolactinemia/prolactin related symptoms compared with other drugs in the class, the benefit-risk profile is thought to be favorable for the use of clinically effective doses of TAK-906 in DG/IG subjects.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To assess the efficacy of treatment with 2 dose levels of TAK-906 in adult subjects with gastroparesis compared with placebo during 12 weeks of treatment.

5.1.2 Secondary Objective

To evaluate the safety and tolerability of TAK-906 doses compared with placebo during 12 weeks of treatment.

5.1.3 Additional Objectives

- To evaluate the PK of TAK-906 in subjects with gastroparesis.
- To evaluate the effect of TAK-906 on quality of life compared with placebo.

5.2 Endpoints

5.2.1 Primary Endpoint

- Change from baseline to Week 12 of the treatment period in the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD) composite score (nausea, early satiety, upper abdominal pain, and postprandial fullness).

5.2.2 Secondary Endpoints

- Proportion of subjects with at least 50% reduction from baseline in ANMS GCSI-DD composite score at Week 12.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD nausea symptom score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD early satiety symptom score.

- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD postprandial fullness symptom score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD upper abdominal pain symptom score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD recorded vomiting frequency.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD overall severity of gastroparesis symptoms score.
- Change from baseline to Week 12 of the treatment period in the bloating severity scale score.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD total score (nausea, early satiety, upper abdominal pain, postprandial fullness, bloating, and vomiting).
- Proportion of symptomatic weeks (weeks with average composite symptom score assessed as >mild [ANMS GCSI-DD score ≥2]) during 12 weeks of treatment.
- Change from baseline to Week 12 of the treatment period in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) total score.

5.2.3 Safety and Tolerability Endpoints

- Safety and tolerability will be evaluated using the following general assessments:
  - Treatment-emergent AEs.
  - Vital signs.
  - 12-lead ECGs.
  - Clinical laboratory parameters (hematology, clinical chemistry, and urinalysis).

5.2.4 Additional Endpoints

- Percentage of symptomatic days (days with symptoms assessed as >mild [ANMS GCSI-DD Score ≥2]) using the ANMS GCSI-DD during 12 weeks of treatment.
- Proportion of subjects with ≥20% reduction in ANMS GCSI-DD composite score from baseline in the last 6 consecutive weeks of the study.
- Change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD core symptom score (nausea, early satiety, upper abdominal pain, postprandial fullness, and vomiting).
- Change from baseline to Week 12 of the treatment period in Clinician Symptom Severity Rating form.
- Change from baseline to Week 12 of the treatment period in Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index (PAGI-QOL) total score.

- Differences at Week 12 in Overall Treatment Effect (OTE) Scales.
- Change from baseline to Week 12 in Clinical Global Impression Scale–Severity of Illness Scale (CGI-S).
- Differences at Week 12 in Clinical Global Impression Scale–Global Improvement Scale (CGI-I).
- Change from baseline to Week 12 in Patient Global Impression of Severity (PGI-S).
- Differences at Week 12 in Patient Global Impression of Change (PGI-C).
- TAK-906 predose (trough) plasma concentration at Week 12.
- Change from baseline to Week 12 of the treatment period in Short Form-12 (SF12) Health Survey subscale scores.
- Use of rescue medication during the 12-week treatment period.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a global multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b study to evaluate the efficacy and safety of BID PO capsule administration of a peripherally acting DA receptor D_2/D_3 antagonist, TAK-906, in adult male and female subjects aged 18 to 85 years, inclusive, with symptomatic IG or DG. Gastroparesis is a disorder of the stomach characterized by delayed gastric emptying, in the absence of mechanical obstruction.

The study is designed to characterize the dose-response relationship to support dose selection for evaluation of subjects to be enrolled in the planned phase 3 studies.

Subjects will attend the study site for a screening/consent visit (Visit 1, Day -35), when their consent will be obtained, and general eligibility to participate in the study will be reviewed. After signing the informed consent form, subjects will have a blood sample taken to assess their laboratory values. Subjects will discontinue all excluded medications and return to the site 3 to 17 days later to perform a 4-hour ^{13}C-Spirulina GEBT (Visit 2, Day -21). Subjects who have confirmation of delayed gastric emptying confirmed by an accepted diagnostic testing method (ie, scintigraphy, GEBT, or wireless motility capsule) that is documented in the subject's medical records prior to screening, are not required to undergo the Visit 2 GEBT, and may proceed directly to Visit 3 for instruction on use of the electronic patient reported outcomes tool. Subjects who are not taking any medications at the screening visit that require washout may attend the clinic for Visit 2 earlier than 2 weeks and only after laboratory results have been reviewed by the investigator. An 8-hour fast is required before the GEBT. Subjects will then complete Visit 3 (Day -14) within 7 days after the GEBT visit to confirm their eligibility based on the gastric emptying criteria. At Visit 3, subjects confirmed to have delayed gastric emptying will be instructed on the use of an electronic patient reported outcomes tool (ePRO) for collecting the daily symptoms of gastroparesis, daily dosing and meal time recordings, and capture of rescue

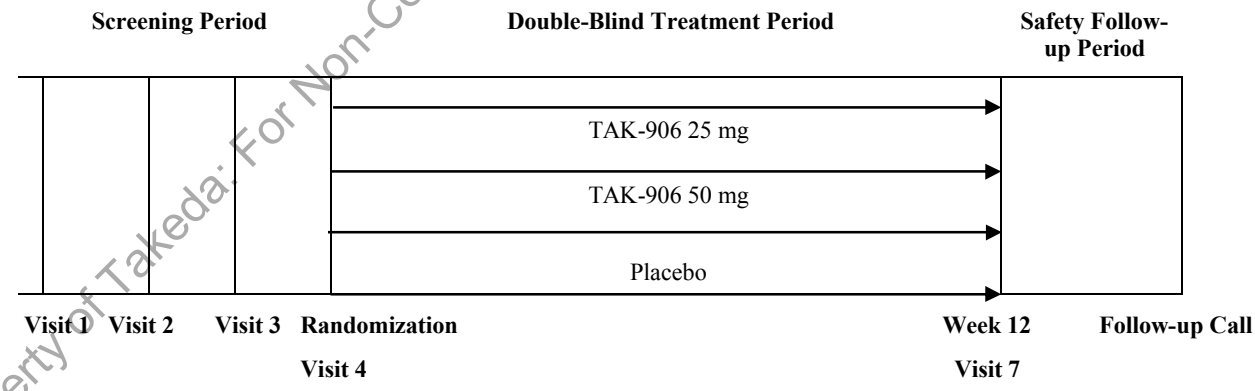
medication use. The instrument used to capture symptom data will be the ANMS GCSI-DD along with a bloating severity scale. Subjects will record their symptoms once daily (in the evening) and will return to the clinic approximately 2 weeks later to assess their gastroparesis symptom eligibility based on the ANMS GCSI-DD (Visit 4, randomization). Subjects need to be compliant with completing the Daily Symptom Diary, defined as ≥80% diary completions, during the 2-week symptom assessment period.

Subjects will be randomized 1:1:1 into 1 of 3 treatment groups: TAK-906 maleate (TAK-906M) 25, and 50 mg capsule BID or matching placebo BID, stratified by IG and DG. Medication should be taken 1 dose in the morning approximately 1 hour before the first meal of the day and another dose in the evening approximately 1 hour before the main last meal of the day, at a regular dose interval. Subjects will take their first dose of study medication at the randomization visit (Day 1) and will take their morning dose in clinic at Visits 5, 6, and 7. Subjects will complete the Daily Symptom Diary daily for 12 weeks and attend the clinic at Weeks 4 (Visit 5), 8 (Visit 6), and 12 (Visit 7). At Day 1 and Weeks 4, 8, and 12/early termination, PK samples will be taken both predose and postdose. A safety follow-up phone call will be made approximately 30 days after last dose of study medication.

Subjects who withdraw prematurely will be seen by the physician for an early termination visit as soon as possible and will continue completing the Daily Symptom Diary until this termination visit using the ePRO device. They will then be contacted for a follow-up safety call approximately 30 days after the last dose of study medication to check if any AEs occurred during this follow-up period.

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



*Provides view of updated schematic following discontinuation of randomization into the 5 mg treatment arm

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Rationale for Study Design

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b study to evaluate the efficacy and safety of BID PO administration of a peripherally acting DA receptor D_2/D_3 antagonist, TAK-906 in adult male and female subjects aged 18 to 85 years inclusive, with symptomatic IG or DG. Subjects will be eligible for enrollment if they have a body mass index (BMI) ≥18 to ≤40 kg/m^2 and a minimum of 3-month history of symptoms consistent with gastroparesis as assessed by a physician (eg, postprandial fullness, nausea, vomiting, upper abdominal pain, and early satiety [at least intermittently]). Subjects need to be compliant with completing the Daily Symptom Diary, defined as ≥80% diary completions during the 2-week symptom assessment period (+3-day window). Subjects without previous confirmation of delayed gastric emptying prior to screening will undergo a GEBT after they have stopped taking prohibited medications.

Subjects who have a history of gastroparesis symptoms and confirmed slow gastric emptying meeting entry criteria will be instructed on the use of an ePRO tool to record their baseline symptoms. They must have an average composite ANMS GCSI-DD symptom score ≥2 during the last week of the screening period. The predominant symptom experienced by subjects must not be abdominal pain and subjects must also experience nausea: nausea subscale (of ANMS GCSI-DD) symptom score ≥2 at least 4 of 7 days or an average nausea subscale symptom score ≥2 during the last week of the screening period. Nausea symptoms should not be attributable to a central disorder.

Subjects with diabetes must qualify by having diabetes mellitus with glycosylated hemoglobin (HbA1c) ≤11% at screening, before randomization.

The comprehensive inclusion criteria outlined with the focus on delayed gastric emptying, history of gastroparesis symptoms, and moderate-to-severe gastroparesis symptoms at baseline, before receiving study drug, will ensure the enrollment of an appropriate population of subjects with moderate-to-severe symptomatic gastroparesis most likely to respond to and benefit from treatment with TAK-906.

The study will be randomized, double-blind, placebo-controlled, parallel-group enrollment with 3 treatment arms (2 active doses and placebo) to characterize the dose-response relationship for TAK-906. The use of randomization and blinding will remove bias on allocating subjects to treatment arms and on treatment outcomes. There will be a screening period of up to 5 weeks, during which gastric motility and gastroparesis symptoms will be assessed. The run-in period is of sufficient duration to allow subjects to stop taking their prescribed GI motility drugs before measuring their GI motility using the GEBT, where required. It will also allow subjects to become proficient at using the ePRO device and providing sufficient and accurate baseline symptom data to assess their suitability for randomization. Subjects will then be treated for 12 weeks during which time their symptoms will be recorded daily. A 12-week treatment period has been selected for this study as this is a sufficient duration to allow for the drug to take effect and for the collection of symptom data to evaluate efficacy and for the collection of safety data.

The study will also be used to perform final validation of the ePRO tool (Daily Symptom Diary) [13] for use in the phase 3 studies.

Overall, the design of the study, including the use of randomization, blinding, size, duration, subject population, and endpoints will provide good quality efficacy and safety data in a safe study environment to show if there is a treatment effect of study drug.

6.2.2 Rationale for Dose

This study was originally designed with 3 active treatment doses that were chosen based on the data in healthy subjects from the phase 1 Study AT-01C. The TAK-906 5, 25, and 50 mg BID doses are expected to maximize therapeutic effect and minimize potential safety and tolerability concerns. Under Protocol Amendment 8, randomization into the 5 mg dose arm has been discontinued. Randomization into the 5 mg dose arm was halted to improve operational feasibility in the setting of the COVID-19 pandemic and to reduce the number of subjects being exposed to a potentially minimally efficacious dose that likely approaches the lower end of the dose response curve. This change was not necessitated by safety findings. Several drug-related parameters were evaluated for dose-selection including safety, tolerability, PK, and PD. In general, oral administration of single (5 to 300 mg) or multiple (50 or 100 mg BID over 5 days) doses of TAK-906 was well tolerated in healthy male and female subjects. Prolactin has been used as a measure of target engagement. At a TAK-906 plasma concentration of approximately 20 ng/mL (~C_{max} of 50 mg dose), the TAK-906–prolactin concentration relationship reached near maximum, and without clinically meaningful adverse effects. TAK-906 plasma concentration of approximately 2 ng/mL (~C_{max} of 5 mg dose) is expected to be the minimum effective concentration. The 25 mg dose is between the estimated minimum and maximum effect concentration and is expected to be a safe and efficacious dose. The 10-fold window in PK exposure (2 ng/mL to 20 ng/mL) will permit adequate characterization of the exposure/response relationships for TAK-906.

6.2.3 Rationale for Placebo

Currently in the US, there are no approved therapies for the chronic treatment of DG. Metoclopramide is indicated for the short-term treatment of acute and recurrent DG and has been limited in dose and duration of treatment by well-documented toxicities, the most notable of which are a category of movement disorders known as EPS, including tardive dyskinesia, a severe and often irreversible EPS [5]. The risk of developing tardive dyskinesia increases with dose level and duration of treatment and as such, the US package insert includes a black box warning regarding the chronic use of metoclopramide for longer than 12 weeks.

Domperidone is a DA receptor D_2/D_3 antagonist marketed for use as an antiemetic and prokinetic agent in a number of countries worldwide, although not in the US because of its cardiovascular safety profile, which includes a risk for drug-induced long QT syndrome, torsades de pointes, and sudden cardiac death [7].

Erythromycin is a macrolide antibiotic with prokinetic properties. In addition to the risk of developing antimicrobial resistances, tachyphylaxis develops in patients receiving chronic

erythromycin therapy, due to down-regulation of motilin receptors, which can develop as early as a few days of initiating therapy [14].

Therefore, because of safety concerns associated with the above treatments and the fact that this will be a global study including the US, there is no suitable active comparator that can be used in a clinical study of 12 weeks duration.

There is often a significant treatment response to placebo in patients with functional GI disease including gastroparesis and this has been observed in clinical trials using experimental GI motility compounds such as relamorelin [15]. It is therefore important to take this potential for a placebo effect into account by having a placebo treatment arm when designing the study to show that there is a positive treatment effect over placebo and not just from baseline to the end of the study.

The study is therefore placebo-controlled as the choice of competitors is severely limited by potential side effects (metoclopramide, domperidone) or tachyphylaxis (erythromycin) and to observe any potential for a placebo response in the study population.

During screening, there will be no restrictions on the use of rescue medication until Visit 3 (Day -14). After Visit 3, the use of rescue medication will be limited to 2 doses per day for up to 3 days per week only when subjects experience nausea and/or vomiting (oral intake decreased without significant weight loss, dehydration or malnutrition) of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or greater. Note that during the randomized treatment period, rescue medication use will be limited to BID for up to 3 days per week. If the subject uses rescue medication BID for 3 days per week for 2 consecutive weeks, the subject will be discontinued from the study due to lack of efficacy. All types and doses of antinausea/antivomiting rescue medication will be documented and the rescue medication will be provided by the subject's treating physician.

Antinausea/antivomiting rescue medication is recommended for use as nausea and vomiting are likely to be the most debilitating and commonly reported symptoms in the gastroparesis population [2,16,17]. The preferred rescue medication is ondansetron 4 mg given orally. Alternatively, antiemetics such as diphenhydramine, dimenhydrinate, promethazine, or others may be provided based on local guidelines and principal investigator (PI) and subject preference. All types and doses of antinausea/antivomiting rescue medication prescription will be documented and the rescue medication will be provided by the subject's study investigator.

6.2.4 Rationale for Endpoints

Gastroparesis is a disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction and is associated with symptoms consisting of nausea, vomiting, early satiety, abdominal pain, and postprandial fullness that are chronic with episodic symptom exacerbation [14]. The core signs and symptoms of gastroparesis, reported by incidence, are nausea (92% to 96%), vomiting (68% to 88%), postprandial fullness (54% to 77%), early satiety (42% to 86%), and upper abdominal pain (36% to 85%) [2,16,17]. Given that gastroparesis is a symptomatic disease, it is important to assess improvement in symptoms as a clinical outcome. Symptom data will be used for the primary endpoint in the study which is

change from baseline to Week 12 of the treatment period in the ANMS GCSI-DD Composite Score (nausea, early satiety, upper abdominal pain, and postprandial fullness). Symptom data will be captured each evening using the Daily Symptom Diary on an ePRO device.

As part of the Daily Symptom Diary, the ANMS GCSI-DD has been selected for use in this study as it is currently under development to measure symptoms to evaluate potential new treatments in DG and IG clinical trials. The ANMS GCSI-DD was based on the original Gastroparesis Cardinal Symptom Index (GCSI) [18,19], which is the most frequently used symptom severity measure in gastroparesis clinical trials and other clinical studies [16,20-27], including the National Institutes of Health Gastroparesis Clinical Research Consortium Gastroparesis Registry study [28,29].

Efficacy will be based on a significant difference between group means. The primary endpoint will be between group differences on the ANMS CGSI-DD composite score of nausea, upper abdominal pain, early satiety, and postprandial fullness. Furthermore, item level responses will be evaluated as secondary endpoints to determine which symptom item(s) are driving changes in the overall composite score, and to evaluate if any symptoms within the composite score are worsening. Of note, bloating will also be recorded using the electronic diary along with the other symptoms routinely captured in the ANMS GCSI-DD (nausea, early satiety, upper abdominal pain, postprandial fullness, vomiting episodes, and overall symptom severity) for ease of patient use. Bloating is being captured as an additional endpoint using the electronic diary and is currently not part of the ANMS GCSI-DD.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit-risk profile for TAK-906 such that the benefit-risk is no longer favorable for subjects participating in the study. This may include (but not limited to):
  - Extrapyramidal symptoms and other clinically relevant CNS or neuropsychiatric disease including tardive dyskinesia, neuroleptic malignant syndrome, acute dystonia, parkinsonian-like symptoms, convulsive seizure, severe mental depression, and hallucinations.
  - Evidence of other serious clinical problems that would put subjects exposed to TAK-906 at risk.
  - Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

The Independent Data Monitoring Committee (IDMC) will assess the incidence and nature of safety events and will make appropriate recommendations, which could include continue, modify, temporarily suspend, or terminate the study.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

If the sponsor, an institutional review board (IRB)/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization before the initiation of any study procedures.
3. The subject should have symptoms of gastroparesis (eg, postprandial fullness, nausea, vomiting, upper abdominal pain, and early satiety) for at least 3 months before screening as assessed by a physician.
4. The subject must have confirmed delayed gastric emptying by meeting 1 of the following criteria:
   a) Confirmed by an accepted diagnostic testing method (GEBT, scintigraphy, or wireless motility capsule) that is documented in the subject's medical records prior to screening; OR
   b) Subjects without previous confirmation of delayed gastric emptying prior to screening will undergo a GEBT after they have stopped taking prohibited medications.
5. The subject must have an average composite ANMS GCSI-DD symptom score ≥2 during the 7 days before randomization. The predominant symptom experienced by subjects must not be abdominal pain.

6. The subject must experience nausea: nausea subscale (of ANMS GCSI-DD) symptom score ≥2 at least 4 of 7 days or an average nausea subscale symptom score ≥2 during the 7 days before randomization. Nausea symptoms must not be attributable to a central disorder (eg, motion sickness, glaucoma, menstrual cycles, migraine headache).
7. The subject is an adult man or woman aged 18 to 85 years, inclusive, at the first screening visit.
8. The subject has a BMI of ≥18 to ≤40 kg/m^2 inclusive.
9. Absence of gastric outlet obstruction confirmed by upper GI, computed tomography or endoscopy.
10. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use barrier method of contraception (eg, condom with or without spermicide)* from signing of informed consent throughout the duration of the study and for 95 days after last dose. The female partner of childbearing potential of the male subject should also use a highly effective method of contraception* during this period.
11. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use a highly effective method of contraception* from signing of informed consent throughout the duration of the study and for 35 days after the last dose.

*Definitions and highly effective methods of contraception are defined in Section 9.1.11 and reporting responsibilities are defined in Section 9.1.12.

Special Inclusion for Subjects With Diabetes Mellitus

12. A subject with diabetes mellitus must have HbA1c ≤11% before the randomization visit.

During Screening Period

13. The subject has shown compliance with the completion of the Daily Symptom Diary, defined as ≥80% diary completions for a minimum of 14 days during the symptom assessment period.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days or 5 half-lives, whichever is longer, before screening.
2. The subject's predominant symptom is epigastric pain, diffuse abdominal pain, or pain associated with bowel movement.
3. The subject has received TAK-906 in a previous clinical study or as a therapeutic agent.
4. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

5. The subject has, in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at screening.
6. The subject takes or is required to take excluded medications (see Section 7.3).
7. If female, the subject is pregnant, lactating, breastfeeding, or has breastfed within 6 months or is intending to become pregnant before participating in this study, during the study, and within 35 days after last dose of the study drug; or intending to donate ova during such time period.
8. If male, the subject intends to donate sperm during the course of this study or for 95 days thereafter.
9. The subject has known secondary causes of gastroparesis including but not limited to Parkinson disease, cancer, viral illness, or connective tissue diseases.
10. The subject has a history of gastric surgery, including but not limited to gastrectomy, gastric bypass, gastric banding, bariatric surgery, pyloroplasty, vagotomy, or fundoplication, which has manipulated the natural anatomy of the stomach.
11. The subject has a presence of thyroid dysfunction not controlled by treatment.
12. The subject has a known or history of inflammatory bowel disease.
13. The subject has current chronic diarrhea (defined as >3 loose bowel movements daily for at least 2 weeks).
14. The subject has a history of intrapyloric botulinum toxin injection within 3 months of screening or currently has functioning implantable gastric electric stimulator.
15. The subject has had a nasogastric, percutaneous endoscopic gastrostomy, or percutaneous endoscopic jejunostomy feeding tube or inpatient hospitalization for gastroparesis within 2 weeks before the screening visit.
16. The subject has had required parenteral nutrition for treatment of gastroparesis within 2 months before the screening visit.
17. The subject has a previous diagnosis of gastric bezoar (the presence of retained liquid, bile, or small amounts of poorly organized food residue is permitted).
18. The subject has a clinically significant known disorder of small intestinal absorption (eg, refractory celiac disease), exocrine pancreatic function (eg, chronic pancreatitis), and pulmonary function (eg, severe chronic obstructive pulmonary disease or O_2 requirements).
19. The subject has a history of alcohol or drug abuse or dependence within the last year before screening or a positive drug test result at screening.
20. The subject is a chronic smoker who is unable or unwilling to abstain from smoking during the performed GEBT at Visit 2.

21. The subject has experienced poor control of diabetes within 30 days prior to randomization, including diabetic ketoacidosis, hypoglycemia requiring medical intervention, admission for control of diabetes, or diabetic complications.
22. The subject has a history of anorexia nervosa, binge eating or bulimia within 5 years of screening.
23. The subject has a history of acute myocardial infarction or unstable angina within 12 months before study entry.
24. The subject has a severe cardiovascular autonomic neuropathy.
25. The subject has any clinically important abnormalities in rate, rhythm, conduction, or morphology of resting ECG.
26. The subject has prolonged QTcF interval (≥450 msec) or risk factors of QT interval prolongation, for example, clinically relevant electrolyte imbalance and family history of QT interval prolongation.
27. The subject uses a cardiac medical device such as pacemakers and defibrillators (bladder stimulators, spinal stimulators, medication infusion devices, insulin pumps, continuous glucose monitors are permitted).
28. The subject has a lifestyle in which drowsiness may risk personal or public safety.
29. The subject has an elevated serum prolactin (>upper limit of normal [ULN]) at screening. A high prolactin level at the screening visit that is considered to be due to stress of venipuncture, chest wall stimulation, or other physiological causes may be retested after a few days and if normal, the subject may be enrolled in the study.
30. The subject has concurrent hypogonadism, current clinically significant menstrual abnormalities such as amenorrhea or oligomenorrhea related to hyperprolactinemia, or other clinical features of hyperprolactinemia such as galactorrhea or gynecomastia.
31. The subject has any signs/symptoms or history of extrapyramidal system disease and other clinically relevant CNS or neuropsychiatric disease including but not limited to tardive dyskinesia, neuroleptic malignant syndrome, acute dystonia, parkinsonian like symptoms, severe mental depression, and history of suicide attempt.
32. The subject has acute or chronic liver disease meeting any of the criteria described below:
    - The subject has an alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin >2.0 times the ULN.
    - The subject has pre-existing liver cirrhosis that meets Child-Pugh Class B (moderate; total score 7 to 9 points) or C (severe; total score 10 to 15 points) (see Appendix B).
    - The subject has acute or chronic hepatitis B or C virus infection, manifesting as one of the following at screening:
        - Positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). NOTE: if a subject tests negative for HBsAg, but positive for HBcAb, the subject

would be eligible if the Investigator has documentation of other test results showing that the subject does not have active hepatitis B infection.

- Subjects with positive hepatitis C antibody (HCV IgG) and quantitative HCV polymerase chain reaction (PCR). HCV PCR is performed only if HCV IgG is positive.

33. The subject has a history of any psychiatric disorder or cognitive impairment that would interfere with participation in the study.
34. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, HIV infection, organ transplantation).
35. The subject has renal impairment, defined as a lower limit of (eGFR) <30 mL/min at screening visit.
36. The subject has active neoplastic disease or history of neoplastic disease within 5 years of screening visit (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix that has been definitively treated with standard of care approaches).
37. The subject has poor venous access or inability to tolerate venipuncture.
38. The subject has hypersensitivity to Spirulina, egg, milk, or wheat allergens.
39. The subject has a history of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator contraindicates their participation.
40. The subject has any other significant, uncontrolled organic or systemic medical condition or social circumstance that, in the investigator's opinion, would mean it was not appropriate for the subject to participate in this clinical study.
41. The subject has known COVID-19 infection, or suspected COVID-19 infection (as assessed by the investigator).

7.3 Excluded Medications

The following medications are not permitted during the course of the study, starting from the screening visit, unless specified otherwise:

- Use of OATP1B1 or OATP1B3 inhibitors as concomitant medication (these include but are not limited to clarithromycin, erythromycin, gemfibrozil, cyclosporine, lapatinib, eltrombopag, atazanavir, ritonavir, lopinavir and ritonavir, simeprevir, and rifampin).
- Use of metoclopramide, erythromycin, domperidone, prucalopride, or other prokinetic GI motility agents for at least 2 weeks before GEBT assessment (Visit 2, Day -21) is not permitted, and subjects must be willing not to take these medications during the course of the clinical study.
- Opiates.

- Anticholinergic agents (eg, dicyclomine, hyoscyamine, scopolamine, otilonium bromide/Spasmomen).
- Dopamine agonists and antagonists. Promethazine can be used as part of protocol specific rescue medication.
- Glucagon-like peptide-1 agonists (eg, exenatide, liraglutide) and amylin analogues (eg, pramlintide). Note that other medications for the treatment of diabetes are permitted.
- Cannabinoid use.
- Medications that prolong QT/corrected QT interval or are at risk of causing Torsades de Pointes. Including but not limited to amiodarone, arsenic trioxide, astemizole, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sotalol, sparfloxacin, terfenadine, thioridazine, vandetanib. Note that the use of ondansetron at a maximal dose of 8 mg twice a day is allowed as part of protocol specific rescue medication.
- Medications that can cause EPS or persistently elevate serum prolactin.
- Use of antinausea/antivomiting rescue medication is permitted for moderate nausea and/or vomiting CTCAE Grade 2 (for nausea, oral intake decreased without significant weight loss, dehydration or malnutrition; for vomiting, outpatient IV hydration required) or higher. Rescue medication use is limited to BID for up to 3 days per week. If the subject takes this dose regimen for 2 consecutive weeks, they will be discontinued from the study due to lack of efficacy. The prescription for rescue medication will be provided by study investigator. The preferred rescue medication is ondansetron 4 mg given orally. Alternatively, other antiemetics such as diphenhydramine, dimenhydrinate or promethazine may be provided based on local guidelines, PI and subject preference. Although there is a risk of dose-related prolonged QT with ondansetron and development of EPS symptoms with promethazine, this risk is considered low based on the minimal doses being given for a short period of time.

Permitted concomitant medications

Permitted concomitant medications must be stable for at least 2 weeks leading up to the initial screening/consent visit (Visit 1, Day -35) and must be maintained at the same doses during the study (daily adjustments of insulin doses are permitted). Changes to permitted medications (eg, laxatives taken as needed) need to be documented.

Subjects must be instructed not to take any medications including over-the-counter or herbal products, without first consulting with the investigator.

The following medications are permitted only in the following circumstances:

- A stable dose of a single antidepressant for the treatment of depression. Note that an additional antidepressant can be allowed if used for another indication such as chronic pain or insomnia.

- Antibiotic use should be recorded for acute or returning conditions but excluded for chronic use. Acute or chronic treatment with macrolides antibiotics such as erythromycin, azithromycin, and clarithromycin is not allowed as these might have prokinetic properties.

7.4 Diet, Fluid, Activity Control

Subjects will be instructed to take medication 1 dose in the morning approximately 1 hour before the first meal of the day and another dose in the evening approximately 1 hour before the main last meal of the day, at a regular dose interval. An 8-hour fast is required before the GEBT procedure is to be performed.

There should be no lifestyle changes during the study including no changes to the amount of alcohol, caffeine, and tobacco consumed. The subject must be willing to abstain from smoking during the visit when the GEBT is being performed. Consumption of alcohol, caffeine and tobacco should not be excessive, per investigator discretion, for the duration of the study. Exercise should be moderate and be consistent for the duration of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.16.

1. Treatment discontinuation due to an AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the AE. Such events may include, but are not limited to:
   - Extrapyramidal symptoms and other clinically relevant CNS or neuropsychiatric disease including tardive dyskinesia, neuroleptic malignant syndrome, acute dystonia, parkinsonian-like symptoms, convulsive seizure, severe mental depression, and hallucinations (please refer to Section 10.1.5. Guidance to Investigators for Management of Extrapyramidal System Disorders).
   - Clinically relevant symptoms related to hyperprolactinemia (please refer to Section 10.1.5. Guidance to Investigators for Management of Elevated Serum Prolactin).
   - Subjects who develop an illness that in the opinion of investigator may expose them to undue risk or could interfere with his/her continued participation in the study.
   - Any subject identified with COVID-19 infection during the study.
2. Liver Function Test (LFT) Abnormalities

   Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.10), if the following circumstances occur at any time during study drug treatment:
   - ALT or AST >8×ULN, or

- ALT or AST >5×ULN and persists for more than 2 weeks, or
- ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or international normalized ratio (INR) >1.5, or
- ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

3. Important protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health, following consultation with the sponsor or designee.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, must be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).
6. Study termination. The sponsor, IRB/IEC or regulatory agency terminates the study.
7. Pregnancy. The subject is confirmed to be pregnant.

   Note: If the subject is confirmed to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.12.
8. Lack of efficacy. The investigator has determined that the subject has a significant worsening of symptoms and is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject, or subjects who use antinausea/antivomit ing rescue medication (only after the subject has reported nausea or vomiting of moderate (CTCAE Grade 2) or greater severity for 3 days/week for 2 consecutive weeks.
9. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject from study drug or study participation at any time during the study when the subject meets the discontinuation or withdrawal criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for discontinuation or termination must be recorded by the investigator. In addition,

efforts should be made to perform all procedures scheduled for the early termination visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

- TAK-906M capsules in strengths of 5, 25, and 50 mg.
- Matching placebo capsules.

The study drug is TAK-906 maleate salt in an immediate-release capsule formulation, which contains 5, 25, or 50 mg of TAK-906 calculated on the basis of the free base. The 3 strengths of capsules have an identical appearance in capsule size and color. Matching placebo capsules are also provided.

The study medication will be packaged in high-density polyethylene bottles. Each bottle contains 65 TAK-906M capsules for 4-week dosing plus 9 extra capsules. Each subject will receive 1 bottle at each visit. The study subjects will be instructed to take 1 capsule at each dosing time.

Randomization into the 5 mg dose arm was halted in Protocol Amendment 8 to improve operational feasibility in the setting of the COVID-19 pandemic and to reduce the number of subjects being exposed to a potentially minimally efficacious dose that likely approaches the lower end of the dose response curve. This change was not necessitated by safety findings.

Rescue Medication

During screening, there will be no restrictions on the use of rescue medication until Visit 3 (Day -14). After Visit 3, the use of rescue medication will be limited to 2 doses per day for up to 3 days per week only when subjects experience nausea and/or vomiting (oral intake decreased without significant weight loss, dehydration or malnutrition) of CTCAE Grade 2 or greater. Note that during the randomized treatment period, rescue medication use will be limited to BID for up to 3 days per week. If the subject uses rescue medication BID for 3 days per week for 2 consecutive weeks, the subject will be discontinued from the study due to lack of efficacy. All types and doses of antinausea/antivomiting rescue medication will be documented and the rescue medication will be provided by the subject's treating physician. The preferred rescue medication will be ondansetron 4 mg given orally. Other routes of administration of ondansetron are allowed if clinically indicated (eg, intravenous in case of vomiting). Alternatively, other antiemetics may be provided based on local guidelines and PI and subject preference if not prohibited per protocol. Examples of alternative allowed rescue medications include diphenhydramine, dimenhydrinate or promethazine.

8.1.2 Storage

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label until dispensed or returned to the sponsor or designee for destruction. The capsules should remain in the original container until dispensed.

8.1.3 Dose and Regimen

Subjects will take their first dose of study medication at the randomization visit and their morning dose in clinic at Visits 5 (Week 4), 6 (Week 8), and 7 (Week 12). Subjects will be instructed to take medication 1 dose in the morning approximately 1 hour before the first meal of the day and another dose in the evening approximately 1 hour before the main last meal of the day, at a regular dose interval. If a subject missed any individual dose, they may take the dose within a 4-hour window from the normal expected dosage time. If not taken within a 4-hour window, they should not take that dose and proceed to take the normal dose at the next scheduled time point.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

To date, the effects of an overdose of TAK-906 have not been characterized. TAK-906 has been investigated in clinical studies up to a maximum single oral dose of TAK-906M 300 mg and 100 mg BID for 9 days. Treatment-emergent adverse events (TEAEs) observed at various dose levels include mild facial swelling, constipation, headache, dizziness and fatigue. All TEAEs were mild to moderate in intensity.

In the event of an overdose, discontinue the study drug and treat the subject symptomatically and provide supportive care as needed. In the event of drug overdose, the next scheduled dose should be withheld, and the subjects should be treated considering their clinical presentation per local guidelines. Regular dosing may resume after discussion with the medical monitor after the subject recovers from effects of overdose.

8.2 Study Drug Assignment and Dispensing Procedures

The investigator or the investigator's designee will access the interactive response technology (IRT) at screening to obtain the subject study number. The investigator or the investigator's designee will use the IRT to randomize the subject into the study at Visit 4 (Day 1) should they

qualify. Randomization into the 5 mg dose arm is discontinued in Protocol Amendment 8. Subjects will be assigned in a 1:1:1 ratio to 1 of the 3 treatment arms of TAK-906M 25 or 50 mg or placebo BID.

During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication identification (ID) number of the study drug to be dispensed will then be provided by the IRT. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IRT. (Refer to IRT manual provided separately.) At subsequent drug-dispensing visits, the investigator or designee will again access IRT to request additional study drug (and other sponsor-supplied drug[s]) for a subject. The medication ID number of the study drug to be dispensed will be provided by the IRT and entered onto the appropriate drug accountability log.

8.3 Randomization Code Creation and Storage

The Sponsor's randomization personnel or designee will generate the randomization schedule for the study; an IRT will be used in a centralized fashion for subject randomization and study medication assignments. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The study medication blind will be maintained using the IRT. The principal investigator at each study site will receive instructions on obtaining the medication assignment through the IRT.

During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform accountability of study drug inventory. All assigned/unassigned treatment medication will be reconciled and returned to the sponsor or a designee or authorized for on-site destruction or return at study closure.

After removal of the 5 mg treatment arm in Protocol Amendment 8, the study team will remain blinded to subject's treatment allocation.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessments should be performed, if possible, before unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the study drug blind can be obtained by the investigator through the IRT.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and eCRF/IRT.

If any site personnel are unblinded, study drug must be stopped immediately, and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or authorized for destruction.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivered to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

On receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda or designee must be contacted to resolve the issue. All packing lists should be filed in the investigator's essential document or pharmacy file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if (expiry date/retest date) is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor or designee must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed. All log entries must be timely and legible, and all must be accompanied by the initials, signature, or seal of the person completing the noted action.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation. In all cases, this will be performed before sponsor-supplied drugs are returned to the sponsor or its designee or before destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and a copy will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained before the subject enters into the study and before any protocol-directed procedures are performed.

A unique subject ID number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.1.1 PGx Informed Consent Procedure

A separate informed consent form pertaining to collection, storage, and analysis of the sample must be obtained before collecting a blood sample for PGx research for this study. The provision of consent to collect and analyze the PGx sample is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age as dictated by local law, sex, Hispanic ethnicity, race described by the subject, height, weight, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.9).

Medication history information to be obtained includes any medication relevant to eligibility criteria (and efficacy/safety evaluation) stopped at or within 90 days before signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment before first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) GI system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment before first dose examination. Any clinically significant changes from the baseline examination will be recorded as an AE.

9.1.4 Assessment of the Extrapyramidal System

A detailed assessment of the extrapyramidal system will be performed at study entry, Weeks 4, 8, and 12 or study exit by a healthcare professional qualified to perform this assessment using the guidance provided by Takeda. Subjects with any neurologic abnormalities will be referred to a neurologist for appropriate medical evaluation and any AEs should be reported as per AE reporting procedures provided in Section 10.0 of this protocol. A copy of the Guidance for Assessment of the Extrapyramidal System is provided in Appendix C.

9.1.5 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = weight\ (kg)/height\ (m)^2$

The eCRF will perform the BMI calculation based on the height and weight values entered.

9.1.6 Vital Signs Procedure

Vital signs will include body temperature (oral, tympanic, or axillary measurement), respiratory rate (supine/semisupine), blood pressure (systolic and diastolic) and pulse (beats per minute). Vital signs can be performed in supine or semisupine position but should be performed after resting for 5 minutes and consistently for each subject.

Vital signs assessment should occur before the study drug is taken. When vital signs are scheduled at the same time as blood sampling, vital signs will take priority and vital signs will be obtained within 0.5 hour before the scheduled blood draw.

9.1.7 Primary Efficacy Measurement

The ANMS GCSI-DD will be used to capture gastroparesis symptoms, which will be used as the primary efficacy measurement (Appendix I). Subjects need to be compliant with providing symptom data defined as ≥80% daily diary completion, during the 2-week symptom assessment period (Day -14 to randomization; +3-day window). The electronic diary should be completed at approximately the same time each day (evening) during the 12 weeks of treatment.

9.1.8 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter and is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.9 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the screening/baseline examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be documented.

9.1.10 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures and after screening all samples will be collected fasted. Early termination visits will be fasting if visit circumstances allow. Details of these procedures and required safety monitoring will be given in the laboratory manual. Timing of these procedures are detailed in Appendix A.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells	ALT	Albumin
White blood cells	Albumin	Protein
including differential	Alkaline phosphatase	Glucose
Hemoglobin	AST	pH
Hematocrit	Total and direct bilirubin	Leukocytes
Platelets	Total protein	Blood
HbA1c [a]	Creatinine	Bilirubin
Mean corpuscular hemoglobin	Blood urea nitrogen	Urobilinogen
PT/INR	Creatine kinase	Ketone
	GGT	Creatinine
	Potassium	
	Prolactin [b]	
	Sodium	
	Calcium	
	Chloride	
	Magnesium	
	Phosphate	
	Total cholesterol	
	Low-density lipoprotein cholesterol	
	High-density lipoprotein cholesterol	
	Triglycerides	
	Uric acid	
	Glucose	

Serum	Urine
HIV test (confirmatory testing is allowed; most sensitive test should take precedence).	Female subjects only: hCG (for pregnancy)
Hepatitis panel, including HBsAg, anti-HBcAb, and anti-HCV [c].	Drug Screen
Female subjects only:	
Beta hCG (for pregnancy).	
Female subjects of childbearing potential:	
FSH if menopause is suspected	
Thyroid Stimulating Hormone (TSH)	

ALT; alanine aminotransferase; anti-HBcAb: antibody to hepatitis B core antibody; AST: aspartate aminotransferase; DG: diabetic gastroparesis; FSH: follicle-stimulating hormone; GGT: γ-glutamyl transferase; HbA1c: glycosylated hemoglobin; HBsAg: hepatitis B virus surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HIV: human immunodeficiency; INR: international normalized ratio; PT: prothrombin time; RNA: ribonucleic acid.

[a] HbA1c to be measured only in subjects with DG.

[b] Prolactin to be evaluated as part of clinical laboratory tests in all the scheduled visits and any necessary unscheduled visit as needed to confirm eligibility. Investigators will be blinded to prolactin measurements beginning with Visit 4 (Day 1). A subset of samples maybe used for prolactin assay bridging studies as needed.

[c] HCV RNA viral load will be tested only in the subjects who test positive for hepatitis C antibody.

The results of laboratory tests will be returned to the PI, who is responsible for ensuring that these results are reviewed and filed by a qualified designee.

If subjects experience ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase [GGT], and INR) should be performed within a maximum of 3 days and preferably within 24 to 48 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.3 for the appropriate guidance on reporting abnormal LFTs.)

If ALT or AST remains elevated >3×ULN on these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3).

9.1.11 Contraception and Pregnancy Avoidance Procedure

9.1.11.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must not donate sperm during this period. Women of childbearing potential* who are partners of male subjects must also use highly effective contraception during this period as shown in the list below.

9.1.11.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 35 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (from the list below).

In addition, they must be advised not to donate ova during this period.

9.1.11.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, that is, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. 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 (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea with an FSH >40 IU/L or at least 5 years since last regular menses, a single FSH measurement is insufficient.

** Sterilized men should be at least 1-year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchiectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
    - Nonhormonal methods:
        - Intrauterine device.
        - Bilateral tubal occlusion.
        - Vasectomized partner (provided that partner is the sole sexual partner of the study participant) and that the vasectomized partner has received medical assessment of the surgical success.
    - Hormonal methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months:
            - Oral.
            - Intravaginal (eg, ring).
            - Transdermal.
        - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a

barrier method (male condom, female condom, or diaphragm) if shorter till she has been on contraceptive for 3 months.

- Oral.
- Injectable/implantable.

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova and sperm donation during the study.
4. During the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   - Contraceptive requirements of the study.
   - Reasons for use of barrier methods (ie, condom) in male subjects with pregnant partners.
   - Assessment of subject compliance through questions such as:
     - Have you used the contraception consistently and correctly since the last visit?
     - Have you forgotten to use contraception since the last visit?
     - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes").
     - Is there a chance you could be pregnant?
5. In addition to a negative serum hCG pregnancy test at screening, female subjects of childbearing potential must also have a negative urine hCG pregnancy test before receiving any dose of study medication [as close as possible and before the first dose of study medication, preferably on the same day].

In women of childbearing potential who present with amenorrhea or signs/symptoms suggestive of pregnancy or delayed/missed menstrual period by >5 days (whichever comes first), the study drug must be immediately discontinued, a serum pregnancy test must be perform and if negative, the subject may restart the study drug. In cases of positive pregnancy, the subjects must be managed as described in Section 9.1.12.

An onsite end of study pregnancy test should be performed for subjects with menstrual irregularities, variable menstrual cycle length by more than ±5 days or missed last menstrual period by more than 5 days at the time of the safety follow-up call.

9.1.12 Pregnancy

If any subject is confirmed to be pregnant during the study, the subject should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject occurring during study conduct or within 95 days after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug, for example, after the randomization visit, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.13 ECG Procedure

A standard 12-lead ECG will be recorded. Subject should have rested in supine or semisupine position for at least 5 minutes before ECG. When the timing of these measurements coincides with a blood collection, the ECG should be obtained before the nominal time of the blood collection. Triplicate tracings of ECGs should be performed. ECG will be assessed at Visit 1 (Day -35), and approximately 1 to 2 hours postdose at Visit 4 (Day 1), Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) on those visit days requiring study dosing, and at early termination (as specified in Appendix A). The time that the ECG was performed will be recorded.

The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. ECGs assessed as abnormal and clinically significant must be sent to the sponsor's or designee's medical monitor for assessment and to confirm if the subject should continue in the study.

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, PR, QT and QTc, and QRS intervals.

QTc interval will be calculated using Fridericia's formula: $QTcF=QT/RR^{1/3}$.

9.1.14 PGx and PK Sample Collection

Table 9.b Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Primary Use	Sample Collection
Plasma sample for TAK-906 PK	Plasma		PK measurements	Mandatory

PK: pharmacokinetics.

9.1.14.1 PGx Measurements

Blood samples for deoxyribonucleic acid (DNA) for PGx analysis will be collected as specified in the Schedule of Study Procedures (Appendix A). Details on the collection, storage, processing, handling, and shipping of the samples are provided in the Laboratory Manual.

9.1.15 PK Sample Collection and Analysis

Samples for PK analysis will be collected as specified in the Schedule of Study Procedures (Appendix A). Please refer to the Laboratory Manual for information on the collection, processing, and shipment of samples to the central laboratory. Metabolites may be analyzed if deemed necessary.

The actual date and times of all PK blood draws should be recorded for each subject on the eCRF. The actual dates and times of the dose administration in the clinic should be recorded in addition to the 2 previous doses. Placebo samples will not be analyzed.

9.1.16 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn during screening, the investigator should complete the eCRF. The IRT should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).

- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject ID numbers assigned to subjects who fail screening should not be reused.

9.1.17 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

Please refer to the study manual provided.

9.1.18 Other Procedures

9.1.18.1 GEBT

For subjects who do not have documented delayed gastric emptying using an accepted diagnostic method (see Section 7.1), a 4-hour ^{13}C-Spirulina GEBT will be performed at Visit 2 (up to approximately 14 days after consent). The GEBT is preceded by a test meal and an 8-hour fast is required before the GEBT test meal.

The GEBT is simple to administer and the test meal is manufactured under highly-controlled drug manufacturing procedures and subject's breath samples are analyzed using sophisticated gas isotope ratio mass spectrometry, a US Food and Drug Administration (FDA) approved, validated analytical system.

The test is conducted over a 4-hour evaluation period after an 8-hour fast and is designed to show how rapidly the stomach empties solids by measuring carbon dioxide in a patient's breath. Premeal breath samples are collected at the start of the test. Subjects then eat a special test meal. After consuming the meal, additional breath samples are collected at specified times. To ensure that the samples are evaluable, subjects are required to consume the entire test meal (egg mixture and at least 4 of the meal crackers).

Delayed gastric emptying by GEBT is defined as $t_{1/2} \geq 79$ minutes (80th percentile).

If GEBT falls between 67 to 79 minutes, then site must confirm the diagnostic detail of the prior history:

- If patient has had confirmed gastric emptying delay consistent with the diagnosis of gastroparesis or evidence of retained food in a previous upper endoscopy or other

imaging test (eg, ultrasound) and is clinically symptomatic, that subject can be retested with a second GEBT.

- GEBT second test equal to or above 79 minutes – the subject proceeds with screening
- GEBT second test – below 79 minutes – the subject is excluded from the trial.

Further details regarding the GEBT will be provided in the study manual.

9.1.18.2 Patient Outcome Measures

The following questionnaires will be used to support the primary efficacy measurement (ANMS GCSI-DD) and copies for reference will be provided in the study manual:

- Bloating Severity Scale (Appendix J).
- PAGI-SYM.
- Clinician Symptom Severity Rating Form.
- PAGI-QOL.
- OTE Scale (subject and physician).
- CGI-S.
- CGI-I.
- An updated PGI-S Scale (updated version included in Appendix D) will replace existing PGI-S scale.
- The PGI-C scale (updated changes scale included in Appendix D) will replace existing Patient Global Impression of Improvement (PGI-I) scale.
- SF12 Health Survey.

The Schedule of Questionnaire assessments is provided in Appendix D.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study drug containers/unused study drugs to each site visit. Dosing date and time will be recorded daily.

If a subject is persistently noncompliant with the study drug (eg, <80% compliant or ≥6 consecutive missed doses since the last study visit), the subject will be re-educated about the importance of being consistent with their dosing as per the protocol. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Poststudy Care

Study drug will not be available on completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

9.4 Biological Sample Retention and Destruction

In this study, specimens for PGx will be retained for up to but not longer than 15 years or as required by applicable law. After that time, the samples will be destroyed.

9.5 Possible Changes to the Procedures to Address Interruptions Due to Pandemic Outbreak

The following is intended to give guidance about which changes to the procedures could be accepted in case any study participants or study sites are impacted by the COVID-19 pandemic outbreak. The guidance takes references from the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards, March 2020 and the update from 11 May 2020, and the EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 3 (28/04/2020).

As the COVID-19 pandemic outbreak may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case by case basis following consultation with the medical monitor, with patient safety as the priority.

In case there are restrictions to conduct procedures as originally planned in consequence to the COVID-19 pandemic:

- Informed consent form procedure for investigational sites and study participants related to the COVID-19 pandemic situation: If necessary, informed consent from a potential or current trial participant may be obtained via electronic informed consent (eIC) capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site.
- Sites will employ all efforts to see subjects as described in the clinical assessments. In unavoidable circumstances, such as the COVID-19 pandemic, exceptions may be granted for alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such instances will be documented in the study records. These data collected with alternative methods may be handled differently in the final data analysis, with this documented in the statistical analysis plan.
- Procedures for clinical laboratory samples:
  - Allow blood draws or other diagnostic tests to be performed by the investigator or the study coordinator or by a qualified nurse who can enter the trial participant's home.
  - Allow blood draws or other diagnostic tests to be conducted at a local laboratory (or relevant clinical or office facility) authorized/certified to perform such tests routinely.

Starting with Visit 4 (Day 1), if samples are collected and analyzed by local lab, prolactin will not be evaluated, in order to maintain investigator blinding.

- Assessment of the Extrapyramidal System: Allow the assessment via video to observe whether typical EPS symptoms (eg, pseudoparkinsonism, acute dystonia, tardive dyskinesia, akathisia) are present.
- ECG, weight, and vital sign procedures: In situations when an on-site visit is not possible, ECGs, weight, and vital signs may be performed by a qualified health care professional, or at a local healthcare facility, which is authorized/certified to perform such tests routinely.
- Allow the use of web-based back-up system on electronic devices.
- Deviations from the protocol (eg, missing required bloodwork, visit performed outside of window) will be noted as a protocol deviation related to COVID-19.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment SAEs

Pretreatment SAEs are the only AEs to be collected from the time a subject signs informed consent until the subject is first administered study drug (Day 1) or until screen failure.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest and/or continued monitoring of an abnormal value or finding is not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. If the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs/SAEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs/SAEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an overdose page of the eCRF. Any manifested side effects will be considered as an AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
COVID-19-related disease	Neuroleptic malignant syndrome/malignant hyperthermia
COVID-19 pneumonia	Spontaneous abortion/stillbirth and fetal death

AE: adverse events; COVID-19: coronavirus disease 2019.
Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.1.5 AEs of Special Interest

An AE of special interest ([AESI]; serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda. The following events are AESI for this study:

1. Extrapyramidal symptoms and other clinically relevant CNS or neuropsychiatric disease including tardive dyskinesia, neuroleptic malignant syndrome, acute dystonia, parkinsonian-like symptoms, convulsive seizure, severe mental depression, and hallucinations.
2. Clinically relevant hyperprolactinemia (see below).

Guidance to investigators for management of extrapyramidal symptoms and central nervous system/neuropsychiatric AEs

Extrapyramidal symptoms including tardive dyskinesia, acute dystonic reactions, parkinsonian-like symptoms [30] and akathisia are considered to be mainly caused by the blockade of D_2 receptor in the dorsal striatum in the brain. These side effects have been reported with all centrally acting DA receptor D_2 antagonists such as metoclopramide and atypical neuroleptics. TAK-906 is considered as a peripherally selective DA receptor D_2/D_3 antagonist with limited penetration of the blood brain barrier, hence it is considered to have a low potential

for causing extrapyramidal symptoms compared with metoclopramide or atypical neuroleptics. However, as TAK-906 is in early development and its complete safety profile is not characterized at this time, Takeda is closely monitoring medical events that may potentially be extrapyramidal in nature.

Of greatest concern is tardive dyskinesia, a severe and often irreversible and disfiguring disorder characterized by involuntary movements of the face, tongue, mouth, or jaw, and trunk and/or extremities. Although the risk for developing tardive dyskinesia in the general population may be increased among the elderly, women, and individuals with diabetes, it is not possible to predict which patients will develop D_2 receptor antagonist-induced tardive dyskinesia.

There is no known effective treatment of established cases of tardive dyskinesia, although in some patients, tardive dyskinesia may remit, partially or completely, within several weeks to months after discontinuation of causative agent.

In subjects with suspected EPS, study drug should be immediately interrupted, and subjects referred for appropriate neurological consultation. If, after neurological consultation, EPS is confirmed, study drug should be discontinued, and the subject withdrawn from the study. In the remaining cases restarting of the study drug should be evaluated individually after discussion with the medical monitor.

In subjects who develop suspected CTCAE Grade 1 CNS/neuropsychiatric AEs, the study drug may be continued at investigator's discretion after discussion with the medical monitor. However, in subjects with CTCAE ≥ Grade 2 CNS/neuropsychiatric AEs, the study drug should be immediately interrupted, and subjects referred for appropriate neurological consultation. If after neurological consultation, a CNS/neuropsychiatric AE is confirmed and considered related to the study drug, the study drug should be discontinued, and the subject withdrawn from the study. In the remaining cases restarting of the study drug should be evaluated individually after discussion with the medical monitor. If the study drug is interrupted for more than 10 days, the subject should be discontinued form the study and procedures stated in Section 7.6 "Procedures for Discontinuation or Withdrawal of a Subject" should be followed.

Guidance to investigator for management of elevated serum prolactin

Several physiologic and pathologic conditions for example, pregnancy, breastfeeding, breast stimulation, prolactinomas, vascular disorders, autoimmune disorders, chronic renal failure, chest wall trauma, seizures, and stress can result in increased plasma prolactin levels [31].

TAK-906 is a D_2 receptor antagonist, which increases prolactin release by inhibiting the negative control mechanism of DA on prolactin, a pharmacological class effect shared with other D_2 receptor antagonists. It is anticipated that TAK-906 will also increase serum prolactin levels.

The most frequent symptoms of chronic hyperprolactinemia include reproductive dysfunction (anovulation, menstrual irregularity, subfertility, decreased estrogen and testosterone production), sexual impairment (diminished libido, erectile dysfunction, retrograde or painful ejaculation, orgasmic dysfunction, impotence), breast pathology (galactorrhea and breast enlargement) [32].

Medication-induced hyperprolactinemia is usually associated with prolactin levels ranging from 25 to 100 µg/L; however, TAK-906 in some cases may lead to serum prolactin levels exceeding 200 µg/L.

In subjects with symptoms suggestive of hyperprolactinemia, the investigator should manage the subject as clinically indicated. In these subjects, the benefit-risk of continued participation in the study should be evaluated and documented in the eCRF.

Only prolactin related symptoms leading to discontinuation of a subject from the study should be reported as an AESI and recorded as an AE in the eCRF and reported as per Section 10.2.2 should they meet the criteria for SAE (Section 10.1.4).

Prolactin related symptoms not leading to discontinuation of a subject from the study should not be reported as an AESI but recorded as an AE in the eCRF and reported as per Section 10.2.2 should they meet the criteria for SAE (Section 10.1.4).

Elevated serum prolactin without clinical manifestations (asymptomatic hyperprolactinemia) should not be reported as an AESI, AE, or SAE; however, serum prolactin levels >ULN will be summarized as per statistical analysis plan (SAP) of this study.

Subjects will be withdrawn from the study if the investigator requires unblinding of the study treatment or serum prolactin level because of suspected hyperprolactinemia.

In woman of childbearing potential who present with postdosing amenorrhea or signs/symptoms suggestive of pregnancy or delayed/missed menstrual period by >5 days (whichever comes first), the study drug must be immediately discontinued, a serum pregnancy test must be performed and if negative, the subject may restart the study drug. In cases of positive pregnancy, the subjects must be managed as described in Section 9.1.12.

The AESI should be recorded in an AE of special interest named Form and reported to the clinical contract research organization (CRO)/Pharmacovigilance department within 24 hours. AEs of special interest must be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

If an AESI also meets the criteria of SAE (Section 10.1.4), it should be reported using both the AESI named Form AND the SAE Form.

10.1.6 Severity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to CTCAE Version 4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06 14_QuickReference_8.5x11.pdf).

AEs not listed by the NCI CTCAE will be graded as below:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL) (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Fatal AE; an event that results in the death of the subject.

10.1.7 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of the AE/SAE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.10 Stop Date

The stop date of the AE/SAE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs/SAE or those that occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Drug

- Drug withdrawn: a study drug is stopped due to the particular AE.
- Dose interrupted: the dose was interrupted due to the particular AE.
- Dose not changed: the particular AE did not require stopping a study drug.
- Unknown: only to be used if it has not been possible to determine what action has been taken.
- Not applicable: a study drug was stopped for a reason other than the particular AE, for example, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.

10.1.13 Outcome

- Recovered/resolved: subject returned to first assessment status with respect to the AE.
- Recovering/resolving: the intensity is lowered by 1 or more stages: the diagnosed AE or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the reference range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved: there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosed AE, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Resolved with sequelae: the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal: the AEs which are considered as the cause of death.
- Unknown: the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

After informed consent, but before initiation of study medications, only SAEs will be collected.

Collection of all AEs (serious and nonserious) will commence from the time that the subject is first administered study drug (randomization visit). Routine collection of AEs will continue for each subject throughout the study until 30 days after the last dose of study drug is taken.

If an AE is ongoing at the end of the study for a subject, follow-up should be provided until resolution/stable level of sequelae is achieved, or until the investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow-up is provided, the investigator must provide a justification. The follow-up will be continued for up to 8 weeks after the subject has discontinued his/her investigational medicinal product. Information on SAEs obtained after clinical database lock will be captured through the safety database without limitation of time.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change.

All subjects experiencing AEs (postdose), whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug
8. Outcome of event.
9. Seriousness.

The Daily Symptom Diary will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.2 Collection and Reporting of SAEs/AESI

When an SAE and/or AESI occurs through the AE collection period it should be reported according to the following procedure:

As soon as an SAE/AESI is entered into the electronic data capture system, an alert is sent to the attention of the contact listed in Section 1.1 and to the safety database.

The SAE/AESI eCRF should be transmitted within 24 hours of first onset or notification of the event. However, as a back-up, if required, the SAE form should be completed and reported to the attention of the contact listed in Section 1.1.

The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject ID number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

Any SAE/AESI spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3×ULN and total bilirubin >2×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported per Section 10.2.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.10 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately, within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor or designee will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 IDMC

An IDMC will be used during this study to allow study team members to remain blinded to subject treatment during the study. The IDMC will perform the customary duties of safeguarding the interest of study participants, assessing the safety of the interventions during the study, and for monitoring the overall conduct of the clinical study. The IDMC will provide recommendations about stopping or continuing the study. To enhance the integrity of the study, the IDMC may also formulate recommendations relating to the selection/recruitment/retention of participants, management of the study participants, improving adherence to protocol-specific regimens, and the procedures for data management and quality control.

Details of the IDMC including meeting frequency will be captured in a charter before the start of the study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHO).

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent. The sponsor or its designee will supply study sites with access to eCRFs. These forms are used to transmit the

information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A SAP will be prepared and finalized before unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted before unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The safety set will include all subjects who were randomized and received at least 1 dose of double-blind study medication. In safety summaries, subjects will be analyzed according to the treatment they received. If a subject receives more than 1 treatment, the actual treatment will be defined as the one that is used most frequently. If the 2 most common treatments are used with equal frequency, then the randomized treatment will be used for safety summaries.

The full analysis set (FAS) will include all subjects who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. In FAS efficacy summaries, subjects will be analyzed by the treatment to which they were randomized.

The per protocol set (PPS) will include all FAS subjects who had no major protocol violations. If more than 5% of the total subjects in the FAS have major protocol violations, analyses based on the PPS will be performed for the primary efficacy variable only.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics including sex, age, race, height, weight, BMI, and subject disease population (DG and IG) will be listed and summarized for each treatment group and overall. The demographic and baseline characteristics summary will be based on all randomized subjects.

Baseline values for efficacy parameters (ANMS GCSI-DD, PAGI-SYM, and Clinician Symptom Severity Rating, etc.) will also be presented for each treatment group and overall based on all randomized subjects.

Height and weight values will be presented in metric units (cm and kg respectively). BMI is calculated as [weight (kg)/height $(m)^2$], using the weight collected at the first screening visit.

For continuous variables, number of nonmissing values and the mean, median, SD, minimum and maximum will be tabulated by treatment group and overall. For the categorical variables, the count and percentages of each possible value will be tabulated by treatment group and overall.

For continuous variables, comparability of treatment groups will be assessed using an analysis of variance (ANOVA) with treatment, subject disease population and center as fixed factors. For

discrete variables, comparability will be assessed using the Cochran-Mantel-Haenszel general association test, stratified by center and subject disease population. P-values will be displayed as descriptive statistics of comparability.

All individual demographic and baseline data will be listed by treatment, study center and subject number.

13.1.3 Efficacy Analysis

The efficacy analyses and summaries will be based on the FAS.

13.1.3.1 Primary Efficacy Analysis

Change from baseline to Week 12 in weekly ANMS GCSI-DD composite score (nausea, early satiety, upper abdominal pain, postprandial fullness) will be the primary endpoint. Analysis will be based on a mixed model for repeated measurements (MMRM) with treatment, center, week, subject disease population, and treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured covariance structure, if applicable. The point-estimates, nominal p-values and confidence intervals (CIs) for the primary analysis will be based on the Week 12 statistical comparisons between each of the 2 TAK-906 dose groups and placebo, with respect to the primary endpoint. The 2 statistical tests for the primary efficacy analysis are 1-sided and will be conducted using a 5% level of significance. Nominal p-values will be evaluated for statistical significance. In addition, point estimates and CIs along with descriptive statistics for change from baseline scores in ANMS GCSI-DD at earlier time points, will be presented. The MMRM-based analysis assumes that missing data follow a missing-at-random (MAR) assumption.

As a sensitivity analysis, a method for missing value imputation based on pattern mixture models will be implemented.

13.1.3.2 Secondary Efficacy Analyses

For change from baseline in the continuous secondary variables (ANMS GCSI-DD total score, ANMS GCSI-DD individual symptom score, ANMS GCSI-DD overall severity of gastroparesis symptoms score, bloating severity scale score, and PAGI-SYM total score), comparisons between different doses of TAK-906 and placebo will be based on the similar methodology described for the primary efficacy analysis.

The proportion of subjects with at least 50% reduction from baseline in ANMS GCSI-DD composite score will be analyzed at all time points by logistic regression adjusting for baseline score, subject disease population, and treatment using the last observation carried forward method to handle missing data.

Percentage of symptomatic weeks (weeks with symptoms assessed as >mild) using the ANMS GCSI-DD after 12 weeks of treatment will be analyzed using ANOVA with treatment, subject disease population and center as fixed factors.

13.1.4 PK Analysis

No formal noncompartmental PK analyses will be performed on concentration-time data. Individual concentration-time data will be included in listings only. Additional analyses may be conducted if deemed necessary for the interpretation of the data.

A more detailed description of these analyses will be given in a separate analysis plan. The results from these analyses will not be included in the clinical study report and will be a stand-alone report.

13.1.5 Other Analyses

The PGx samples will be stored and may be analyzed at a later date, if required. A separate PGx analysis plan will be created.

13.1.6 Safety Analysis

Safety summaries will be based on the safety set.

13.1.6.1 AEs

AEs will be reported throughout the study.

The definition of treatment-emergent AEs will be provided in the SAP. AEs will be coded using MedDRA and will be summarized by system organ class and preferred term in the core treatment period and entire study.

AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

13.1.6.2 Other Safety Evaluations

Absolute values and changes from screening/baseline in clinical safety laboratory tests, vital signs, ECG parameters, and weight will be summarized for each treatment group using descriptive techniques. Values outside reference ranges and markedly abnormal values will be flagged and tabulated.

13.2 Interim Analysis

No interim analysis of efficacy data will be conducted.

Periodic interim safety data reviews will be performed by IDMC. Frequency of IDMC safety review meetings and procedures to protect the study blinding will be documented fully in the IDMC charter.

In addition, blinded sample size re-estimation may be performed if the variance of the primary endpoint or study dropout rate is much larger than originally assumed.

13.3 Determination of Sample Size

In order to manage the likelihood of statistical, clinical, and operational success of this study in the setting of the COVID-19 pandemic, the sample-size considerations are revisited in Protocol Amendment 8. The statistical testing is revised from 2-sided (with a significance level of 5%) to 1-sided (with a significance level of 5%), the planned sample size is reduced by 10 subjects per arm and randomization into the 5 mg dose arm is to be discontinued.

The sample-size rationale for the resultant reduced sample size and updated 1-sided statistical testing is as follows: Assuming a SD of 1.25 and a true difference of 0.625 between TAK-906M active dose and placebo in the change from baseline in the ANMS GCSI-DD composite score, and a 15% dropout rate, a total of 205 subjects is sufficient to achieve approximately 80% power to detect the treatment effect of 0.625 at a 1-sided 5% significance level. The total of 205 subjects consists of approximately 25 subjects who have already been randomized to receive 5 mg capsule BID prior to terminating randomization of subjects into the 5 mg dose arm, and 60 subjects per treatment groups of placebo, TAK-906M 25 mg, and TAK-906M 50 mg.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of an important deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Important deviations include, but are not limited to, those that involve fraud or

misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, European National Agencies). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix F. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has

confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification, no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent are given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date

the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a PGx sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, European National Agencies), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by

law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment of injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

	Screening				Treatment				
	Visit 1 Day -35 [a]	**Visit 2 Day -21** [b]	**Visit 3 Day -14** [c]	**Visit 4 Randomization Visit (Day 1)** [d]	**Visit 5 Week 4**	**Visit 6 Week 8**	**Visit 7 Week 12/ End of Treatment**	**Early Termination** [e]	**Safety Follow-up** [f] **(30 Days After Last Dose)**
Visit Window		-11 to +3 days	±3 days	+3 days	±3 days	±3 days	±3 days		±5 days
Informed consent [g]	X								
Inclusion/exclusion criteria	X	X	X	X					
Demographics and medical history	X								
Medication history	X								
Physical examination including assessment of the extrapyramidal system [h]	X			X	X	X	X	X	
Vital signs [i]	X			X	X	X	X	X	
Height, weight, and BMI [J]	X			X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X								
12-lead ECG [k]	X			X	X	X	X	X	
TSH	X								
HbA1c (DG only)	X			X			X		
Finger stick glucose (only for DG subjects undergoing GEBT)		X							
Clinical laboratory evaluations [l]	X			X	X	X	X	X	
Urine drug and alcohol screen	X								
Pregnancy test (hCG) [m]	X			X	X	X	X	X	X [n]
FSH [o]	X								
HIV	X								
HBsAg, anti-HBcAb, and anti-HCV	X								

	Screening				Treatment				
	Visit 1 Day -35 [a]	**Visit 2 Day -21** [b]	**Visit 3 Day -14** [c]	**Visit 4 Randomization Visit (Day 1)** [d]	**Visit 5 Week 4**	**Visit 6 Week 8**	**Visit 7 Week 12/ End of Treatment**	**Early Termination** [e]	**Safety Follow-up** [f] **(30 Days After Last Dose)**
Visit Window		-11 to +3 days	±3 days	+3 days	±3 days	±3 days	±3 days		±5 days
Study drug dispensed				X	X	X			
Study drug dosing [p]				X	X	X	X		
GEBT [q]		X							
Daily Study Diary [r]			X	X	X	X	X	X	
PAGI-SYM				X	X	X	X	X	
SF12				X			X	X	
Clinician Symptom Severity Rating				X			X	X	
OTE Scale: subject							X	X	
OTE Scale: clinician							X	X	
PAGI-QOL				X	X	X	X	X	
CGI-S				X	X	X	X	X	
CGI-I							X	X	
PGI-S				X	X	X	X	X	
PGI-C							X	X	
Blood sample for DNA PGx [s]				X					
Plasma samples for TAK-906 PK [t]				X	X	X	X	X	
Serum samples for prolactin [u]	X	X (if required)	X (if required)	X	X	X	X	X	
AE assessment [v]	X	X	X	X	X	X	X	X	X

	Screening				Treatment				
	Visit 1 Day -35 [a]	**Visit 2 Day -21** [b]	**Visit 3 Day -14** [c]	**Visit 4 Randomization Visit (Day 1)** [d]	**Visit 5 Week 4**	**Visit 6 Week 8**	**Visit 7 Week 12/ End of Treatment**	**Early Termination** [e]	**Safety Follow-up** [f] **(30 Days After Last Dose)**
Visit Window		-11 to +3 days	±3 days	+3 days	±3 days	±3 days	±3 days		±5 days

AE: adverse event; ANMS GCSI-DD: American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary; BMI: body mass index; CGI-I: Clinical Global Impression Scale–Global Improvement Scale; CGI-S: Clinical Global Impression Scale–Severity of Illness Scale, DG: diabetic gastroparesis; DNA: deoxyribonucleic acid; ECG: electrocardiogram; ePRO: electronic patient reported outcomes; FSH: follicle-stimulating hormone; GEBT: Gastric Emptying Breath Test; GCI-I: Clinical Global Impression Scale-Global Improvement Scale; CGI-S: Clinical Global Impression Scale-Severity of Illness Scale; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B virus surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HIV: human immunodeficiency; PAGI-QOL: Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index; 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; PGx: pharmacogenomics; PK: pharmacokinetics; OTE: overall treatment effect; SAE: serious adverse event; SF12:Short Form-12 Health Survey; TSH: thyrotropin.

[a] Subjects will discontinue all medications to treat gastroparesis or the symptoms of gastroparesis. Treatment naïve subjects or subjects who have not been treated with prokinetics in the previous 2 weeks may proceed with Visit 2 after all laboratory results from Visit 1 have been evaluated. Subjects taking medications for gastroparesis that require washout should return for Visit 2, 14 to 17 days after Visit 1.

[b] Subjects requiring a washout period of their current gastroparesis medication(s) will use the 14+3 day window between Visit 1 and Visit 2. Treatment naïve subjects or subjects who have not been treated with prokinetics in the previous 2 weeks may return after receipt and evaluation of all Visit 1 study procedures (approximately 3 days).

[c] Subjects will complete Visit 3 once their GEBT results have been received and evaluated by the site (7±3 days from Visit 2). Subjects begin ANMS GCSI-DD.

[d] Subjects must be 80% compliant with the ePRO device for a minimum of 14 days between Visits 3 and 4.

[e] Subjects who withdraw prematurely will be seen for an early termination visit as soon as possible and will then be contacted for a follow-up approximately 30 days (30±5 days) after the last dose of study medication. These subjects will continue entering the Daily Symptom Diary until the early termination visit.

[f] A safety follow-up phone call will be made approximately 30 days after last dose of study medication.

[g] Informed consent must be signed before any study-specific procedures are performed.

[h] All physical examinations (including assessment of the extrapyramidal system) are to be performed by the investigator, subinvestigator, or a qualified healthcare professional. Assessment of the extrapyramidal system should be performed by a healthcare professional qualified to perform this assessment using the guidance provided by Takeda. Subjects with any abnormalities will be referred for appropriate medical consultation and AEs should be reported as per AE reporting procedures provided in Section 10.0 of this protocol.

[i] Vital signs (eg, oral/tympanic/axillary temperature, respiration, pulse, and blood pressure) will be assessed at Visit 1 (Day -35), and predose at Visit 4 (Day 1), and onward at Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) on those visit days requiring study dosing, and at early termination. Vital signs should be measured after 5 minutes resting in the supine or semi-supine position and consistently for each subject. When the timing of the vital signs coincides with a blood collection, vital signs should be obtained before the nominal time of the blood collection and before the study medication is taken.

[j] Height and weight are measured, and BMI is calculated at initial screening visit only. Weight only is measured at subsequent visits.

[k] Subject should have rested in supine or semisupine position for at least 5 minutes before ECG. When the timing of these measurements coincides with a blood collection, the ECG should be obtained before the nominal time of the blood collection. Triplicate tracings of ECGs should be performed. ECG will be assessed at Visit 1 (Day -35), and approximately 1 to 2 hours postdose at Visit 4 (Day 1), Visit 5 (Week 4), Visit 6 (Week 8), and Visit 7 (Week 12) on those visit days requiring study dosing, and at early termination.

[l] Clinical laboratory tests (chemistry, hematology) will be assessed at Visit 1 (Day -35), and predose at Visit 4 (Day 1), and onward at Visit 5 (Week 4), Visit 6 (Week 8), and Visit

	Screening				Treatment				
	Visit 1 Day -35 [a]	**Visit 2 Day -21** [b]	**Visit 3 Day -14** [c]	**Visit 4 Randomization Visit (Day 1)** [d]	**Visit 5 Week 4**	**Visit 6 Week 8**	**Visit 7 Week 12/ End of Treatment**	**Early Termination** [e]	**Safety Follow-up** [f] **(30 Days After Last Dose)**
Visit Window		-11 to +3 days	±3 days	+3 days	±3 days	±3 days	±3 days		±5 days

7 (Week 12) on those visit days requiring study dosing, and at early termination. Clinical laboratory tests (chemistry, hematology) to be collected under fasted conditions after screening. Early termination visits will be fasting if visit circumstances allow. Urinalysis to be performed at Visit 1 only.

[m] For women of child-bearing potential. Must be confirmed negative by serum hCG at screening and by urine hCG before medication dispensing at randomization and study visits.

[n] Onsite end of study pregnancy test must be performed for subjects with menstrual irregularities, variable menstrual cycle length by more than ±5 days or missed last menstrual period by more than 5 days.

[o] FSH level will be obtained for female subjects at screening if they are postmenopausal by history (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/mL or at least 5 years since last regular menses, confirmed before any study medication is implemented) and not surgically sterile. The FSH result must be >40 IU/mL for the subject to be permitted not to use adequate contraception.

[p] Subjects will take their first dose of study medication at the randomization visit. Subjects will take their morning dose in clinic at Visits 5, 6, and 7. Subjects will be instructed to take medication 1 dose in the morning approximately 1 hour before the first meal of the day and another dose in the evening approximately 1 hour before the main last meal of the day, at a regular dose interval. If a subject missed any individual dose, they may take the dose within a 4-hour window from the normal expected dosage time. If not taken within a 4-hour window, they should not take that dose and proceed to take the normal dose at the next scheduled time point.

[q] A 4-hour ^{13}C-Spirulina GEBT, which is preceded by test meal. An 8-hour fast is required prior to the GEBT test meal. GEBT is not required for subjects who have confirmed delayed gastric emptying by an accepted diagnostic method (scintigraphy, GEBT, or wireless motility capsule) that is documented in the subject's medical records prior to screening.

[r] The Daily Study Diary is inclusive of: Daily Symptom Diary (including ANMS-GCSI-DD plus bloating severity scale), daily dosing, and meal time recordings, and capture of rescue medication use. Compliance with the daily completion of the Daily Symptom Diary, defined ≥80% diary completions, from the 2-week symptom assessment period (Day -14 to randomization; +3-day window). Diary should be completed daily at approximately the same time each day (evening) in e-format with the ePRO device.

[s] The sample for PGx may be drawn before dosing on Day 1.

[t] PK: Subjects will be asked to take their morning dose of study medication at the clinic when PK samples are being collected. The blood samples for PK analysis will collected on Day 1, Weeks 4, 8, 12 at the following time-points: Day 1: predose sample, Week 4: predose and 1 postdose sample at 0.5-1 h window, Week 8: predose and 1 postdose sample at 1-3 h window and Week 12: predose and 2 postdose samples at 0.5-1 h and 2-4 h window or immediately before leaving the clinic, respectively. One blood sample will be collected at early termination. The actual date and times of all PK blood draws will be recorded for each subject on the eCRFs. The actual dates and times of the dose administration in the clinic should be recorded. PK sampling may be performed during unscheduled visits.

[u] Samples for prolactin measurement to be collected and analyzed as part of clinical laboratory evaluations at Visit 1, at scheduled Visits 4 to 7, and any necessary unscheduled visit. A high screening prolactin level at screening visit 1, which is considered to be due to stress of venipuncture, chest wall stimulation, or other physiological causes, may be retested at Visits 2 or 3. Then, if prolactin levels are normal or falling within the allowable range, the subjects may be enrolled in the study. A subset of samples may be used for prolactin assay bridging studies as needed. As TAK-906 may increase serum prolactin levels, investigators will be blinded to prolactin measurements beginning with Visit 4. In cases where investigators request unblinding of the study treatment or serum prolactin level, the subject must be withdrawn from the study immediately.

[v] SAEs will be collected from the time the subject signs an informed consent form through the duration of the study up to 30 days post–end of treatment. All nonserious AEs, in addition to SAEs, are collected from the first dosing through 30 days post–end of treatment.

Appendix B Hepatic Function Categories Based on Child-Pugh Score

Classification of clinical severity:
Mild (Class A): total score 5-6 points.
Moderate (Class B): total score 7-9 points.
Severe (Class C): total score 10-15 points.

Assessment Parameters	Points Scored for Observed Findings		
	1 point	**2 points**	**3 points**
Encephalopathy grade [a]	none	1 or 2	3 or 4
Ascites	absence	slight	moderate
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

Source: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.
INR: international normalized ratio.
[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second (cps) waves.
Grade 2: Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: Unarousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

Appendix C Guidance for Assessment of the Extrapyramidal System

Any clinically relevant findings in this assessment should be reported and managed as per protocol Section 10.0 of this protocol.

Posture

For example, abnormalities in sitting, standing or walking posture

Gait

For example, shuffling, festinating gait with reduced arm swing, difficulty starting, stopping, and turning.

Speech

For example, monotonous, low volume, lacks normal rhythm, soft, quiet, and hesitant speech or hyperkinetic dysarthria

Face

For example, expressionless, unblinking face, drooling, titubation, blepharoclonus, positive glabellar tap reflex), puckering and smacking.

Jaw

For example, biting, clenching, chewing, mouth opening and lateral movement.

Tongue

For example, abnormalities in darting in and out of mouth and tongue thrusting.

Abnormal movements in upper and lower limbs

Abnormal movements in neck, shoulders and hips

For example, rocking, twisting, squirming and pelvic gyrations

Coordination in upper and lower limbs

For example, abnormal coordination using rapid alternating movements or finger-nose test, abnormal coordination using foot tapping or heel–shin test

Tremor

For example, pill-rolling flexion at the thumb and forefinger.

Appendix D Schedule of Questionnaire Assessments

Instrument	Administered [a]	Estimated Subject Burden (Average Time to Complete)
Daily Symptom Diary	Daily (evening)	1 minute
PAGI-SYM	At Visit 4 (predose) to capture baseline values and thereafter at each scheduled study visit	5 minutes
Clinician Symptom Severity Rating Form	At Visit 4 (predose) to capture baseline values and at Visit 7 or early termination visit	NA it is clinician reported
OTE rated by the subject	At Visit 7 or early termination visit	1 minute
OTE rated by clinician	At Visit 7 or early termination visit	NA it is clinician reported
SF12	At Visit 4 (predose) to capture baseline values and at Visit 7	4 minutes
PAGI QOL	At Visit 4 (predose) to capture baseline values and thereafter at each scheduled study visit	7 minutes
CGI-S	At Visit 4 (predose) to capture baseline values and thereafter at each scheduled study visit	NA
CGI-I	At Visit 7 or early termination visit	NA
PGI-S	At Visit 4 (predose) to capture baseline values and thereafter at each scheduled study visit	1 minute
PGI-C	At Visit 7 or early termination visit	1 minute

ANMS GCSI-DD: American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary; CGI-I: Clinical Global Impression Scale–Global Improvement Scale; CGI-S: Clinical Global Impression Scale–Severity of Illness Scale, NA: not applicable; OTE: overall treatment effect; PAGI-QOL: Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index; 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; SF12: Short Form-12 Health Survey.

[a] For subjects who withdraw prematurely, ANMS GCSI-DD will be completed daily until the early termination visit and all the other questionnaires will be completed at the early termination visit.

Appendix E Patient Global Impression Scales

New PGI-S Scale replacing the existing PGI-S scale:

Please choose the response below that best describes the overall severity of your gastroparesis symptoms over the past 7 days:

- □ None
- □ Mild
- □ Moderate
- □ Severe

PGI-C scale replacing the existing PGI-I scale:

Please choose the response below that best describes the overall change in your gastroparesis symptoms since you started taking the study medication:

- □ Much better
- □ A little better
- □ No change
- □ A little worse
- □ Much worse

Appendix F Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. This responsibility lies on the appropriate individual, designated by the site in Japan.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix G Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the

subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) on withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential if study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study, and for 35 days after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued, and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 95 days after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix H Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix I ANMS GCSI-DD

This is to illustrate the contents of ANMS GCSI-DD question items and does not reflect the exact appearance (such as instructions) in the actual administration mode.

Participant Number: _____ Date: _____ Time: _____

ANMS GASTROPARESIS CARDINAL SYMPTOM INDEX – DAILY DIARY

Instructions: These questions ask about symptoms you may have each day. Please complete the daily diary at about the same time every evening.

For each symptom listed below, please mark with an X the box that best describes the worst severity of each symptom during the past 24 hours. Please be sure to answer each question.

	None	Mild	Moderate	Severe	Very Severe
1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	□	□	□	□	□
2. Not able to finish a normal-sized meal (for a healthy person)	□	□	□	□	□
3. Feeling excessively full after meals	□	□	□	□	□
4. Upper abdominal pain (above the navel)	□	□	□	□	□

The next question asks you to record the number of times vomiting occurred in the last 24 hours. Please record the number of vomits (throwing up with food or liquid coming out) that occurred in the last 24 hours. Record zero if you have not vomited during the past 24 hours. If you vomited, write down the number of all vomits. If you vomited once, record one. If you vomited 3 times during the day, record 3. If you vomited 3 times, whether it was during the same trip to the bathroom or 3 separate trips, record 3 as the number of episodes of vomiting.

5. During the past 24 hours, how many episodes of vomiting did you have? ____

	None	Mild	Moderate	Severe	Very Severe
6. In thinking about your gastroparesis disorder, what was the overall severity of your gastroparesis symptoms today (during the past 24 hours)?	□	□	□	□	□

Appendix J Bloating Severity Scale

This is to illustrate the contents of the Bloating Severity Scale and does not reflect the exact appearance (such as instructions) in the actual administration mode.

DAILY DIARY

Instructions: These questions ask about bloating severity you may have each day. Please complete the Bloating Severity Scale at about the same time every evening.

For the bloating symptom below, please mark with an X the box that best describes the worst severity of bloating during the past 24 hours. Please be sure to answer each question.

	None	Mild	Moderate	Severe	Very Severe
Bloating (feeling like you need to loosen your clothes)	□	□	□	□	□

Appendix K Protocol History

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
13 July 2020	Amendment 8	Substantial	Global
27 August 2019	Amendment 7	Nonsubstantial	Japan
08 August 2019	Amendment 6	Substantial	Global
23 May 2019	Amendment 5	Nonsubstantial	Belgium
15 November 2018	Amendment 4	Nonsubstantial	Japan
26 September 2018	Amendment 3	Nonsubstantial	Japan
06 August 2018	Amendment 2	Substantial	Global
16 July 2018	Amendment 1	Substantial	Global
23 March 2018	Initial protocol	Not applicable	Global

Protocol Amendment 7 was a local amendment and is not applicable to the global protocol.

Rationale for Amendment 6

This document describes the changes from the protocol incorporating Amendment No. 6. Through feedback from investigators, the Sponsor has determined the need to revise the list of prohibited medications, add a rationale for the use of ondansetron and promethazine as rescue medications, clarify rescue medication use, clarify the estimated glomerular filtration rate (eGFR) eligibility criteria, clarify Gastric Emptying Breath Test (GEBT) and eligibility for retesting, revise the interim analysis adding a futility analysis, and clarify the duties and responsibilities of the Independent Data Monitoring Committee (IDMC).

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 6:

1. Updated the signatories in Section 1.2.
2. Updated and revised Section 4.2.3 Pharmacokinetics and Product Metabolism with new metabolism data.
3. Revised Section 4.3.1 Clinical Pharmacology to show effects of eGFR on exposure of TAK-906 and the effects of coadministration of esomeprazole on the area under the concentration-time curve from time 0 to infinity (AUC_{∞}) and maximum observed concentration (C_{max}) of TAK-906.
4. Revised wording in Section 5.2.4 Additional Endpoints regarding change from baseline to Week 12 of the treatment period in the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD).

5. Deleted the requirement for medication to be taken "on an empty stomach (at least 2 hours of fasting except for water); Section 6.1 Study Design.
6. Revised the interim analysis by adding a futility analysis; Section 6.1 Study Design.
7. Clarified the use of rescue medication (Section 6.2.3 Rationale for Placebo).
8. Revised exclusion Criterion No. 26 to define prolonged QT interval with Fridericia correction method (QTcF) as ≥450 msec and to exclude subjects with risk factors for QT interval prolongation.
9. Clarified the exclusion Criterion No. 30 for significant menstrual abnormalities such as amenorrhea or oligomenorrhea.
10. Revised exclusion Criterion No. 31 to exclude subjects who have any signs/symptoms or history of extrapyramidal system disease or history of suicide attempt.
11. Changed exclusion Criterion No. 37 to exclude subjects with renal impairment, defined as a lower limit of eGFR <30 mL/min at screening visit and deleted the formulas for calculating eGFR in various subject populations.
12. Removed proton pump inhibitors and histamine H_2 receptor antagonists, and CYP2C8 strong inhibitors and inducers as excluded medication and clarified the remaining list of excluded medication (Section 7.3 Excluded Medications).
13. Clarified the conditions for use of certain permitted concomitant medications.
14. Removed the stipulation that subjects who had taken <80% of study drug in the previous 4-week period would be withdrawn from the study because of noncompliance with study medication (Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject).
15. Clarified the use of rescue medication and defined the preferred rescue medication. (Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling).
16. Remove the requirement for confirmed menses in the month before first dosing (no delayed menses; Section 9.1.11.3 Definitions and Procedures for Contraception and Pregnancy Avoidance).
17. Clarified and defined gastric emptying by GEBT and clarified when retesting could be done (Section 9.1.18.1 GEBT).
18. Revised Section 9.2 Monitoring Subject Treatment Compliance to add the criteria that subjects who are <80% compliant or who missed ≥6 consecutive doses since the last study visit will be re-educated about the importance of being consistent with their dosing as per the protocol.
19. Clarified duties of IDMC (Section 11.1 IDMC).
20. Clarified that concomitant medication information would be collected during the safety follow-up period (Appendix A Schedule of Study Procedures).

Rationale for Amendment 5

This document describes the changes from the protocol incorporating Amendment No. 2. The primary reason for this Amendment 5 for Belgium is to update the exclusion criteria for clarification, in response to the Belgian Ethics Committee's (EC's) recommendations.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 5

1. Updated exclusion Criterion No. 31 in response to the Belgian EC's recommendations.

Protocol Amendment 4 was a local amendment and is not applicable to the global protocol.

Protocol Amendment 3 was a local amendment and is not applicable to the global protocol.

Rationale for Amendment 2

This document describes the changes in reference to the protocol incorporating Amendment No. 1. The primary reason for this amendment is.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 2:

1. Updated the secondary endpoints.
2. Updated the biomarkers to be analyzed.
3. Updated and clarified the Schedule of Study Procedures, including timing and procedures performed.
4. Clarified the clinical laboratory tests performed.
5. Clarified the timing, collection, and reporting of adverse events, serious adverse events, and adverse events of interest.
6. Clarified the inclusion criterion.

Rationale for Amendment 1

This document describes the changes in reference to the protocol incorporating Amendment No. 1. The primary reason for this amendment is.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 1:

1. Update nonclinical information with most recent toxicology data.
2. Update the biomarkers to be analyzed and rationales.
3. Clarify the objective and endpoint for the Gastric Emptying Breath Test (GEBT).
4. Clarify that the bloating severity scale is not part of the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD), but will be collected in the Daily Symptom Diary.
5. Clarify the criteria for use of rescue medication for nausea and vomiting.
6. Update the subject eligibility criteria.
7. Update the list of Excluded Medications.
8. Clarify the storage information for the study drug.
9. Clarify timing of GEBT relative to dosing of study drug.
10. Update the safety section with guidance to investigators for management of extrapyramidal symptoms and central nervous system (CNS)/neuropsychiatric adverse events.
11. Remove use of paper serious adverse event (SAE) reporting for Japan.
12. Clarify the primary efficacy analysis.
13. Update and clarify the Schedule of Study Procedures.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	14-Jul-2020 15:55 UTC
	Clinical Pharmacology Approval	14-Jul-2020 18:17 UTC
	Biostatistics Approval	14-Jul-2020 20:00 UTC